CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761244Orig1s000

MULTI-DISCIPLINE REVIEW

BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761244
Priority or Standard	Priority
Submit Date(s)	10/1/2021
Received Date(s)	10/1/2021
PDUFA Goal Date	9/1/2022
Division/Office	Division of Dermatology and Dentistry/Office of Immunology and Inflammation
Review Completion Date	8-29-2022
Established/Proper Name	spesolimab-sbzo
(Proposed) Trade Name	Spevigo
Pharmacologic Class	Interleukin-36 receptor antagonist
Code name	BI 655130
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Dosage form	Injection
Applicant proposed Dosing Regimen	Administer as a single 900 mg (2 x 450 mg/7.5 mL vials) intravenous infusion over 90 minutes. If flare symptoms persist, an additional intravenous 900 mg dose may be administered 1 week after the initial dose.
Applicant Proposed Indication(s)/Population(s)	Spevigo is an interleukin-36 receptor antagonist indicated for the treatment of flares in adult patients with generalized pustular psoriasis.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	238612002 |Generalized pustular psoriasis (disorder)|
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of flares in adult patients with generalized pustular psoriasis
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	238612002 |Generalized pustular psoriasis (disorder)|
Recommended Dosing Regimen	Same as proposed by applicant

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COA=Clinical Outcomes and Assessments
DNI=Division of Neurology I
DPM=Division of Pharmacometrics
DPMH=Division of Pediatric and Maternal Health
DTPM=Division of Translational and Precision Medicine
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
PLT=Patient Labeling Team
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality

OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1 Product Introduction

SPEVIGO (spesolimab) injection, for intravenous use, is a humanized monoclonal immunoglobulin G1 antibody that inhibits interleukin-36 (IL-36) signaling by specifically binding to the IL-36 receptor (IL36R). Binding of spesolimab to IL36R prevents the subsequent activation of IL36R by cognate ligands (IL-36 α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways. Spesolimab is a new molecular entity (NME). The proposed indication is the treatment of flares in adult patients with generalized pustular psoriasis. The proposed dose is a single 900 mg intravenous infusion over 90 minutes. If flare symptoms persist, an additional intravenous 900 mg dose may be administered 1 week after the initial dose. The proposed commercial presentation for the spesolimab drug product is a 450 mg/7.5 mL (60 mg/mL) solution in a single-dose vial.

The Agency concluded that the proposed proprietary name, SPEVIGO, was acceptable from both a promotional and safety perspective under BLA 761244 [see Proprietary Name Review by Madhuri R. Patel, PharmD, Division of Medication Error Prevention and Analysis (DMEPA) dated November 23, 2021]. The Agency also concluded that the proposed nonproprietary name suffix for spesolimab-sbzo was conditionally acceptable under BLA 761244 [see Suffix Review for Nonproprietary Name by Carlos M Mena-Grillasca, BS Pharm and Irene Z. Chan, PharmD, BCPS, DMEPA 1 dated March 11, 2022].

1.2 Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from one adequate and well-controlled trial [Trial 1368-0013 (Effisayil-1)] with supportive evidence from trials 1368-0011 (phase 1, completed), 1368-0025 (phase 2, ongoing), and 1368-0027 (phase 2, ongoing) (see 7.1 Table of Clinical Studies), which provided evidence of the effectiveness of spesolimab for the treatment of GPP flare in adults. The Effisayil-1 trial assessed the changes from baseline flare to Week 1 compared to placebo in the primary efficacy endpoint:

- the proportion of subjects with a GPPPGA pustulation sub score of 0 (indicating no visible pustules) at Week 1 after treatment.

Spesolimab was statistically superior to placebo for the primary efficacy endpoint (one-sided p-value = 0.0004). The Applicant demonstrated that spesolimab is effective for its intended use in the target population and has met the evidentiary standard required by 21 CFR 314.126 to support approval.

1.3 Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Generalized pustular psoriasis (GPP) is a rare, potentially life-threatening dermatological disease that presents with widespread sterile pustules with or without systemic symptoms and with or without a history of psoriasis. The pustules of GPP are painful and can coalesce into large "lakes of pus," significantly impacting patients' quality of life. The clinical course is mostly chronic with unpredictable relapsing and remitting periods of flares over several years. Life-threatening complications can occur and include sepsis, neutrophilic cholangitis, neutrophilic pneumonitis, acute respiratory distress syndrome, renal abnormalities, and death.[1] Reported mortality rates range from 2 to 16%.[2,3,4,5]

SPEVIGO (spesolimab) injection, for intravenous use is proposed for the treatment of GPP flare in adults. Spesolimab, the active ingredient in SPEVIGO, is a new molecular entity. Spesolimab is a humanized monoclonal immunoglobulin G1 antibody that inhibits interleukin-36 (IL-36) signaling by specifically binding to the IL-36 receptor (IL36R). Binding of spesolimab to IL36R prevents the subsequent activation of IL36R by cognate ligands (IL-36 α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways. The precise mechanism linking reduced IL36R activity and the treatment of GPP flares is unclear.

There are no approved treatments for GPP in the United States. Current off-label therapeutic options include systemic small molecule drugs (acitretin, methotrexate, and cyclosporine) and biologic products. 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. There is a lack of high-quality efficacy evidence to support current

[1] https://www.uptodate.com/contents/pustular-psoriasis-pathogenesis-clinical-manifestations-and-diagnosis
[2] Choon SE, Navarini AA, Pinter A. Clinical Course and Characteristics of Generalized Pustular Psoriasis. *Am J Clin Dermatol*. 2022;23(Suppl 1):21-29. doi:10.1007/s40257-021-00654-z
[3] Choon SE, Lai NM, Mohammad NA, Nanu NM, Tey KE, Chew SF. Clinical profle, 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):676–84.
[4] Baker H, Ryan TJ. Generalized pustular psoriasis: a clinical and epidemiological study of 104 cases. Br J Dermatol. 1968;80(12):771–93.
[5] Augey F, Renaudier P, Nicolas J-F. Generalized pustular psoriasis (Zumbusch): a French epidemiological survey. Eur J Dermatol. 2006;16(6):669–73.

off-label treatment options and no product produces a response in all patients or provides a permanent cure. All the systemic products may have one or more serious adverse reactions, including malignancy, serious infections, teratogenicity, depression, nephrotoxicity, hepatoxicity, and bone marrow suppression. Due to these limitations and lack of approved therapies for GPP in the United States, there is a recognizable need for therapeutic options for GPP.

Substantial efficacy was demonstrated in one pivotal Trial 1368-0013, which enrolled 53 adult subjects with GPP flare of moderate-to-severe intensity defined as a Generalized Pustular Psoriasis Physician Global Assessment (GPPPGA) total score of at least 3 (moderate) [the total GPPPGA score ranges from 0 (clear) to 4 (severe)], the presence of fresh pustules (new appearance or worsening of pustules), GPPPGA pustulation sub score of at least 2 (mild), and at least 5% body surface area covered with erythema and the presence of pustules. In the trial, subjects were randomized (2:1) to either a single intravenous dose of 900 mg of spesolimab (N=35) or placebo (N=18). The primary efficacy endpoint of the trial was the proportion of subjects with a GPPPGA pustulation sub score of 0 (indicating no visible pustules) at Week 1 after treatment. In trial 1368-0013, spesolimab was superior to placebo on GPPPGA pustulation sub score of 0 at Week 1 (54% vs 6%; one-sided p-value = 0.0004).

Supportive clinical evidence was demonstrated in trials 1368-0011 (phase 1, completed), 1368-0025 (phase 2, ongoing), and 1368-0027 (phase 2, ongoing) (see 7.1 Table of Clinical Studies).

The primary safety database, which consisted of data from Phase 2 trial 1368-0013, and additional supportive safety data were adequate to characterize the safety profile of SPEVIGO (spesolimab) injection for the proposed indication. The supportive safety database consisted of data from phase 1 trial 1368-0011 and information provided from the ongoing phase 2 trial 1368-0027. Given the rarity of GPP, safety was also informed by auxiliary safety cohorts, i.e. exposure of subjects to spesolimab in other developmental programs for other diseases and healthy volunteers at various doses and dosage forms (subcutaneous and intravenous). No deaths were reported in the trials for GPP. No cases of anaphylaxis were reported in subjects exposed to spesolimab in the development program. However, serious adverse events included two reported cases of drug reaction with eosinophilia and systemic symptoms (DRESS) in two subjects exposed to spesolimab in trial 1368-0013. One case was determined as unlikely to be DRESS and the other case was determined as a possible case of DRESS ("no case" and "possible," respectively, based on the Regi-SCAR criteria) and the risk of DRESS is recommended to be included in product labeling. Of three reported cases of Guillain-Barre syndrome in other spesolimab development programs, two were deemed probable; all will be included in labeling.

Treatment with spesolimab was not associated with an increased incidence of major adverse cardiovascular events (MACE). No cases of active tuberculosis occurred in the development program in subjects who received spesolimab. One case of latent tuberculosis was reported in trial 1368-0013 after the subject received open-label spesolimab. Infections such as urinary tract infections, bacteremia, bacteriuria, cellulitis,

herpes dermatitis and oral herpes, and upper respiratory infection occurred more frequently in subjects who received spesolimab compared to subjects who received placebo (14% vs 6% through Week 1). Serious infection (urinary tract infection) was reported in 1 subject treated with spesolimab and no subjects treated with placebo through Week 1. All other cases of infection were mild to moderate in severity and did not lead to discontinuation of spesolimab. Other adverse reactions, occurring in greater than or equal to 1 subject (≥1%) and observed more frequently in subjects receiving spesolimab through Week 1, included asthenia and fatigue, nausea and vomiting, headache, pruritis and prurigo, infusion site hematoma and bruising, dyspnea, eye edema, and urticaria. These identified adverse reactions will be conveyed in product labeling.

In trial 1368-0013, additional adverse reactions that occurred through Week 12 in subjects treated with 1 single dose of randomized spesolimab were mild to moderate infections: device-related infection, subcutaneous abscess, furuncle, and influenza. Additional adverse reactions that occurred through Week 17 in subjects treated with a single dose of open-label spesolimab at Week 1 (second dose and first dose for subjects in the spesolimab and placebo groups, respectively) were mild to moderate infections: otitis externa, vulvovaginal candidiasis, vulvovaginal mycotic infection, and latent tuberculosis, diarrhea, and gastritis. No new adverse reactions were identified for up to 16 weeks in subjects treated with a single dose of open-label rescue spesolimab from Week 1 to Week 12 (range 1-3 total doses).

Post-marketing safety studies to assess the risk of immunogenicity, serious hypersensitivity reactions, including DRESS, anaphylaxis, and infusion related reactions, serious infections, and other serious adverse events are recommended.

Prescription and patient labeling, including a Medication Guide, as well as pharmacovigilance are adequate to manage the risk of SPEVIGO in the post market setting. A Risk Evaluation and Mitigation Strategy (REMS) is not needed. Recommended postmarketing requirements under 505(o)(3): 1) an immunogenicity study, 2) submission of safety findings from currently ongoing trials 1368-0027 and 1368-0025, and 3) submission of the final study report from the planned voluntary European Post-Authorization Safety Study (PASS).

Given the potentially life-threatening nature of GPP and lack of approved therapies for GPP in the United States, there is a need for therapeutic options for GPP. Based on the efficacy data, spesolimab demonstrated superiority compared to placebo on the primary efficacy endpoint of the proportion of subjects with a GPPPGA pustulation sub score of 0 at Week 1 (54% vs 6%) which is a clinically meaningful endpoint, the absence of pustules. The safety data provided also supports the approval for treatment of flares in GPP which is a rare disease with an estimated prevalence of 1 to 9 per million worldwide or 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 in the United States based on claims based data. Thus, we conclude that the benefits of treatment with spesolimab in adults with generalized pustular psoriasis flare

outweigh its potential risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Generalized pustular psoriasis (GPP) is a rare, potentially life-threatning dermatological disease that presents with widespread sterile pustules with or without systemic symptoms and with or without a history of psoriasis. The pustules of GPP are painful and can coalesce into large "lakes of pus," significantly impacting patients' quality of life. The exact prevalence of GPP is unknown but estimates have ranged from 1 to 9 per million.[6] Claims based data[7] 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. The clinical course is mostly chronic with unpredictable relapsing and remitting periods of flares over several years. Life-threatening complications can occur and include sepsis, neutrophilic cholangitis, neutrophilic pneumonitis, acute respiratory distress syndrome, renal abnormalities, and death.[8] Reported	Generalized pustular psoriasis is a serious disease because of its potential for life-threatening complications, chronicity, and impact on quality of life.

[6] https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=247353
[7] US Truven MarketScan administrative claims from 01 Oct 2015 to 30 Sep 2016 and Optum US claims database using data from 01 Oct 2015 to 30 Jun 2017
[8] https://www.uptodate.com/contents/pustular-psoriasis-pathogenesis-clinical-manifestations-and-diagnosis

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	mortality rates range from 2 to 16%.[9,10,11,12]	
Current Treatment Options	• There are no approved treatments for GPP in the United States. • For stable GPP, off-label standard of care therapies include acitretin and methotrexate. For more severe, acute GPP, cyclosporine and infliximab are used off-label. 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. • Current off-label treatment options may be associated with the risk of serious adverse reactions. Teratogenicity and hyperlipidemia are labeled risks with acitretin. Methotrexate has teratogenic, hepatotoxic, nephrotoxic effects and may cause bone marrow toxicity and pulmonary fibrosis. Cyclosporine has risks of renal and hepatic toxicity, infections, and malignancy. Biologic products may be associated with loss of effect and serious hypersensitivity reactions.	There is a lack of high-quality efficacy evidence to support current off-label treatment options. Furthermore, current off-label treatment options are associated with one or more serious risks and may be complicated by the presence of various comorbidities or concomitant illnesses/conditions, inadequate response, and/or loss of response. As such, there is a need for therapeutic options supported by high-quality efficacy evidence for GPP.

[9] Choon SE, Navarini AA, Pinter A. Clinical Course and Characteristics of Generalized Pustular Psoriasis. *Am J Clin Dermatol*. 2022;23(Suppl 1):21-29. doi:10.1007/s40257-021-00654-z
[10] Choon SE, Lai NM, Mohammad NA, Nanu NM, Tey KE, Chew SF. Clinical profle, 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):676–84.
[11] Baker H, Ryan TJ. Generalized pustular psoriasis: a clinical and epidemiological study of 104 cases. Br J Dermatol. 1968;80(12):771–93.
[12] Augey F, Renaudier P, Nicolas J-F. Generalized pustular psoriasis (Zumbusch): a French epidemiological survey. Eur J Dermatol. 2006;16(6):669–73.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Data from Trial 1368-0013 provided substantial evidence of the effectiveness of spesolimab for the treatment of GPP flare. The trial enrolled 53 adult subjects with GPP flare of moderate-to-severe intensity defined as a Generalized Pustular Psoriasis Physician Global Assessment (GPPPGA) total score of at least 3 (moderate) [the total GPPPGA score ranges from 0 (clear) to 4 (severe)], the presence of fresh pustules (new appearance or worsening of pustules), GPPPGA pustulation sub score of at least 2 (mild), and at least 5% body surface area covered with erythema and the presence of pustules. In the trial, subjects were randomized (2:1) to either a single intravenous dose of 900 mg of spesolimab (N=35) or placebo (N=18). The primary endpoint of the trial was the proportion of subjects with a GPPPGA pustulation sub score of 0 (indicating no visible pustules) at Week 1 after treatment. • In trial 1368-0013, spesolimab was superior to placebo on the primary efficacy endpoint of the proportion of subjects with a GPPPGA pustulation sub score of 0 at Week 1 (54% vs 6%). • At Week 1, subjects in either treatment group who continued to experience flare symptoms were eligible to receive a single open-label intravenous dose of 900 mg of spesolimab (second dose and first dose for subjects in the spesolimab and placebo groups, respectively). At Week 1, 12 (34%) subjects and 15 subjects (83%) in the spesolimab and placebo groups, respectively, received open-label spesolimab. In subjects who were randomized to spesolimab and received an open-label dose of spesolimab at Week 1, 5 (42%) subjects had a GPPPGA pustulation sub score of 0 at Week 2 (one week after their second dose of spesolimab).	The data submitted by the Applicant met the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use, particularly for this potentially life-threatnening, rare disease with an unmet medical need and significant impact on quality of life. The trial was adequate and well-controlled. The results are persuasive. Achievement of clear pustules is a clinically meaningful outcome for a dermatologic pustular disease such as GPP. The data suggest that a patient with GPP flare of moderate-to-severe intensity treated with a single intravenous dose of 900 mg spesolimab is likely to achieve clear pustules by Week 1.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The primary safety database (trial 1368-0013) included 51 subjects with GPP flare who received at least 1 dose of spesolimab at the proposed dose of a single intravenous dose of 900 mg (includes randomized, open-label, and rescue doses) and followed for 16 weeks. Thirty-six subjects received 1 dose, 13 subjects received 2 doses, and 2 subjects received 3 doses (maximum allowed in the trial) of spesolimab throughout trial 1368-0013. The supportive safety database included 7 subjects with GPP flare who received at least 1 dose of spesolimab at a single dose of 10 mg/kg (trial 1368-0011) and 22 subjects with GPP flare who received at least 1 dose of spesolimab at the proposed dose of a single intravenous dose of 900 mg (trial 1368-0027). Given the rarity of GPP, safety was also informed by auxiliary safety cohorts, i.e. exposure of subjects to spesolimab in other developmental programs for other diseases and healthy volunteers at various doses and dosage forms (subcutaneous and intravenous). • Infections occurred more frequently in subjects who received spesolimab compared to subjects who received placebo (14% vs 6% through Week 1). • No cases of active tuberculosis occurred in the development program in subjects who received spesolimab. One case of latent tuberculosis was reported in trial 1368-0013 after the subject received open-label spesolimab. Subjects were screened for tuberculosis prior to enrollment in the pivotal trial, and screening is recommended in product labeling. • Given that sepsis is a known, potentially life-threatening complication that occurs in GPP, submission of safety results from ongoing clinical trials 1368-0027 and 1368-0025 to characterize the risk of serious and opportunistic infections of spesolimab and submission of the final	The safety database is adequate given the rarity of GPP based on prevalence estimates for GPP. While the premarket safety database is adequate currently, it is nevertheless limited due to the rarity of GPP. Thus, the safety profile will be better informed by data from ongoing clinical trials and post market data. Based on the current premarket safety data, spesolimab has an acceptable risk-benefit profile for the indication of the treatment of GPP flare in adults.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	study report for the planned voluntary European PASS will be required in the postmarket setting. • Serious hypersensitivity reactions including drug reaction with eosinophilia and systemic symptoms (DRESS) were reported in two subjects exposed to spesolimab in trial 1368-0013 (one case "no case" and another case "possible" under the Regi-SCAR criteria) and the risk of DRESS is recommended to include in product labeling. No cases of anaphylaxis were reported in subjects exposed to spesolimab in the development program. Postmarket requirements for 1) an immunogenicity study, 2) submission of safety findings from currently ongoing trials 1368-0027 and 1368-0025, and 3) submission of the final study report from the planned voluntary European Post-Authorization Safety Study (PASS) is recommended to better characterize this risk. • No deaths were reported in any GPP trial (trials 1368-0011, 1368-0013, 1368-0025, 1368-0027). • In trial 1368-0013, additional adverse reactions that occurred through Week 12 in subjects treated with 1 single dose of randomized spesolimab were mild to moderate infections: device-related infection, subcutaneous abscess, furincle, and influenza. Additional adverse reactions that occurred through Week 17 in subjects treated with a single dose of open-label spesolimab at Week 1 (second dose and first dose for subjects in the spesolimab and placebo groups, respectively) were mild to moderate infections: otitis externa, vulvovaginal candidiasis, vulvovaginal mycotic infection, and latent tuberculosis, diarrhea, and gastritis. No new adverse reactions were identified for up to 16 weeks in subjects treated with a single dose of open-label rescue spesolimab from Week 1 to Week 12 (range 1-3 total doses).	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• There is lack of clinical data on the use of spesolimab in pregnant women. Pregnant individuals were excluded from clinical trials across the development program with spesolimab. The three reports of pregnancy in the development program for spesolimab contain incomplete information and cannot assist to identify any safety concerns for use during pregnancy. The animal data have not identified adverse embryofetal developmental effects. Given there are no approved therapies for GPP, pregnancy can trigger the onset of GPP flare, and GPP 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. Recommend enhanced pharmacovigilance to monitor for adverse events in pregnant patients and pregnancy-related outcomes with spesolimab use.	
Risk Management	• The following PMRs (1-3) are recommended: 1. Conduct an open label safety study to assess the effect of immunogenicity on pharmacokinetics (PK), safety, and efficacy on re-treatment of flares that occur after the first flare incidence has been treated and resolved. 2. Submit the final study reports with safety results from ongoing trials 1) Effisayil-2 (clinicaltrials.gov identifier: NCT04399837, other study ID number: 1368-0027): Multi-center, Randomized, Parallel Group, Double Blind, Placebo Controlled, Phase IIb Dose-finding Study to Evaluate Efficacy and Safety of BI 655130 (Spesolimab) Compared to Placebo in Preventing Generalized Pustular Psoriasis (GPP) Flares in Patients With History of GPP and 2) Effisayil-ON (clinicaltrials.gov identifier: NCT03886246, other study ID number: 1368-0025): An Open-label, Long Term Extension Study to Assess the Safety and	Prescription labeling, patient labeling (including Medication Guide) and both routine and enhanced pharmacovigilance, in conjunction with the postmarketing requirements, are adequate to manage the risks of the product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Efficacy of BI 655130 Treatment in Patients With Generalized Pustular Psoriasis (GPP). 3. Submit the final study report for the planned voluntary European Post-Authorization Safety Study (PASS). • Labeling: Prescription labeling adequately addresses the risks identified during product development and conveys the lack of data from human exposure during pregnancy. A Medication Guide and Instructions for Use for the proposed presentation are included in patient labeling and are appropriate to inform patients of potential risks. • A REMS is not recommended.	

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that were submitted as part of the application include:			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	Patient experience data was not submitted as part of this application.			

2 Therapeutic Context

2.1 Analysis of Condition

Generalized pustular psoriasis (GPP) is a rare, potentially life-threatening dermatological disease that presents with widespread sterile pustules with or without systemic symptoms and with or without a history of psoriasis. The exact prevalence of GPP is unknown but estimates have ranged from 1 to 9 per million[13], with a higher reported prevalence in Asians compared to Caucasians (prevalence in a Japanese population estimated to be 7.46 per million and in a French population, estimated to be 1.76 per million). Claims based data[14] 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.

The European Rare and Severe Psoriasis Network (ERASPEN) classifies pustular psoriasis into three types: GPP, acrodermatitis continua of Hallopeau, and palmoplantar pustulosis (PPP). GPP is further divided into acute generalized pustular psoriasis (or generalized pustular psoriasis of von Zumbusch) and generalized annular pustular psoriasis (or subacute GPP). Acute GPP presents with systemic symptoms, sudden onset of pustules, and widespread erythema. Generalized annular pustular psoriasis is often less severe. For the diagnosis of GPP, the ERASPEN has defined GPP as primary, sterile, macroscopically visible pustules on non-acral skin (excluding cases where pustulation is restricted to psoriatic plaques) with three sub-classifiers: 1) with or without systemic inflammation (using the American Society of Chest Physicians definition of fever >38 ^{o}C and leukocytosis (WBC >12x10^{9}/L)), 2) with or without psoriasis vulgaris and 3) either relapsing (>1 episode) or persistent (>3 months)[15].

The exact pathogenesis of GPP is unknown. Genetic factors have been noted with mutations in *IL-36RN* gene that encodes the interleukin-36 receptor antagonist (IL-36Ra), an anti-inflammatory cytokine in the IL-1 family that inhibits proinflammatory signaling, detected in some individuals with GPP and other pustular skin diseases. Triggers include infections, withdrawal or administration of certain medications (including those used to treat GPP such as corticosteroids and methotrexate), and pregnancy (impetigo herpetiformis) however, cases can present with an unidentifiable trigger.

GPP can present in two main types: 1) acute GPP (generalized pustular psoriasis of von Zumbusch) and 2) generalized annular pustular psoriasis, the subacute type. Acute GPP

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[13] https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=247353
[14] US Truven MarketScan administrative claims from 01 Oct 2015 to 30 Sep 2016 and Optum US claims database using data from 01 Oct 2015 to 30 Jun 2017
[15] Navarini AA, Burden AD, Capon F, et al. European consensus statement on phenotypes of pustular psoriasis. *J Eur Acad Dermatol Venereol*. 2017;31(11):1792-1799. doi:10.1111/jdv.14386

presents with an abrupt onset of widespread painful pustules which can coalesce into larger, "lakes of pus" overlying painful erythema. Pustules resolve within days to weeks with residual erythema and scaling taking longer to improve. In one retrospective study of 110 patients with GPP admitted to a hospital in China from January 2014 to December 2019, the pustules completely resolved in 94/110 (85%) patients and the mean time was 9.3 ± 6.6 days with treatment regimens varying amongst this retrospective cohort[16]. The mean time for pustular clearance was shorter in patients without fever compared to patients with fever in this retrospective study (7.4 ± 5.0 vs. 11.1 ± 7.4, $p<0.05$). Systemic symptoms are generally present with fever, chills, malaise. In the retrospective study of 110 patients, 58 patients (52%) had fever. Laboratory findings include leukocytosis, elevated erythrocyte sedimentation rate (ESR), hypocalcemia, electrolyte imbalances, lymphopenia, elevated liver enzymes, and hypoalbuminemia.

Generalized annular pustular psoriasis is the less severe form and presents with recurring annular or figurate erythematous, potentially expanding, plaques with peripheral pustules and scales. This form can also be associated with fever and laboratory abnormalities.

The clinical course is mostly chronic with unpredictable relapsing and remitting periods over several years. Some individuals may go into remission for several years before experiencing a flare whereas others have several flares per year.

Life-threatening complications can occur and include sepsis, neutrophilic cholangitis, neutrophilic pneumonitis, acute respiratory distress syndrome, renal abnormalities, and death.[17] Reported mortality rates directly attributable to GPP or its associated treatment, specifically with the use of systemic corticosteroids, range from 2 to 16%.[18,19,20,21] One study in Japan using a national inpatient database demonstrated an overall in-hospital mortality rate of 4.2% among 1513 patients with GPP.[22] The mortality rate was highest in patients receiving

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[16] Zheng J, Chen W, Gao Y, et al. Clinical analysis of generalized pustular psoriasis in Chinese patients: A retrospective study of 110 patients. *J Dermatol*. 2021;48(9):1336-1342. doi:10.1111/1346-8138.15958
[17] https://www.uptodate.com/contents/pustular-psoriasis-pathogenesis-clinical-manifestations-and-diagnosis
[18] Choon SE, Navarini AA, Pinter A. Clinical Course and Characteristics of Generalized Pustular Psoriasis. *Am J Clin Dermatol*. 2022;23(Suppl 1):21-29. doi:10.1007/s40257-021-00654-z
[19] Choon SE, Lai NM, Mohammad NA, Nanu NM, Tey KE, Chew SF. Clinical profle, 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):676–84.
[20] Baker H, Ryan TJ. Generalized pustular psoriasis: a clinical and epidemiological study of 104 cases. Br J Dermatol. 1968;80(12):771–93.
[21] Augey F, Renaudier P, Nicolas J-F. Generalized pustular psoriasis (Zumbusch): a French epidemiological survey. Eur J Dermatol. 2006;16(6):669–73.
[22] . Miyachi H, Konishi T, Kumazawa R, Matsui H, Shimizu S, Fushimi K, et al. Treatments and outcomes of generalized pustular psoriasis: a cohort of 1516 patients in a nationwide inpatient database in Japan. J Am Acad Dermatol. 2021. https://doi.org/10.1016/j. jaad.2021.06.008.

systemic corticosteroid monotherapy and lowest in patients receiving biologics, at 9% and 1%, respectively.

2.2 Analysis of Current Treatment Options

There are no approved treatments for GPP in the United States and there is a lack of high-quality efficacy evidence to support current treatment options.

For stable GPP, off-label standard of care therapies include acitretin and methotrexate. Acitretin and methotrexate are relatively well-tolerated and can be used long-term as maintenance therapy, however, with certain adverse events limiting their long-term use (i.e. liver and bone marrow toxicity for methotrexate and renal and hepatic dysfunction for acitretin). Acitretin and methotrexate are used for stable GPP given their slower onset of action. Improvement in pustules and other clinical signs has been reported within 7 to 10 days, with a complete response in 2 to 3 months with oral retinoids. Data from one Japanese study noted 84% of 188 individuals with GPP treated with retinoids responded. The treatment regimens with retinoids varied and individuals were typically treated with etretinate which was withdrawn from the United States market in 2003 because it posed a greater risk of birth defects than acitretin, the product that replaced etretinate, and with concomitant medications.[23] Data regarding methotrexate's efficacy to treat GPP comes from the same study in Japan which reported 76% of 41 individuals treated with methotrexate alone or with concomitant therapies responding. Another retrospective study of 63 individuals hospitalized for GPP at Mayo Clinic affiliated-hospitals between 1961 and 1989 noted improvement in 3/8 individuals with acute GPP and 2/2 individuals with annular pustular psoriasis treated with methotrexate.[24] Both acitretin and methotrexate are contraindicated in pregnancy with individuals of childbearing potential required to abstain from pregnancy for three years after acitretin treatment.

For more severe, acute GPP, cyclosporine and infliximab have a faster onset of action. Data to support the efficacy of cyclosporine and infliximab is limited and mainly based on retrospective and case studies. With cyclosporine, rapid improvement in GPP is noted within a few days. One retrospective study of 385 cases of GPP in Japan reported the effectiveness of cyclosporine in 70% in conjunction with other therapies.[25] However, the risk of renal and hepatic toxicity, infections, and malignancy precludes its long-term use. Infliximab also has a rapid onset of

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[23] Ozawa A, Ohkido M, Haruki Y, et al. Treatments of generalized pustular psoriasis: a multicenter study in Japan. *J Dermatol*. 1999;26(3):141-149. doi:10.1111/j.1346-8138.1999.tb03444.x

[24] Zelickson BD, Muller SA. Generalized pustular psoriasis. A review of 63 cases. *Arch Dermatol*. 1991;127(9):1339-1345

[25] Ozawa A, Ohkido M, Haruki Y, et al. Treatments of generalized pustular psoriasis: a multicenter study in Japan. *J Dermatol*. 1999;26(3):141-149. doi:10.1111/j.1346-8138.1999.tb03444.x

action with improvement noted within several days. One retrospective study reported improvement with pustules cleared in a median of 2 days (range: 1 to 8 days) in 8/10 individuals with GPP who were treated with infliximab.[26]

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.

[26] Viguier M, Aubin F, Delaporte E, et al. Efficacy and safety of tumor necrosis factor inhibitors in acute generalized pustular psoriasis. *Arch Dermatol*. 2012;148(12):1423-1425. doi:10.1001/2013.jamadermatol.80

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

Spesolimab is a new molecular entity (NME) and is not currently marketed in the U.S.

3.2 Summary of Presubmission/Submission Regulatory Activity

One major development issue raised by the Agency throughout the presubmission activities is the Applicant's GPPPGA scoring paradigm. The Agency has reiterated the issue that the GPPPGA is a calculated mean score of erythema, pustulosis, and scaling/crusting and may be driven by one component at the Type B Pre-IND meeting on January 29, 2018, when IND 131311 for spesolimab (BI 655130) was opened in the U.S. for the treatment of GPP, at the type C guidance meeting on February 6, 2019, and at the Pre-BLA meeting on July 21, 2021. Furthermore, the issue of having the pustule assessment counted twice (one time on its own and another time as a component of the GPPPGA), making it difficult to interpret study findings, was also raised throughout the development program.

The Agency recommended that the sponsor conduct a Phase 2 dose ranging study prior to initiation of Phase 3 trials to select the appropriate dose and dosing regimen (dose, duration, and frequency of administration) throughout the development program.

BI 655130 for the treatment of generalized pustular psoriasis was granted Orphan Drug designation on October 3, 2018 and Breakthrough Therapy designation on April 30, 2021.

At the Pre-BLA meeting on July 21, 2021, the Agency recommended that a more robust package would include complete confirmatory data from study 1368-0027.

BLA 761244 was submitted on October 1, 2021 and granted priority review on November 30, 2021.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

The overall quality of the clinical information contained in this submission is adequate. The Division requested that the Office of Scientific Investigations (OSI) conduct clinical inspections of international sites.

The site which was selected for inspection had the highest enrollment numbers for trial 1368-0013 (site FRA1, clinical investigator, Dr. Bachelez), with consideration of enrollment numbers for ongoing trial 1368-0027. TUN3, clinical investigator, Dr. Turki was also considered for the higher enrollment numbers for trial 1368-0013, with consideration of enrollment numbers for ongoing trial 1368-0027, and due to the reported "possible" case of DRESS under the Regi-SCAR criteria. However, due to the COVID-19 pandemic, travel to Tunisia for inspecton of Site TUN3 was not possible. Sites MYS1, MYS4, and TWN1 were considered for inspection due to the higher enrollment numbers for trial 1368-0013, with consideration of enrollment numbers for ongoing trial 1368-0027, but were unable to be inspected due to limited feasibility due to the COVID-19 pandemic.

Refer to the Clinical Inspection Summary (CIS) by Phil Phuc Nguyen, MD, dated April 20, 2022. For study site FRA1, there was no evidence of under-reporting of protocol deviations. The inspection revealed no deficiencies with maintenance of the blind. Dr. Phil Phuc L Nguyen concluded that the conduct of the trial(s) appears to be adequate and the data generated by these sites appears acceptable to support the use of this product for the proposed indication.

4.2 Product Quality

See the Office of Pharmaceutical Quality Executive Summary Integrated Quality Assessment (entered as a separate review).

4.3 Clinical Microbiology

4.4 Not applicable.Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

Spesolimab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) against interleukin-36 (IL-36) receptor. Binding of spesolimab to IL-36 receptor (IL36R) blocks the receptor's binding with its ligands IL-36 α, β, and γ. Currently, there is no IL36R blocking antibody approved in the US. The drug product under BLA 761244, i.e., spesolimab concentrate for solution for infusion, 60 mg/mL, has been proposed to treat flares in adult patients with generalized pustular psoriasis.

Spesolimab does not bind to IL36R in common nonclinical species. Therefore, BI 674304, a surrogate monoclonal antibody that specifically binds to mouse IL36R was developed to assess the pharmacology and toxicology of IL36R inactivation in mice. BI 674304 was evaluated in a battery of nonclinical studies that included evaluation of PK, immunotoxicity, repeat-dose toxicity, and reproductive and developmental toxicology. Genotoxicity and stand-alone safety pharmacology studies were not conducted. Safety pharmacology studies were not embedded in the repeat-dose toxicity studies. Immunotoxicity was evaluated as a part of the repeat-dose toxicity studies. Carcinogenicity was assessed based on data from chronic dosing of BI 674304 in mice, scientific literature on the potential role of IL36R in tumor promotion, and clinical data from spesolimab clinical trials.

BI 674304 was evaluated in a pivotal 26-week repeat-dose general toxicity study in CD-1 mice. BI 674304 was administered via intravenous injection, twice weekly, at the doses of 0, 10, and 50 mg/kg. There were no BI 674304-related mortalities or clinical signs observed. There were no BI 674304-related effects on body weight or food consumption. There were no significant BI 674304-related gross or histopathology findings. Anti-drug antibody (ADA) was detected in 4 of 17 samples at 10 mg/kg/dose and 3 of 23 samples at 50 mg/kg/dose. The NOAEL for the 6-month toxicity study was 50 mg/kg/dose, the highest dose evaluated in this study.

In mouse fertility and early embryonic development studies, BI 674304 (0, 10, and 50 mg/kg/dose, twice weekly) administered via intravenous injection had no adverse effects on mating and fertility in males, and mating, fertility, and early embryonic development in females. The NOAEL was 50 mg/kg/dose for male and female fertility and early embryonic development.

In a mouse embryofetal development study, BI 674304 (0, 10, and 50 mg/kg/dose) was administered via intravenous injection on gestation days 6, 9, 12, and 15. BI 674304 had no adverse effects on maternal health or embryofetal development. The NOAEL was 50 mg/kg/dose for both maternal and embryofetal developmental toxicity.

In a mouse pre- and postnatal developmental study, BI 674304 (0, 10, and 50 mg/kg/dose, twice weekly) was administered via intravenous injection starting on gestation day 6 through lactation day 18. BI 674304 had no adverse effects on maternal reproductive function or effects on survival, sexual maturation, neurobehavioral, or reproductive function of the F1 offspring. The maternal and developmental NOAELs were both 50 mg/kg/dose.

In vitro incubation of spesolimab with human whole blood did not cause cytokine release as measured by changes of IL-2, IL-6, IL-8, TNF-α, or IFN-γ levels.

Regarding carcinogenesis, based on data from the 6-month general toxicity study of BI 674304 in mice, scientific literature on the potential role of IL36R in tumor promotion, and clinical data from spesolimab clinical trials, there are no concrete reasons to believe that inhibition of IL36R by spesolimab would lead to carcinogenicity. The Executive Carcinogenicity Assessment committee (ECAC) concurred with this conclusion.

Spesolimab drug substance impurities are adequately controlled. The drug product, spesolimab concentrate for solution for infusion, 60 mg/mL, does not contain novel excipients. All excipients are present at the same or lower levels when compared to levels in previously approved intravenous biologic products.

This BLA is approvable from a nonclinical perspective. There are no recommended nonclinical postmarketing commitments or postmarketing requirements for this BLA.

5.2 Referenced NDAs, BLAs, DMFs

None.

5.3 Pharmacology

Spesolimab is a humanized IgG1 mAb against IL36R. Spesolimab bound to human IL36R with an affinity of 223 pM. Tested at 0.5 μM in vitro, spesolimab did not bind to IL36R from the mouse, mini pig, rhesus money, marmoset, rat, or hamster, and had very low affinity to IL36R from cynomolgus monkey. Binding of spesolimab to human IL36R inhibited the receptor's activation by its ligands IL-36 α, β, and γ, and downstream cellular responses such as NFκB phosphorylation and IL-8 cytokine production.

The mouse surrogate antibody BI 674304 bound to mouse IL36R with an affinity of 164 pM. Binding of BI 674304 with mouse IL36R inhibited cellular responses following IL-36 α, β, or γ stimulation. In vivo, BI 674304 reduced Imiquimod-induced skin inflammation in mice. BI 674304 also reduced IL-36-induced skin inflammation and IL-33 production in the skin of mice.

The established pharmacologic class for spesolimab is "interleukin-36 receptor antagonist". Currently, there is no IL36R antagonist approved in the US. Spesolimab will be a first-in-class drug if approved.

Safety pharmacology

Stand-alone safety pharmacology studies were not conducted. Safety pharmacology studies were not embedded in the repeat-dose toxicity studies. However, no treatment-related organ toxicities or clinical signs indicative of respiratory or neurobehavioral effects were observed in mice after intravenous administration of the surrogate antibody BI 674304 for up to 26 weeks at doses up to 50 mg/kg/dose (twice weekly), or spesolimab for two weeks at doses up to 50 mg/kg/dose (twice weekly). The testing of spesolimab in mice for two weeks was for the assessment of off target toxicity only, since spesolimab does not bind to the IL36R in mice.

5.4 ADME/PK

Individual nonclinical studies determining distribution, metabolism, and excretion of spesolimab following its intravenous administration were not conducted. The PK and immunogenicity of spesolimab were investigated in male cynomolgus monkeys receiving a single intravenous dose of 0.3, 1.5, or 10 mg/kg. The PK were approximately dose linear following intravenous administration. ADAs were observed in 2 out of 3 animals at 10 mg/kg, but not observed at 0.3 or 1.5 mg/kg.

5.5 Toxicology

5.5.1 General Toxicology

Study title/ number: BI 674304: 26-Week (Twice Weekly) Intravenous Injection Toxicity Study in the Mouse with a 4-Week Recovery Period/ 16R072

Key Study Findings

- There were no BI 674304-related mortalities or clinical signs observed.
- There were no BI 674304-related effects on body weight or food consumption.
- There were no BI 674304-related gross or histopathology findings.
- Anti-drug antibody (ADA) was detected in 4 of 17 samples at 10 mg/kg/dose and 3 of 23 samples at 50 mg/kg/dose.
- The NOAEL for the 6-month toxicity study was the highest dose 50 mg/kg/dose.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0 (vehicle), 10, and 50 mg/kg/dose, twice weekly
Route of administration:	Intravenous
Formulation/Vehicle:	20 mM sodium citrate, 230 mM Trehalose, 0.05% w/v polysorbate 80, pH 6.0
Species/Strain:	CD-1 mouse
Number/Sex/Group:	20/sex/group in the main phase (all doses) and 10/sex/group in the recovery phase (0 and 50 mg/kg)
Age:	10 weeks old at the initiation of dosing
Satellite groups/ unique design:	10/sex/group in recovery groups; no separate TK groups. Blood samples were collected from main and recovery animals prior to dosing during Week 12 and at scheduled termination for TK and ADA analysis. BI 674304 dose groups with serum concentrations < 50 µg/mL and their associated pretreatment samples were evaluated for ADA. Overall, 40 qualified samples were of sufficient volume for ADA bioanalysis.
Deviation from study protocol affecting result interpretation:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No BI 674304-related findings.
Clinical Signs	No BI 674304-related findings.
Body Weights	No BI 674304-related findings.
Ophthalmoscopy	No BI 674304-related findings.
Hematology	No BI 674304-related findings.
Clinical Chemistry	No BI 674304-related findings.
Urinalysis	Not conducted.
Gross Pathology	No BI 674304-related findings.
Organ Weights	No BI 674304-related findings.
Histopathology Adequate battery: Yes/No	No BI 674304-related findings.
Immunophenotyping	No BI 674304-related findings.
Anti-Drug Antibody (ADA) analysis	Four out of 17 at 10 mg/kg/dose and 3 out of 23 at 50 mg/kg/dose developed ADA.

5.5.2 Genetic Toxicology

Genetic toxicology studies were not conducted.

5.5.3 Carcinogenicity

The sponsor submitted an assessment of the carcinogenic potential of spesolimab. Spesolimab is a monoclonal antibody that blocks human IL36R and downstream signaling. Humans with

IL36R mutations or IL36R knock-out mice have not shown increased risk of malignancy or proliferative/neoplastic changes. Chronic administration in mice up to six months with the surrogate antibody BI 674304 did not result in adverse effects suggestive of carcinogenic potential. Examining the mechanism of action of spesolimab, it can be suggested that spesolimab may reduce the risk of cancer by decreasing inflammation. It could also be suggested that blocking IL36R by spesolimab may decrease immune surveillance, thereby increasing the likelihood of tumor formation, although there was no evidence of immunosuppression in mice after chronic administration of BI 674304 at doses up to 50 mg/kg/week. Studies of individuals with IL36R gene mutations or with homozygous loss-of-function IL-36 gene mutation are of limited sample size but have shown no correlations between inactivation of IL36R signaling and cancer. For all these reasons, there are no concrete reasons to believe that inhibition of IL36R would lead to carcinogenicity. The ECAC committee concurred with this conclusion.

5.5.4 Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title/ number: BI 674304: An Intravenous Injection Fertility and Early Embryonic Development Study in the Mouse/ 17R018

Key Study Findings

- BI 674304 had no adverse effects on mating and fertility in males.
- BI 674304 had no adverse effects on mating, fertility, and early embryonic development in females.
- The NOAEL for male and female fertility and early embryonic development was 50 mg/kg/dose.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0 (vehicle), 10, and 50 mg/kg, twice weekly
Route of administration:	Intravenous
Formulation/Vehicle:	20 mM sodium citrate, 230 mM Trehalose, 0.05% w/v polysorbate 80, pH 6.0
Species/Strain:	CD-1 mouse
Number/Sex/Group:	22/sex/group
Satellite groups:	N/A
Study design:	There were four dosing groups, 0 (vehicle), 10, 50, and 50 mg/kg/dose, twice weekly. Males in Groups 1-3 were dosed prior to and during cohabitation, continuing through the day

	prior to euthanasia. Females in Groups 1-3 were dosed for two weeks prior to mating and during mating and early gestation, up to gestation day 7 (GD 7). Group 1 females were also treated on GDs 9 and 12. Group 4 females but not males were treated during the period of organogenesis on GDs 6, 9 and 12. Group 4 was added to further investigate the equivocal effect on post-implantation loss (higher than the concurrent control group but within the historical control range) noted in a previously conducted embryo-fetal development study.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	No BI 674304-related findings.
Clinical Signs	No BI 674304-related findings.
Body Weights	No BI 674304-related findings.
Necropsy findings	No BI 674304-related effects on post-implantation loss. No other BI 674304-related findings.

Embryo-Fetal Development

Study title/ number: BI 674304: An Intravenous Injection Embryo-Fetal Development Study in the Mice/ 15R096

Key Study Findings

- BI 674304 had no adverse effects on maternal health.
- BI 674304 had no adverse effects on embryofetal development.
- The NOAEL for both maternal and embryofetal developmental toxicity was 50 mg/kg/dose.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0 (vehicle), 10, and 50 mg/kg/dose, twice weekly (GDs 6, 9, 12, and 15)
Route of administration:	Intravenous
Formulation/Vehicle:	20 mM sodium citrate, 230 mM Trehalose, 0.05% w/v polysorbate 80, pH 6.0
Species/Strain:	CD-1 mouse
Number/Sex/Group:	25 females/group

Satellite groups:	N/A
Study design:	BI 674304 was dosed to mated females on GD 6 through GD 15 and the animals were euthanized on GD 18.
Deviation from study protocol affecting results interpretation:	No

Observations and Results

Parameters	Major findings
Mortality	No BI 674304-related findings.
Clinical Signs	No BI 674304-related findings.
Body Weights	No BI 674304-related findings.
Necropsy findings Cesarean Section Data	A higher post implantation loss was seen at 50 mg/kg/dose as compared to the control group; however, the data at 50 mg/kg/dose were within the historical control range.
Necropsy findings Offspring	There were no BI 674304-related fetal malformations at any dose.

Prenatal and Postnatal Development

Study title/ number: An Intravenous Injection Pre and Postnatal Developmental Toxicity Study of BI 674304 in the Mouse/ 18R161

Key Study Findings

- BI 674304 had no adverse effects on maternal reproductive function.
- BI 674304 had no adverse effects on survival, sexual maturation, neurobehavioral, or reproductive function of the F1 offspring.
- The maternal and developmental NOAELs were both 50 mg/kg/dose.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0 (vehicle), 10, and 50 mg/kg/dose, twice weekly
Route of administration:	Intravenous
Formulation/Vehicle:	20 mM sodium citrate, 230 mM Trehalose, 0.05% w/v polysorbate 80, pH 6.0
Species/Strain:	CD-1 mouse
Number/Sex/Group:	22 females/group
Satellite groups:	N/A
Study design:	F0 animals were dosed from GD 6 to LD 18, twice weekly (GDs 6, 9, 12, 15, and 17, and LDs 3, 6, 9, 12, 15, and 18), and were euthanized on LD 22. Mated adult F1 females were euthanized on GD 13.

Deviation from study protocol affecting interpretation of results: None

Observations and Results

Generation	Major Findings
F0 Dams	No BI 674304-related findings.
F1 Generation	No BI 674304-related findings. BI 674304 was detected in the blood samples from all BI 674304 dosed litters/pups after dose administration in F0 animals.
F2 Generation	Not tested.

Juvenile Animal Toxicity
Not conduced.

5.5.5 Other Toxicology Studies

In Vitro Cytokine Release Assay
Spesolimab did not cause specific IL-2, IL-6, IL-8, TNF-α, or IFN-γ release in in vitro cytokine release assay using human whole blood from healthy donors.

Impurity Qualification
Spesolimab drug substance impurities are adequately controlled.

Excipient Qualification
Spesolimab concentrate for solution for infusion does not contain novel excipients. All excipients are present at the same or lower levels when compared to levels in previously-approved products for intravenous use.

6 Clinical Pharmacology

6.1 Executive Summary

Boehringer Ingelheim Pharmaceuticals, Inc. submitted a Biologics License Application (BLA) seeking approval of spesolimab for the the treatment of flares in adult patients with Generalized Pustular Psoriasis (GPP). Spesolimab is a humanized antagonistic monoclonal IgG1 antibody. The proposed commercial spesolimab drug product is formulated as a 450 mg/vial intravenous (IV) injection. The proposed dosing regimen is a single 900 mg (2 x 450 mg/7.5 mL vials) intravenous infusion over 90 minutes. If flare symptoms persist, an additional IV 900 mg dose may be administered 1 week after the initial dose.

BLA 761244 consists of 7 clinical studies: 4 Phase 1 clinical pharmacology studies in healthy subjects and 3 studies in GPP patients. Study 1368-0011 was a proof-of-concept study in (N=7) GPP patients. Pivotal efficacy was evaluated in a Phase 2 study (1368-0013) in (N=53) GPP patients. Study 1368-0025 is an ongoing open-label extension evaluated spesolimab for flare prevention that voluntarily enrolled subjects from Study 1368-0013. Patients enrolled in Study 1368-0025 received subcutaneous doses of spesolimab every 6 weeks or every 12 weeks for flare prevention and additionally received IV spesolimab (at the proposed dose) for any flares experienced during the study period.

To support observed efficacy in the pivotal study 1368-0013, an exposure-response analysis for efficacy was conducted for efficacy endpoints, including the primary endpoint of GPPGA pustulation subscore of 0 at Week 1, using data from GPP patients in pivotal study 1368-0013 (N=53). There was a positive correlation between model predicted spesolimab C_{max} and pustule clearance after a single dose.

No drug interaction studies were conducted with spesolimab. Based on the low observed levels of proinflammatory biomarkers outside of a disease flare, treatment with spesolimab is unlikely to reduce exposure of concomitantly administered medications. No dose adjustments due to drug interactions are recommended.

In GPP patients treated with IV spesolimab, anti-drug antibodies (ADAs) were formed in 46% of patients by Week 12-17 with a median onset of 2.3 weeks. Among ADA-postitive patients, those with ADA titer values greater than 4000 (24%), were observed to have significantly decreased plasma spesolimab concentrations from Week 3 onward. In patients with ADA titers below 4000, spesolimab PK was similar to ADA negative patients. ADA development did not impact the efficacy or safety of treatment of a first flare in Study 1368-013 as ADAs generally did not develop until after treatment and resolution of a flare . The impact of ADAs on safety or efficacy for subsequent flares that are treated with spesolimab is unknown due to the limited number of patients (N=9) who experienced a recurrent flare in Study 1368-0025 to-date.

A Post-Marketing Requirement (PMR) is recommended to assess the effect of immunogenicity on pharmacokinetics (PK), safety, and efficacy on re-treatment of flares that occur after the first flare incidence has been treated and resolved.

Recommendation: This BLA is acceptable from a Clinical Pharmacology perspective.

Post Marketing Requirement: Conduct an open label safety study to assess the effect of immunogenicity on pharmacokinetics (PK), safety, and efficacy on re-treatment of flares that occur after the first flare incidence has been treated and resolved.

6.2 Summary of Clinical Pharmacology Assessment

Key review issues and findings for the Clinical Pharmacology review of this BLA submission for the GPP indication is listed below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Efficacy of spesolimab for the treatment of GPP flares was established in Studies 1368-011 and 1368-013 in GPP patients. An E-R analysis for efficacy also determined a positive correlation between spesolimab exposure and efficacy (pustule clearance) after a single-dose.
Impact of immunogenicity on PK and efficacy	Upon first treatment with spesolimab for a GPP flare, development of ADAs (at approximately 2.3 weeks post-dose) is not expected to impact efficacy as ADAs did not develop until after resolution of a disease flare. The impact of ADAs on safety and efficacy for any subsequent flare treated with spesolimab is unknown. A PMR is recommended to evaluate efficacy and safety upon re-treatment with spesolimab.
Drug interactions	Based on the low levels of proinflammatory biomarkers outside of a disease flare, treatment with spesolimab is unlikely to reduce exposure of concomitantly administered medications. No dose adjustments due to drug interactions are recommended.

6.2.1 Pharmacology and Clinical Pharmacokinetics

The key clinical pharmacology and PK findings for IV spesolimab in GPP patients are summarized below:

- A population pharmacokinetic model was developed based on data collected from healthy subjects, patients with GPP, and patients with other diseases. After a single intravenous dose of 900 mg spesolimab, the clinical dose, the population PK model-estimated $AUC_{0-\infty}$ and Cmax (95% CI) in a typical ADA-negative patient with GPP were 4750 ug-day/mL and 238 ug/mL, respectively.
- In GPP patients treated with IV spesolimab, anti-drug antibodies (ADAs) formed in 46%

of patients by Week 12-17 with a median onset of 2.3 weeks. Among ADA-postitive patients, those with ADA titer values greater than 4000 (24%), were observed to have decreased plasma spesolimab concentrations. In patients with ADA titers below 4000, there was no apparent impact on spesolimab PK.

- ADA development did impact the efficacy or safety of treatment of a first flare in Study 1368-013 as ADAs generally did not develop until after treatment and resolution of a flare. The impact of ADAs on safety or efficacy for subsequent flares that are treated with spesolimab is unknown.

6.2.2 General Dosing and Therapeutic Individualization

General Dosing

The recommended dose for the treatment of flares in adults with GPP is a single 900 mg (2 x 450 mg/7.5 mL vials) intravenous infusion over 90 minutes. If flare symptoms persist, an additional intravenous 900 mg dose may be administered 1 week after the initial dose.

Therapeutic Individualization

Not Applicable

Outstanding Issues

Post-Marketing Requirement (PMR): Conduct a study to assess the effect of immunogenicity on pharmacokinetics (PK), safety, and efficacy on re-treatment of flares that occur after the first flare incidence has been treated and resolved.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

The Applicant conducted six healthy volunteer PK studies using the IV formulation: SAD Study 1368-0001, MAD Study 1368-0002, SAD study in Japanese volunteers 1368-0009, and SAD study in Chinese volunteers 1368-0043. Two additional studies were conducted in HV using a subcutaneous formulation (Studies 1368-0003 and 1368-0029) and this will not be a focus of this review as the Applicant did not develop the subcutaneous formulation further.

Additionally, the pharmacokinetics of spesolimab has been characterized in patients with GPP in three studies: the proof-of-concept study 1368-0011, the phase 2 pivotal efficacy and safety study 1368-0013, and the ongoing open label extension study 1368-0025.

Study	Description	Spesolimab Dose	Patient Population
1368-0001	SAD	0.001 mg/kg - 10 mg/kg	N=78 Healthy males

1368-0002	MAD	Once weekly x 4 weeks: 3 mg/kg, 6 mg/kg, and 10 mg/kg Single dose: 20 mg/kg	N=40 Healthy males
1368-0009	SAD	IV doses: 300 mg, 600 mg, and 1200 mg	N=32 Healthy Japanese males
1368-0043	SAD	IV doses: 450 mg, 600 mg, and 1200 mg	N=50 Healthy Chinese subjects
1368-0011	Proof-of-concept	Single 10 mg/kg IV infusion	N=7 GPP patients
1368-0013 (Effisayil-1)	Phase 2 pivotal study	Single 900 mg IV infusion with optional second 900 mg dose on Day 8	N=53 GPP patients
1368-0025	Open-label extension	Prevention: 300 mg SC q12w 300 mg SC q6w3 Treatment: 900 mg IV	N=39 GPP patients (ongoing)

Spesolimab PK was characterized by a PopPK model using pooled PK data from GPP patients in Studies 1368-0011 and 1368-013. For ADA-negative patient with GPP, the typical value of clearance and total volume of distribution are 0.18 L/day and 6.4 L. After a single intravenous dose of 900 mg of spesolimab, the population PK model-estimated $AUC_{0-\infty}$ (95% CI) and C_{max} (95% CI) were 4750 (4510, 4970) mcg·day/mL and 238 (218, 256) mcg/mL, respectively.
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The clinical pharmacology and pharmacokinetics information for spesolimab is further summarized below:

Pharmacology	
Mechanism of Action	Spesolimab is a humanized antagonistic monoclonal immunoglobulin G1 antibody blocking human IL-36R signaling
QT Prolongation	Since this is a monoclonal antibody with a low likelihood of direct ion channel interaction, QT-IRT determined that a thorough QT study is not required (see QT-IRT review in DARRTS dated 8/23/2019 under IND 131311). ECG data were collected in studies 1368-0001 and 1368-0002 and there were no notable findings regarding QT and QTcF intervals, heart rate, PR interval, and QRS complex for any of the subjects.
General Information	
Bioanalysis	All clinical PK samples from submission trials (except 1368-0001) were analyzed for free spesolimab concentrations using a validated second generation spesolimab clinical PK

	GyroLab™ method.
Drug exposure following the therapeutic dosing regimen	Based on a population pharmacokinetic (PopPK) model, following a single IV dose of 900 mg spesolimab, $AUC_{0\text{-}inf}$ and Cmax in an ADA-negative patient with GPP is 4750 mcg-day/mL and 238 mcg/mL, respectively.
Dose Proportionality	At a clinically meaningful dose range (0.3 mg/kg to 20 mg/kg), spesolimab plasma exposure (AUC and Cmax) increased in a dose proportional manner.
Immunogenicity	In GPP patients treated with IV spesolimab, anti-drug antibodies (ADAs) were formed in 46% of patients by Week 12-17 with a median onset of 2.3 weeks. Among ADA-positive patients, those with ADA titer values greater than 4000 (24%), were observed to have decreased plasma spesolimab concentrations. In patients with ADA titers below 4000, there was no apparent impact on spesolimab PK. ADA development did not impact the efficacy or safety of treatment of a first flare in Study 1368-013 as ADAs generally did not develop until after treatment and resolution of a flare. The impact of ADAs on safety or efficacy for subsequent flares that are treated with spesolimab is unknown.
Drug Interactions	As an antagonistic IgG1 monoclonal antibody, spesolimab is not expected to have direct drug-drug interactions. Drug-disease interactions are also unlikely due to the low baseline levels of inflammatory markers and the transient proinflammatory state associated with disease flares in GPP patients.
Absorption	
C_{max}	After a single spesolimab IV dose of 900 mg, the population PK model-estimated $AUC_{0\text{-}\infty}$ (95% CI) and C_{max} (95% CI) in a typical ADA-negative patient with GPP were 4750 (4510, 4970) mcg·day/mL and 238 (218, 256) mcg/mL, respectively.
Distribution	
Volume of distribution	Based on the population pharmacokinetic analysis, the typical total volume of distribution at steady state was 6.4 L.
Elimination	
Terminal half-life	Based on the population PK mode, the terminal half-life in GPP patients was 25.5 (range 24.4 to 26.3) days.
Metabolism/Excretion	As a humanized IgG1 monoclonal antibody, spesolimab is expected to be degraded into small peptides and amino acids by proteolytic enzymes widely distributed in the body.

6.3.2 Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Efficacy of spesolimab for the treatment of GPP flares was established in Studies 1368-011 and 1368-013 in GPP patients (See Sections 7 and 8 for Clinical and Statistical evaluations of efficacy data).

An exposure-response analysis for efficacy was conducted for efficacy endpoints, including the primary endpoint of GPPGA pustulation subscore of 0 at Week 1, using data from GPP patients in pivotal study 1368-0013 (N=53). Although positive correlation between model predicted spesolimab exposure ($AUC_{0\text{-}1wk}$ and C_{max}) and pustule clearance after a single dose was observed, the result is inconclusive and should be treated with caution due to the limited number of patients received one dose level treatment in the study. For 12 patients who received a second dose on Day 8, 9 of them achieved clear or almost clear pustules at Week 2. It is unknown if these patients needed longer time to respond, or if these patients benefitted from increased exposure. See the OCP Appendix on Exposure-Reponse Analysis for further information.

What are the immunogenicity findings?

Incidence of ADAs and nAbs

In Study 1368-011 (N=7) in GPP patients, plasma samples for ADA analysis were collected at baseline until week 20. One patient was excluded from the analysis for a major protocol violation. Following a single IV dose of 10 mg/kg, 3 out of 6 patients (50%) developed ADAs by week 20. Two out of 6 patients (33%) had a maximum ADA titer greater than 4000. All 6 patients were ADA-negative at baseline. NAb response was not determined in this trial.

In Study 1368-0013, plasma samples for ADA analysis were collected at baseline and through week 28. At baseline, all patients were ADA negative. Following administration of 900 mg IV spesolimab, 46% patients developed ADAs by weeks 12-17 with a median onset time of 2.3 weeks. A total of 24% of patients had a maximum ADA titers greater than 4000. Females had a higher immunogenicity response compared to males. The ADA incidence rate and percentage of patients with titer greater than 4000 was 58% and 30% in females, and 24% and 12% in males, respectively. All ADA samples with titer value greater than 4000 were also NAb positive.

There were 39 patients rolled over from Study 1368-0013 into the OLE Study 1368-0025 and 36 of those patients were ADA-evaluable. Of the 36 ADA-evaluable patients, 35 received IV spesolimab. Of the 35 patients, 18 were ADA-positive as defined by at least 1 ADA-positive sample after baseline during the course of Study 1368-013 and/or prior to administration of either subcutaneous or intravenous spesolimab in Study 1368-0025.

Impact of ADAs and nAbs on PK

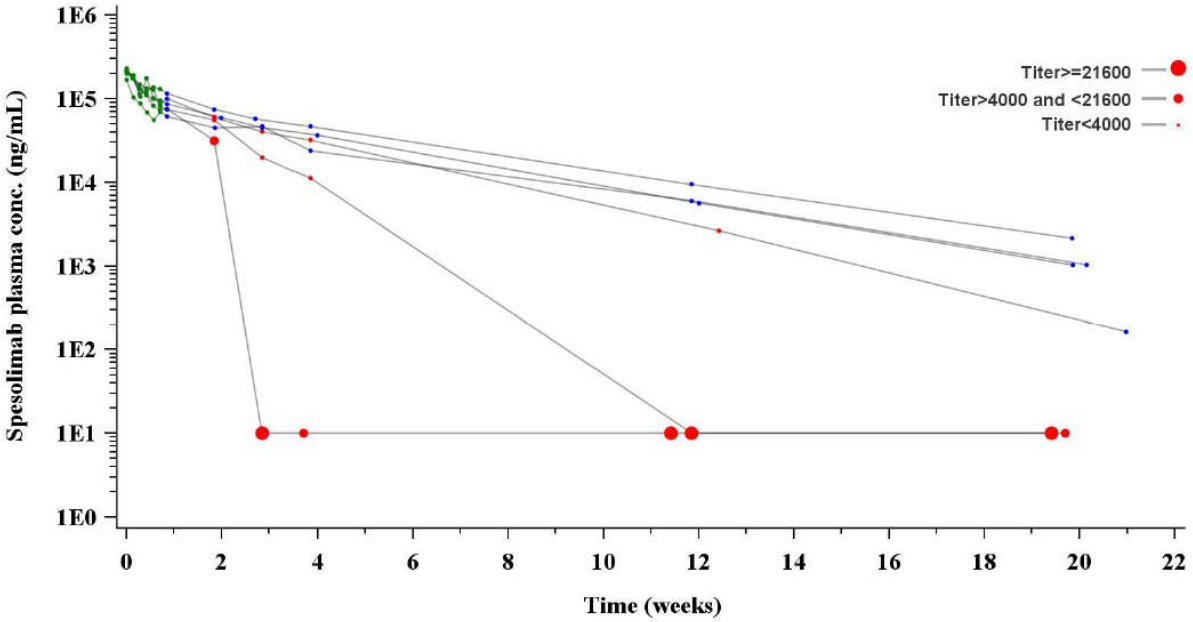
Overall, the impact of ADA on the PK of spesolimab depended on the titer value. Those with titer values of greater than 4000 were observed to affect plasma spesolimab concentrations in some patients. When the titer value was lower than 4000, there was no significant impact of ADA on drug exposure.

In Study 1368-0011, 2 of the 3 ADA+ patients formed ADAs with titer values greater than 4000. This led to a marked decrease in spesolimab concentrations. In patients with ADA titers < 4000, there was no significant impact on spesolimab concentration. NAb response was not determined in this trial.

In Study 1368-0013, higher titer values were associated with reduced PK, similar to Study 1368-0011. Similar PK was observed in ADA+ patients with titer values < 4000 compared to ADA- patients, while ADA+ patients with titers > 4000 had significantly reduced PK. All ADA samples with titer value greater than 4000 were also NAb positive.

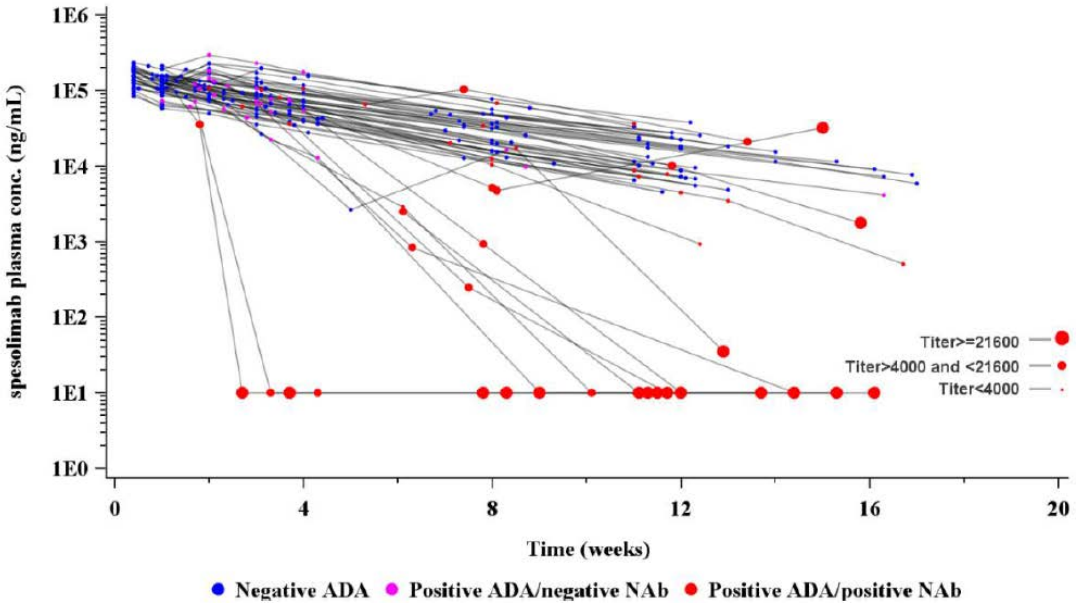
In Study 1368-0025, 39 patients were rolled-over from Study 1368-0013. Of 39 patients that were rolled over, 9 patients experienced a recurrent flare and were treated with IV spesolimab as of the time of BLA submission. Upon re-exposure to spesolimab, ADA+ patients experienced mean reductions in AUC and Cmax of approximately 75% and 10%, respectively, compared to their mean exposures in Study 1368-0013.

Figure 1. Study 1368-0011: Individual spesolimab plasma concentration time profiles with ADA/titer status



Source: Integrated Summary of Immunogenicity, Figure 9, page 78

Figure 2. Study 1368-0013: Individual spesolimab plasma concentration time profiles with ADA/titer status

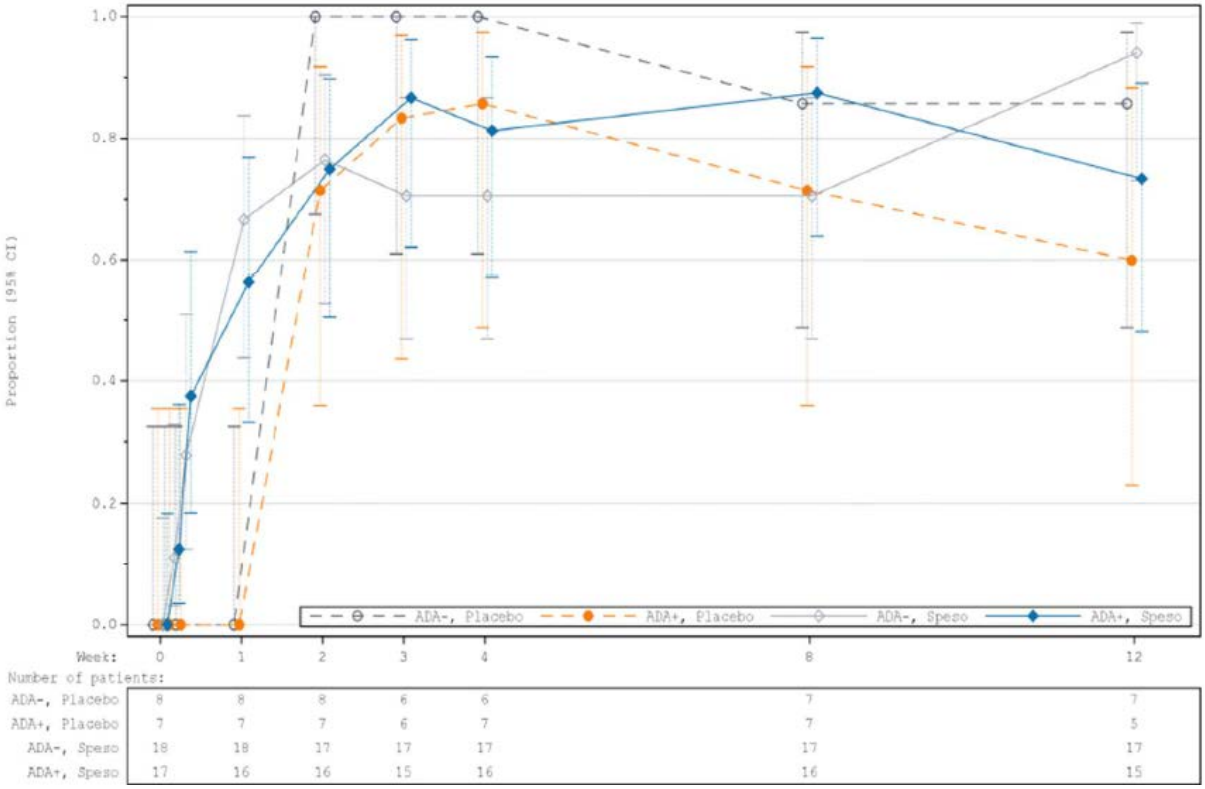


Source: Integrated Summary of Immunogenicity, Figure 12, page 87

Impact of ADAs and NAbs on Efficacy

In Study 1368-0013, GPP patients were excluded from enrollment if they have received prior doses of spesolimab. Therefore, all patients were spesolimab-naïve and were ADA negative at baseline. In this study, the proportion of patients achieving a GPPGA pustulation subscore of 0 or a GPPGA total score of 0 or 1 over time was similar for ADA negative and ADA positive patients. Similar efficacy response rates are observed in patients who develop ADA titer values > 4000 as those with ADA titer values < 4000 as the median onset of ADA was about 2.3 weeks. While there is potentially a reduction in the response rate around week 12, the primary endpoint for flare treatment is measured at week 1 and this reduction at week 12 is not clinically relevant for GPP patients treated with spesolimab for the first time.

Figure 3. Study 1368-0013: Proportion of patients with GPPGA pustulation subscore of 0 over time by ADA status

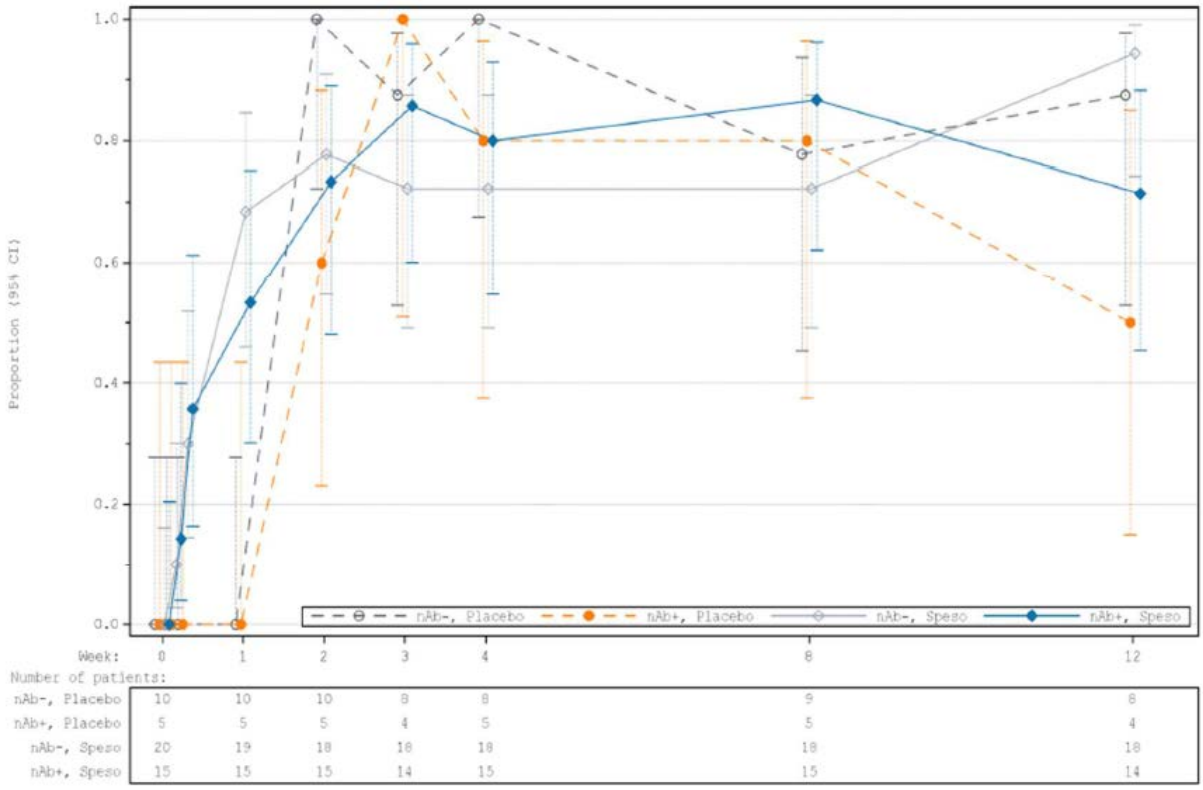


Week:	0	1	2	3	4	8	12
Number of patients:							
ADA-, Placebo	8	8	8	6	6	7	7
ADA+, Placebo	7	7	7	6	7	7	5
ADA-, Speso	18	18	17	17	17	17	17
ADA+, Speso	17	16	16	15	16	16	15

*We note that ADA development in the placebo arm is not well-understood
Source: Integrated Summary of Immunogenicity, Figure 13, page 89

A similar pattern was observed for NAb-negative and NAb-positive patients. Nab-positive and Nab-negative patients achieved similar efficacy for the first flare treatment with spesolimab as measure by a GPPGA total score (or pustulation subscore) of 0 or 1.

Figure 4. Study 1368-0013: Proportion of patients with GPPGA pustulation subscore of 0 over time by NAb status



Source: Integrated Summary of Immunogenicity, Figure 14, page 90

Of 39 patients that were rolled over from Study 1368-0013 into Study 1368-0025, 9 patients experienced a recurrent flare during the course of Study 1368-0025 as of the time of BLA submission. Of these 9 patients, 2 patients were ADA negative and 7 patients were ADA positive. Among the 7 ADA positive patients, 6 patients had an ADA titer values > 4000 at the time of treatment for flare recurrence. Visual examination of the efficacy endpoints of GPPGA total score of 0 or 1 and GPPGA pustulation subscore of 0 show no correlation between ADA group and achievement of efficacy endpoints. Additionally, several subjects GPPGA scores fluctuated over time, creating difficulties with interpretation of efficacy. The small sample size (N=9) likely contributes to the inability to draw meaningful conclusions regarding the impact of ADAs on efficacy during re-treatment.

Table 1. Study 1368-0025: Proportion of patients with GPPGA total score of 0 or 1 over time by ADA group in the first flare treatment period

Visit Treatment	N	n	n/N	95% CI Lower	 Upper
Baseline					
ADA negative	2	0	0.000	0.000	0.658
ADA positive	7	0	0.000	0.000	0.354
Low ADA titer [<= 4000]	1	0	0.000	0.000	0.793
High ADA titer [> 4000]	6	0	0.000	0.000	0.390
ADA negative + Low ADA titer [<= 4000]	3	0	0.000	0.000	0.561
Week 1					
ADA negative	2	1	0.500	0.095	0.905
ADA positive	7	2	0.286	0.082	0.641
Low ADA titer [<= 4000]	1	0	0.000	0.000	0.793
High ADA titer [> 4000]	6	2	0.333	0.097	0.700
ADA negative + Low ADA titer [<= 4000]	3	1	0.333	0.061	0.792
Week 2					
ADA negative	2	1	0.500	0.095	0.905
ADA positive	7	4	0.571	0.250	0.842
Low ADA titer [<= 4000]	1	1	1.000	0.207	1.000
High ADA titer [> 4000]	6	3	0.500	0.188	0.812
ADA negative + Low ADA titer [<= 4000]	3	2	0.667	0.208	0.939
Week 4					
ADA negative	2	2	1.000	0.342	1.000
ADA positive	7	2	0.286	0.082	0.641
Low ADA titer [<= 4000]	1	1	1.000	0.207	1.000
High ADA titer [> 4000]	6	1	0.167	0.030	0.564
ADA negative + Low ADA titer [<= 4000]	3	3	1.000	0.439	1.000
Week 8					
ADA negative	2	2	1.000	0.342	1.000
ADA positive	7	1	0.143	0.026	0.513
Low ADA titer [<= 4000]	1	0	0.000	0.000	0.793
High ADA titer [> 4000]	6	1	0.167	0.030	0.564
ADA negative + Low ADA titer [<= 4000]	3	2	0.667	0.208	0.939
Week 12					
ADA negative	2	1	0.500	0.095	0.905
ADA positive	7	1	0.143	0.026	0.513
Low ADA titer [<= 4000]	1	0	0.000	0.000	0.793
High ADA titer [> 4000]	6	1	0.167	0.030	0.564
ADA negative + Low ADA titer [<= 4000]	3	1	0.333	0.061	0.792

ADA negative = last ADA sample prior to respective flare period negative
ADA positive = last ADA sample prior to respective flare period confirmed positive
Low ADA titer = titer of last ADA sample prior to1st flare period less than or equal to 4,000
High ADA titer = titer of last ADA sample prior to 1st flare period greater than 4,000

An additional patient experienced a recurrent flare in Study 25 on Sep 24, 2021. By the cut-off date of the 3-month Safety Update report of Sep 30, 2021, the ADA status directly prior to the recurrent flare was not available (ADA status at baseline: negative). The patient's GPPGA total score 1 week after flare treatment was 1.

Source: Response to Agency Information Request Received JAN 19, 2022, Table 2

Table 2. Study 1368-0025: Proportion of patients with GPPGA pustulation subscore of 0 over time by ADA group in first flare treatment period

Visit Treatment	N	n	n/N	95% CI Lower	 Upper
Baseline					
ADA negative	2	0	0.000	0.000	0.658
ADA positive	7	0	0.000	0.000	0.354
Low ADA titer [<= 4000]	1	0	0.000	0.000	0.793
High ADA titer [> 4000]	6	0	0.000	0.000	0.390
ADA negative + Low ADA titer [<= 4000]	3	0	0.000	0.000	0.561
Week 1					
ADA negative	2	1	0.500	0.095	0.905
ADA positive	7	4	0.571	0.250	0.842
Low ADA titer [<= 4000]	1	1	1.000	0.207	1.000
High ADA titer [> 4000]	6	3	0.500	0.188	0.812
ADA negative + Low ADA titer [<= 4000]	3	2	0.667	0.208	0.939
Week 2					
ADA negative	2	1	0.500	0.095	0.905
ADA positive	7	4	0.571	0.250	0.842
Low ADA titer [<= 4000]	1	1	1.000	0.207	1.000
High ADA titer [> 4000]	6	3	0.500	0.188	0.812
ADA negative + Low ADA titer [<= 4000]	3	2	0.667	0.208	0.939
Week 4					
ADA negative	2	1	0.500	0.095	0.905
ADA positive	7	1	0.143	0.026	0.513
Low ADA titer [<= 4000]	1	0	0.000	0.000	0.793
High ADA titer [> 4000]	6	1	0.167	0.030	0.564
ADA negative + Low ADA titer [<= 4000]	3	1	0.333	0.061	0.792
Week 8					
ADA negative	2	1	0.500	0.095	0.905
ADA positive	7	0	0.000	0.000	0.354
Low ADA titer [<= 4000]	1	0	0.000	0.000	0.793
High ADA titer [> 4000]	6	0	0.000	0.000	0.390
ADA negative + Low ADA titer [<= 4000]	3	1	0.333	0.061	0.792
Week 12					
ADA negative	2	1	0.500	0.095	0.905
ADA positive	7	1	0.143	0.026	0.513
Low ADA titer [<= 4000]	1	0	0.000	0.000	0.793
High ADA titer [> 4000]	6	1	0.167	0.030	0.564
ADA negative + Low ADA titer [<= 4000]	3	1	0.333	0.061	0.792

ADA negative = last ADA sample prior to respective flare period negative
ADA positive = last ADA sample prior to respective flare period confirmed positive
Low ADA titer = titer of last ADA sample prior to 1st flare period less than or equal to 4,000
High ADA titer = titer of last ADA sample prior to 1st flare period greater than 4,000

Source: Response to Agency Information Request Received JAN 19, 2022, Table 1

Impact of ADAs and NAbs on Safety

Overall, the proportion of patients with hypersensitivity events was low. The frequency and incidence rates of patients with such events was similar before and after ADA/NAb development. Similar hypersensitivity rates were also observed between patients who were ADA positive at any time compared to patients who were ADA negative at all time points. For 4 of the 5 patients with hypersensitivity events, the event started after one IV spesolimab

dose and for 1 (ADA-negative) patient, the event started after the second IV spesolimab dose in the remaining 3 patients.

There were two reported cases of drug reaction with eosinophilia and systemic symptoms (DRESS), both following administration of IV spesolimab. In one patient, the DRESS developed 3 days after the first dose and prior to an ADA-positive sample. In the second patient, DRESS was reported 3 weeks after the first ADA/Nab positive sample. The Applicant has reported that both these events are due to an allergic reaction to antibiotics and GPP flare symptoms, respectively, and are not likely due to spesolimab treatment.

Table 3. Study 1368-0013: Safety event rate before and after ADA or NAb development

	ADA			NAb		
	N (%)	Time at risk (Pt-yrs)	Rate/100 Pt-yrs	N (%)	Time at risk (Pt-yrs)	Rate/100 Pt-yrs
Total number of patients	51 (100)			51 (100)		
with hypersensitivity event before ADA/NAb development	4 (7.8)	7.8	51.0	4 (7.8)	9.0	44.5
Urticaria	2 (3.9)	8.1	24.7	2 (3.9)	9.3	21.6
Dermatitis	1 (2.0)	8.1	12.4	1 (2.0)	9.4	10.7
Eye oedema	1 (2.0)	8.1	12.4	1 (2.0)	9.3	10.7
DRESS	1 (2.0)	8.2	12.1	1 (2.0)	9.5	10.5
Number of ADA-positive patients	24 (100)			20 (100)		
with hypersensitivity event after ADA/NAb development	1 (4.2)	2.0	50.1	1 (5.0)	2.5	40.0
DRESS	1 (4.2)	2.0	50.1	1 (5.0)	2.5	40.0

Total number of patients refers to ADA-positive and ADA-negative patients

ADA-positive patients were defined as patients with at least 1 ADA positive sample in the trial (including baseline)

Before ADA/NAb development included patients with events either before their first ADA/NAb positive sample or without ADA/NAb positive samples throughout

After ADA/NAb development included patients with events from the time point of their first ADA/NAb positive sample

Source: Integrated Summary of Immunogenicity, Table 45, Page 91

Reviewer Conclusions:

- *ADA impact on PK appears to be most significant for patients with ADA titers > 4000. Patients with ADA titers > 4000 were also nAb positive.*
- *Development of ADAs do not impact efficacy of the first flare treatment, as demonstrated by comparison of proportion achieving the primary endpoint in ADA+ and ADA- patients in Study 1368-013. Additionally, the primary endpoint of a GPPGA pustulation subscore of 0 at Week 1 occurs prior to the development of ADAs at approximately week 2.3.*
- *Impact of ADAs on the safety or efficacy of flare re-treatment (flares that occur after a first flare has been treated and resolved) is unknown. A small sample size (N=9) of patients who have undergone re-treatment limits any conclusions that can be made*

regarding the effect of ADA on safety or efficacy. Due to the significant impact of ADA titers > 4000 on PK of spesolimab, there is a potential for decreased efficacy in these patients. A PMR is being recommended to elucidate the impact of ADA development on the safety and efficacy of flare re-treatment. See Section 6.1.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No.
In-vivo studies were not conducted to assess the effect of intrinsic factors. Spesolimab is a monoclonal IgG1 antibody and therefore no significant effect of renal or hepatic impairment on spesolimab PK is anticipated. Study 1368-0013 included GPP patients with normal renal function (N=42, 79%), mild renal impairment (N=7, 13%), and moderate renal impairment (N=1, 2%). In population PK analysis, 418 subjects with normal renal function, 127 subjects with mild renal impairment and 12 subejcts with moderate renal impairment were involved in the analysis. The results showed that mild or moderate renal impairment did not impact the clearance of spesolimab. In population PK analysi, 528 subjects with normal hepatic function (NCIODWG), 26 subjects with mild hepatic impairment and 3 subejcts with moderate hepatic impairment were involved in the analysis. The results showed that mild hepatic impairment did not impact the clearance of spesolimab. The effect of moderate hepatic impairment was not evaluated due to the limited number of subjects involved in the study. No subjects with severe renal or hepatic impairment were involved in the analysis.

<u>IL36RN mutation status</u>
Although the Applicant collected IL36RN mutation status from the patient's historical data at screening if available, patients were enrolled in Trial 1368-0013 regardless of IL36RN mutation status. The Applicant performed exploratory analysis of the impact of mutations on spesolimab response by genotyping blood samples for mutations associated with GPP in several genes, including IL36RN. The genotyping assay and the detailed criteria used to determine potential pathogenicity of the identified variant were unspecified by the Applicant. DNA sequencing was performed in 46 of 53 patients in Trial 1368-0013. The identified IL36RN variants from sequencing were classified as either having a "known link", "no known link", or "possible link" to GPP. Of 46 patients with DNA sequencing results, the Applicant identified four IL36RN variants with "known link" to GPP in 14 patients (spesolimab 900 mg arm, n=8; placebo arm, n=6). The results of the IL36RN mutation status analysis are considered exploratory and insufficient to evaluate the impact of variations in IL36RN in Trial 1368-0013. See Section 8.1.4, Table 14 for analysis of spesolimab response by IL36RN mutation status as determined by the Applicant.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No.

As spesolimab is a biologic administered by IV injection, a food-drug interaction is not applicable. Clinical drug interaction studies have not been conducted with spesolimab. However, spesolimab is not expected to impact the PK of concomitantly administered small-molecule drugs.

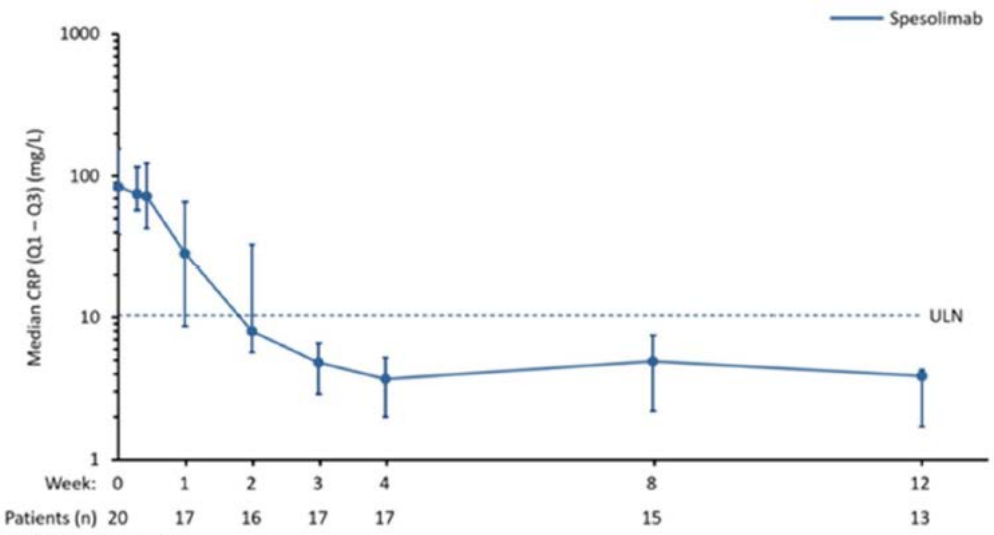
Patients with chronic inflammatory diseases can experience elevated proinflammatory cytokines which downregulate the expression of CYP enzymes, thereby increasing exposure of the small-molecule drugs which are CYP substrates. Therapeutic proteins that reduce cytokine levels, such as spesolimab, can relieve the CYP enzyme downregulation and increase/normalize CYP expression, potentially reducing the exposure of concomitantly administered drugs that are CYP substrates.

Increases in proinflammatory cytokines were not observed in GPP patients outside of a disease flare. In Study 1368-0027 (an ongoing flare prevention trial not included in this review), patients not experiencing flares had a median C-reactive protein (CRP) value of 3.5 mg/L, which is considered within the normal range for healthy adults. In contrast, for GPP patients experiencing flares, the median CRP value was 31.3 mg/L at flare baseline, which was elevated outside the normal range. Median CRP values returned within the normal range by week 2 following flare onset. Similar trends were observed in proof-of-concept Study 1368-0011 in GPP patients. In Study 1368-0011, both CRP and IL-6 levels were reduced to normal levels by approximately week 2.

Reviewer Conclusions:

- *Baseline CRP data from Study 1368-0027 and the time course of elevated CRP in the context of disease flares in Studies 1368-013 and 1368-0011 indicates that the elevated pro-inflammatory state is likely transient in nature.*
- *Exposure of chronically-administered small-molecule CYP substrate drugs is unlikely to be heightened outside of a disease flare given the normal baseline levels of CRP in observed in Study 1368-0027. Therefore, spesolimab's contribution to reducing the transient proinflammatory state observed during diseases flares is unlikely to result in reduced CYP substrate drug concentration due to spesolimab treatment.*
- *No dose adjustments due to drug interactions are recommended.*

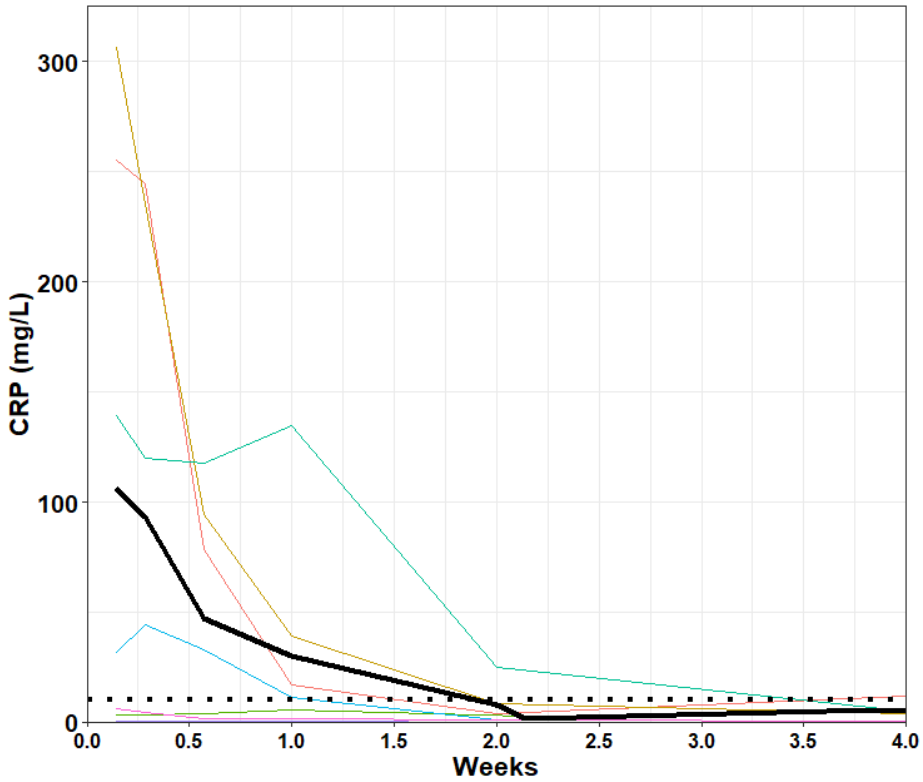
Figure 5. Study 1368-0013: Median (Q1, Q3) C-Reactive Protein (CRP) (mg/L) over time



ULN: upper limit of normal
OC = Observed cases excluding all values after any use of escape medication, OL spesolimab on Day 8, or rescue medication with spesolimab

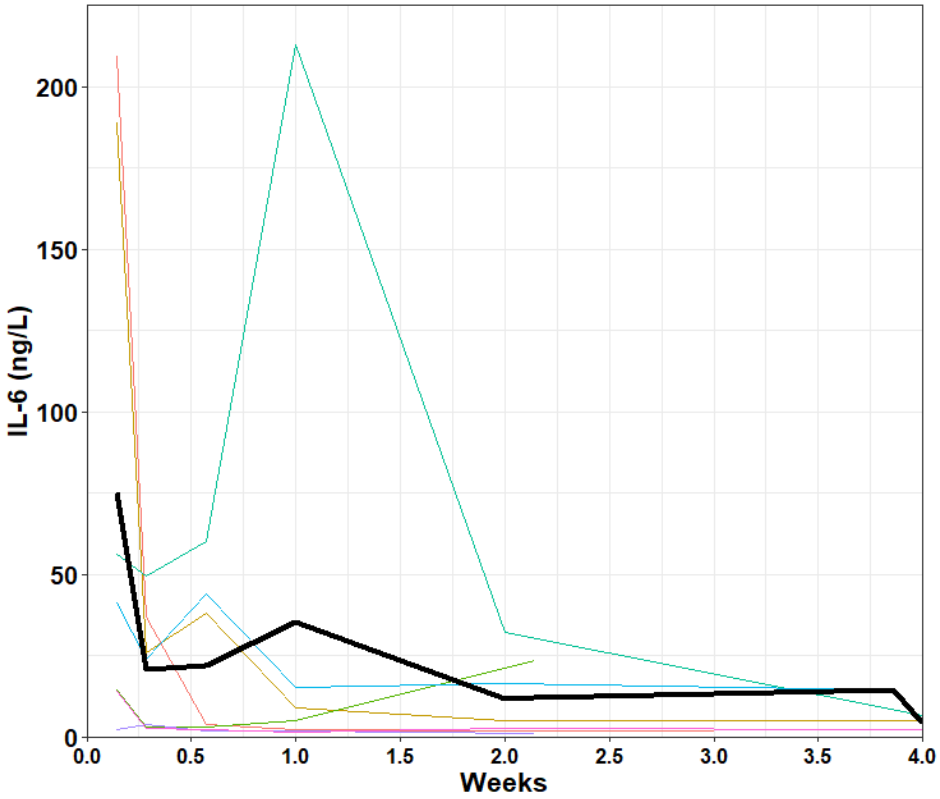
Source: 2.7.2 Summary of Clinical Pharmacology Studies, Figure 24, Page 87

Figure 6. Study 1368-0011 Absolute CRP (mg/L) over time by patient



*Black line indicates mean CRP over time
Source: Reviewer-generated from immunogenicity data from Study 1368-0011

Figure 7. Study 1368-0011: IL-6 values (ng/L) over time by patient



*Black line indicates mean IL-6 over time
Source: Reviewer-generated from immunogenicity data from Study 1368-0011

7 Sources of Clincal Data and Review Strategy

7.1 Table of Clinical Studies

Table 4. Clinical Trials in Support of Efficacy and Safety Determinations for GPP

Trial	Trial Population	Trial Design	Dose	AE reporting periods: Primary/ Secondary/ Residual Effect Period (REP) for analysis	Number of subjects	Number of trial sites and countries/ US sites	Primary and Key Secondary Endpoints
1368-0011	Adult subjects with active GPP	OL, SA	Spesolimab 10 mg/kg body weight i.v. SD	REP for analysis: 20 weeks	7	5 sites from 5 countries 0 US sites	Primary: number of patients with adverse reactions, i.e. drug-related adverse events
1368-0013	Adult subjects with GPP^ presenting with an acute moderate to severe flare^^	R, DB, PG, PC	Spesolimab 1) 900 mg i.v. SD 2) option for OL 900 mg i.v. SD on day 8 for all subjects who met prespecified criteria** 3) option for rescue 900 mg i.v. SD after day 8 (max 1 dose) for all subjects**** Total maximum: 3 doses	Primary: -Up to week 1 Secondary: -Up to week 12 by randomized treatment -Up to end of REP by actual treatment REP for analysis: -16 weeks	Total: 53 Spesolimab: 35 Placebo: 18 -15/18 received OL spesolimab on day 8 -1/18 received OL rescue spesolimab after day 8	26 sites from 11 countries 3 US sites	Primary: proportion of patients who achieved a GPPGA pustulation subscore of 0, indicating no visible pustules, at Week 1. Secondary: proportion of patients who achieved a GPPGA total score of 0 or 1 at Week 1.

1368-0027 (ongoing)	Subjects 12 years of age and older with a history of GPP and presenting at screening and at randomization with a GPPGA score of 0 or 1 (clear or almost clear)	R, DB, PG, PC	Spesolimab 900 mg i.v. (OL flare treatment) (1 or 2 doses flare rescue treatment[#]) then 300 mg s.c. q12w LD 600 mg, then 300 mg s.c. q4w or LD 600 mg, then 300 mg s.c. q12w or LD 300 mg, then 150 mg s.c. q12w (randomized flare prevention)	Primary: -OL i.v. flare rescue treatment Secondary*: -OL maintenance s.c. treatment -Overall treatment REP for analysis: -16 weeks	OL flare treatment: 6	Datasets not provided by the Applicant as study is ongoing	Primary: Time to first GPP flare (defined by increase in GPPGA score by ≥ 2 from baseline and the pustular component of GPPGA ≥2) up to week 48. Secondary: The occurrence of at least one GPP flare (defined by increase in GPPGA score by ≥ 2 from baseline and the pustular component of GPPGA ≥ 2) up to week 48.
1368-0025 (ongoing)	Subjects 12 years of age and older with GPP who have completed trials 1368-0013 or 1368-0027	OL, EX	Spesolimab 900 mg i.v. (OL flare treatment) (1 dose per flare rescue treatment[#]) then 300 mg s.c. q12w Spesolimab 300 mg s.c. q6w or q12w	Primary: -OL i.v. flare rescue treatment Secondary*: -Overall treatment -OL maintenance s.c. treatment REP for analysis: -16 weeks	OL flare treatment: 9 (all from 1368-0013 as of cut-off date of 08 Jan 2021 for the application submission)	Datasets not provided by the Applicant as study is ongoing	Primary: the occurrence of treatment emergent adverse events (TEAEs) up to week 252 of maintenance treatment. Secondary: The reoccurrence of a GPP flare, and In patients who received flare rescue treatment: - Time to first achievement of a GPPGA score of 0 or 1

							-A GPPGA pustulation sub-score of 0, by visit -Change from baseline in Psoriasis Symptom Scale (PSS) score, by visit.

^: GPP diagnosis based on consensus diagnostic criteria defined by ERASPEN which include: Primary, sterile, macroscopically visible pustules on non-acral skin (excluding cases where pustulation is restricted to psoriatic plaques), with or without systemic inflammation, with or without plaque-type psoriasis, and either relapsing (>1 episode) or persistent (>3 months)
^^: GPP flare defined as subjects with a a) Generalized Pustular Psoriasis Physician Global Assessment (GPPPGA) score of at least 3 (moderate), b) presence of fresh pustules (new appearance or worsening of pustules), and c) GPPGA pustulation sub score of at least 2 (mild), d) at least 5% of Body Surface Area (BSA) covered with erythema and the presence of pustules, and who meet inclusion criteria and do not meet any of the exclusion criteria (see protocol for inclusion and exclusion criteria)
**: At week 1/day 8, all trial participants who had GPPGA total score $\geq$2 and GPPGA pustulation subscore $\geq$2 were eligible to receive open-label, single-dose spesolimab 900 mg intravenously.
****: After week 1/day 8 and through week 12, if there was >2 point increase in the GPPPGA score and the pustular component of GPPPGA >2 after achieving a clinical response (GPPPGA 0 or 1) to initial treatment (either with spesolimab at day 1 or placebo at day 1 or escape medication or OL spesolimab at day 8), subjects were eligible to receive rescue treatment with a single-dose spesolimab 900 mg intravenously. A maximum of 3 doses during the trial was allowed.
*: Not all planned secondary AE analyses are available for ongoing trials with interim data or are only available for the time to the interim cut-off date (08 Jan 2021)
#: the option of a second 900 mg i.v. dose of spesolimab 8 days after the first dose (implemented via CTP amendments) had not been in place at the cut-off date for the interim analyses of 08 Jan 2021
Abbreviations: OL, open-label; SA, single-arm; R, randomized; DB, double blind; PG, parallel-group; PC, placebo-controlled
Source: reviewer table (source: Applicant's submission – study 1368-0013, 1368-0025, 1368-0027 protocols, study 1368-0013, 1368-0011 datasets, clinical overview, summary of clinical safety GPP flare treatment)

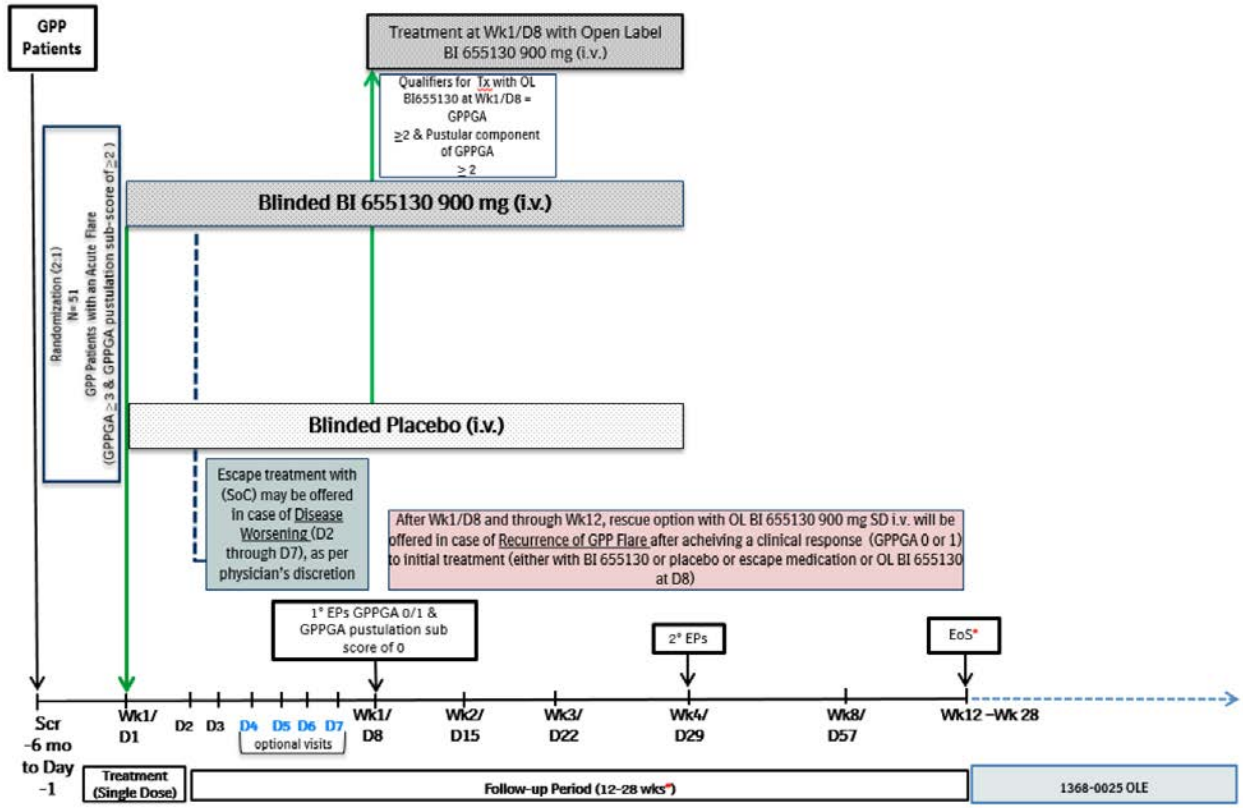
8 Statistical and Clinical and Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Study Design and Endpoints

The Applicant conducted a randomized, multicenter, double-blind, placebo-controlled, Phase 2 trial (1368-0013) to evaluate the safety, efficacy, and tolerability of a single 900 mg intravenous dose of spesolimab (BI 655130) compared with placebo in subjects with GPP presenting with an acute flare. Figure 8 presents the study design schematic for Trial 1368-0013.

Figure 8. Study Design Schematic for Trial 1368-0013



Source: page 37 of the protocol for Trial 1368-0013.

For enrollment/screened (Visit 1), the protocol specified the following key inclusion criteria:

- Male or female, aged 18 to 75 years
- Diagnosis of GPP is based on the consensus diagnostic criteria defined by the European Rare And Severe Psoriasis Expert Network (ERASPEN). These criteria include the presence of primary, sterile, macroscopically visible pustules on non-acral skin (excluding cases where pustulation was restricted to psoriatic plaques), with or without

systemic inflammation, with or without plaque-type psoriasis, either relapsing (>1 episode) or persistent (>3 months).

- Subjects with Physician's Global Assessment for Generalized Pustular Psoriasis (GPPPGA) score of 0 or 1 and a known and documented history of GPP (per ERASPEN criteria) regardless of IL36RN mutation status, and in addition with previous evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leucocytosis with peripheral blood neutrophilia (above ULN)
  OR
  Subjects with 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 IL36RN mutation status, and in addition with previous evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leucocytosis with peripheral blood neutrophilia (above ULN).
  OR
  Subjects with 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 leucocytosis with peripheral blood neutrophilia (above ULN). For these subjects, the diagnosis will be confirmed retrospectively by a central external expert/committee.
- Subjects may or may not be receiving background treatment with retinoids and/or methotrexate and/or cyclosporine. Subjects must discontinue retinoids/methotrexate/cyclosporine prior to receiving the first dose of BI 655130 or placebo.

Treatment (Visit 2; baseline) was initiated immediately in subjects who were presenting with an acute GPP flare with moderate to severe intensity, defined by emergence of:

- GPPPGA total score ≥ 3 (moderate), and
- Presence of fresh pustules (new appearance or worsening of pustules), and
- GPPPGA pustulation score ≥ 2 (mild), and
- ≥5% of Body Surface Area (BSA) covered with erythema and the presence of pustules

The trial was designed to randomize 51 treatment-eligible subjects (i.e., subjects experiencing a an acute GPP flare as defined above) in a 2:1 ratio to receive a single dose of 900 mg of spesolimab or placebo on Day 1 (Visit 2). The protocol specified stratifying the randomization by Japan vs. non-Japan. Study product was administered intravenously (i.v.) over a period of 90 minutes.

If the severity and progression of the disease worsened within the first week (Week 1/Days 2-7), the protocol specified that the investigator could treat the subject with a Standard of Care (SOC) treatment of his/her choice (escape medication). Disease worsening was defined as worsening of clinical status or GPP skin and/or systemic symptoms as defined by the investigator. If the disease condition was stable, the protocol recommended to wait until the primary endpoint visit (Day 8) before prescribing an escape medication since there was an

option to administer open-label spesolimab instead at this time. If escape medication is administered within the first week, the subject was not eligible to receive treatment with open-label single i.v. dose of 900 mg of spesolimab on Day 8.

At the Day 8 visit, the primary and key secondary efficacy endpoints were assessed. Subjects who did not receive escape treatment and who had a GPPPGA total score ≥ 2 at Day 8 and a GPPPGA pustulation sub-score of ≥ 2 at Day 8 were eligible to receive treatment with a single open-label i.v. dose of 900 mg of spesolimab.

After Day 8 and through Week 12, if a subject who previously achieved a clinical response (GPPPGA total score of 0 or 1) experienced a recurrence of a GPP flare, the protocol specified that a rescue treatment with a single i.v. dose of 900 mg of spesolimab may be administered. This could have occurred at a scheduled or unscheduled visit anytime between after Day 8 and Week 12. The protocol specified that only one rescue dose with spesolimab is permitted after Day 8. Subsequent flares were specified to be treated with escape treatment (SOC) per physician's discretion. Recurrence of a GPP flare was defined as a ≥ 2-point increase in the GPPPGA total score and GPPPGA pustulation score ≥ 2 after achieving clinical response (GPPPGA total score 0 or 1).

The protocol-specified primary efficacy endpoint was the proportion of subjects with a GPPPGA pustulation sub-score of 0 (clear) at Week 1 (Day 8).

The protocol specified a single key secondary efficacy endpoint, i.e., the proportion of subjects with a GPPPGA total score of 0 or 1 at Week 1 (Day 8).

The protocol listed the following as secondary efficacy endpoints:

- Proportion of subjects with at least a 75% reduction in the Psoriasis Area and Severity Index for Generalized Pustular Psoriasis (GPPPASI-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

Figure 9. Physician's Global Assessment for Generalized Pustular Psoriasis (GPPPGA)

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

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

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

Source: page 105 of the protocol for Trial 1368-0013.

Figure 10. Psoriasis Area and Severity Index for Generalized Pustular Psoriasis (GPPPASI)

Severity

Erythema					
Head	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Trunk	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Upper Limb	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Lower Limb	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Pustules					
Head	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Trunk	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Upper Limb	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Lower Limb	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Scaling					
Head	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Trunk	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Upper Limb	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Lower Limb	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe

AREA OF INVOLVEMENT

Provide the percentage of involved area in each body region (=area affected by pustules scaling [not the area for each component separately])

Head	☐ 0=0%	☐ 1=1 to < 10%	☐ 2=10 to < 30%	☐ 3=30 to < 50%	☐ 4=50 to < 70%
	☐ 5=70 to < 90%	☐ 6=90 to 100%			
Trunk	☐ 0=0%	☐ 1=1 to < 10%	☐ 2=10 to < 30%	☐ 3=30 to < 50%	☐ 4=50 to < 70%
	☐ 5=70 to < 90%	☐ 6=90 to 100%			
Upper Limb	☐ 0=0%	☐ 1=1 to < 10%	☐ 2=10 to < 30%	☐ 3=30 to < 50%	☐ 4=50 to < 70%
	☐ 5=70 to < 90%	☐ 6=90 to 100%			
Lower Limb	☐ 0=0%	☐ 1=1 to < 10%	☐ 2=10 to < 30%	☐ 3=30 to < 50%	☐ 4=50 to < 70%
	☐ 5=70 to < 90%	☐ 6=90 to 100%			

GPPASI total score is calculated according to the following formula:
GPPASI = 0.1(Eh+Ph+Dh)Ah + 0.3(Et+Pt+Dt)At + 0.2(Eu+Pu+Du)Au + 0.4(El+Pl+Dl)Al
Source: page 106 of the protocol for Trial 1368-0013.

Figure 11. Patient's assessment of Pain Visual Analogue Scale (VAS)

How much pain have you had because of your generalized pustular psoriasis (GPP) in the past week?

Place a vertical (|) mark on the line to indicate the severity of the pain.

No pain — Severe pain

0 ——————————————— 100

Source: page 115 of the protocol for Trial 1368-0013.

Figure 12. Psoriasis Symptom Scale (PSS)

Listed below are a set of problems that people with psoriasis have said are important. For each question, click on the circle that best describes the severity of your symptoms during the past 24 hours. Please answer every question.

1. How severe was your pain from your psoriasis during the past 24 hours?
   - ○ None
   - ○ Mild
   - ○ Moderate
   - ○ Severe
   - ○ Very severe
2. How severe was the redness from your psoriasis during the past 24 hours?
   - ○ None
   - ○ Mild
   - ○ Moderate
   - ○ Severe
   - ○ Very severe
3. How severe was your itching from your psoriasis during the past 24 hours?
   - ○ None
   - ○ Mild
   - ○ Moderate
   - ○ Severe
   - ○ Very severe
4. How severe was your burning from your psoriasis during the past 24 hours?
   - ○ None
   - ○ Mild
   - ○ Moderate
   - ○ Severe
   - ○ Very severe

Source: page 111 of the protocol for Trial 1368-0013.

Figure 13. Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Source: page 110 of the protocol for Trial 1368-0013.

8.1.2 Statistical Methodologies

The protocol-specified primary efficacy analysis population was the Randomized Set (RS), defined as all randomized subjects. The protocol also specified conducting supportive analyses using the Per-Protocol Set (PPS). The PPS was defined as all subjects in the RS who adhered to the protocol without any important protocol violations potentially affecting the study outcome which led to exclusion from the PPS. The protocol specified that important violations of the protocol will include violations of the key inclusion and exclusion criteria, incorrect medications

taken, concomitant use of restricted medications, escape medication given without evidence for disease worsening, and any other violations of the protocol deemed important by the study team.

The protocol specified analyzing binary efficacy endpoints using the Suissa-Shuster Z-pooled test. For the binary efficacy endpoints, the protocol specified that any use of escape medication prior to Week 1 will be considered to represent a non-response. In addition, for subjects who use other restricted medication but not for disease worsening prior to Week 1, the protocol specified that data imputed as non-response.

The protocol specified using the Wilcoxon rank test to analyze the continuous secondary efficacy endpoints. The protocol specified that any assessments after the use of escape medication, open-label spesolimab at Day 8, or rescue medication with spesolimab will be assigned worst case ranks for the analysis.

The protocol specified using a sequential gatekeeping approach to control the Type I error rate for testing the primary and secondary efficacy endpoints. These endpoints were specified to be tested in the following order at the one-sided $\alpha = 0.025$ level:

Proportion of subjects achieving GPPPGA pustulation score of 0 at Week 1 (Day 8)
Proportion of subjects achieving GPPPGA total score of 0 or 1 at Week 1 (Day 8)
Proportion of subjects achieving a GPPPASI-75 at Week 4
Change from baseline in pain VAS at Week 4
Change from baseline in total PSS score at Week 4
Change from baseline in the total FACIT-Fatigue score at Week 4.

For the binary efficacy endpoint, the protocol-specified primary method for handling missing data was non-responder imputation (NRI); however, the protocol also stated:

- If there are available data at the visits both before and after the visit with a missing outcome, then impute as a success only if both the preceding and the following observations also represent a success and there is no use of escape medication, open-label spesolimab at Day 8, or rescue medication with spesolimab within this imputation period;
- Otherwise, impute as a failure to achieve a response (i.e., NRI).

For the continuous secondary efficacy endpoint, the protocol specified that the worst-case ranks will be assigned to those with death, prior escape medication, open-label spesolimab at Day 8, or rescue medication with spesolimab, and for subjects with missing data at Week 4 for other reasons. The protocol specified that the maximum value for the worst possible change from baseline (i.e., the worst possible post-baseline value – best possible baseline value) is 100 for Pain VAS, 16 for PSS and -52 for FACIT-Fatigue scale. Table 5 summarizes the ranking rules for the continuous secondary efficacy endpoints.

Table 5. Ranking Rules for the Continuous Secondary Efficacy Endpoints

	Category	Ranking	Case Description	Imputed change from baseline for further ranking score[1]
1	Missing data at Week 4 but still alive and no use of either escape medication, open-label spesolimab at Day 8 or rescue medication with spesolimab prior to Week 4.	Ranked by imputed value	Subject has available data at visit prior to Week 4	LOCF prior to Week 4
			Subject has no post-baseline value	102 for Pain VAS, 18 for PSS, and -54 for FACIT-Fatigue scale
2	Use of escape medication, open-label spesolimab at Day 8 or rescue medication with spesolimab prior to Week 4 but still alive.	Ranked by open-label spesolimab at Day 8 or time to rescue medication or time to escape medication from randomization;	Subject has open-label spesolimab at Day 8 and has no escape medication or rescue medication prior to Week 4	104 for Pain VAS, 20 for PSS, and -56 for FACIT-Fatigue scale
			Subject has rescue medication with spesolimab x days from randomization and has no escape medication prior to Week 4	106-x/1000 for Pain VAS, 22-x/1000 for PSS, and -58+x/1000 for FACIT-Fatigue scale
			Subject has escape medication y days after randomization and prior to Week 4	108-y/1000 for Pain VAS 24-y/1000 for PSS, and -60+y/1000 for FACIT-Fatigue scale
3	Subject died before the measurement at Week 4	Ranked by time to death from randomization	Subject died z days after randomization	110-z/1000 for Pain VAS, 26-z/1000 for PSS, and -62+z/1000 for FACIT-Fatigue scale

[1] The protocol states: "Ranked values in this table are only for purpose of rank tests but not for any descriptive displays."
Source: page 92 of the protocol for Trial 1368-0013.

8.1.3 Subject Disposition, Demographics, and Baseline Disease Characteristics

Table 6 summarizes the disposition of subjects. A total of 85 subjects were enrolled (screened) across 37 centers in 12 countries. Of the 85 subjects enrolled, 53 subjects were randomized to receive either spesolimab (N=35) or placebo (N=18). A total of 4 subjects prematurely discontinued from the trial; 3 prematurely discontinued due to subject request and 1 subject prematurely discontinued for other reasons (i.e., subject left the country).

Table 6. Disposition of Subjects

	Spesolimab N (%)	Placebo N (%)	Total N (%)
Enrolled	-	-	85
Randomized	35	18	53
Treated on Day 1	35 (100)	18 (100)	53 (100)
Received OL treatment with spesolimab on Day 8	12 (34)	15 (83)	27 (51)
Received rescue treatment with spesolimab	4 (11)	2 (11)	6 (11)
Discontinued from trial	3 (9)	1 (6)	4 (8)
Withdrawal by subject	2 (6)	1 (6)	3 (6)
Other[1]	1 (3)	0	1 (2)
Continued in the extension study	27 (77)	12 (67)	39 (74)

[1] Subject left the country.
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis); ADSL.xpt

Table 7 summarizes the treatment received during the conduct of the trial. A total of 15 (83%) subjects treated with placebo on Day 1 received open-label spesolimab on Day 8 and 12 (34%) subjects treated with spesolimab on Day 1 received open-label spesolimab on Day 8.

Table 7. Treatment Received

Treatment	Number of Subjects
Spesolimab D1 Only	19
Spesolimab D1 → SOC Escape[1]	2
Spesolimab D1 → SOC Escape → Spesolimab Rescue[2]	1
Spesolimab D1 → Spesolimab Rescue[3]	1
Spesolimab D1 → OL Spesolimab D8	7
Spesolimab D1 → OL Spesolimab D8 → SOC Escape[4]	3
Spesolimab D1 → OL Spesolimab D8 → Spesolimab Rescue[5]	2
Placebo D1 Only	2
Placebo D1 → SOC Escape → Spesolimab Rescue[6]	1
Placebo D1 → OL Spesolimab D8	10
Placebo D1 → OL Spesolimab D8 → SOC Escape[7]	4
Placebo D1 → OL Spesolimab D8 → Spesolimab Rescue[8]	1

Abbreviations: D1 = Day 1; D8 = Day 8; OL = open-label; SOC = standard of care
[1] One subject received SOC escape on Day 4 and the other subject on Day 8.
[2] Subject received SOC escape on Day 3 and spesolimab rescue on Day 14.
[3] Subject received spesolimab rescue on Day 37.
[4] One subject received SOC escape on Day 17, one subject on Day 29, and one subject on Day 57.
[5] One subject received spesolimab rescue on Day 38 and the other subject on Day 58.
[6] Subject received SOC escape on Day 2 and spesolimab rescue on Day 44.
[7] One subject received SOC escape on Day 11, one subject on Day 13, one subject on Day 16, and one subject on Day 46.
[8] Subject received spesolimab rescue on Day 68.
Source: Statistical Reviewer's Analysis; ADSL.xpt

Table 8 and Table 9 present the demographics and baseline disease characteristics. The proportions of male subjects and white subjects were higher in the spesolimab group than in the placebo group. In addition, the mean and median baseline body weight was slightly higher in the spesolimab group than in the placebo group. The baseline disease characteristics were generally comparable between the two treatment groups. The proportion of subjects with prior biologic therapy for GPP was slightly higher in the spesolimab group than in the placebo group.

Table 8. Demographics (RS[1])

	Spesolimab (N=35)	Placebo (N=18)	Total (N=53)
Age (years)			
Mean (SD)	43.2 (12.1)	42.6 (8.4)	43.0 (10.9)
Median	41.0	41.5	41.0
Min, Max	21.0, 69.0	30.0, 57.0	21.0, 69.0
Categories, n (%)			
< 65	33 (94)	18 (100)	51 (96)
≥ 65	2 (6)	0	2 (4)
Sex, n (%)			
Male	14 (40)	3 (17)	17 (32)
Female	21 (60)	15 (83)	36 (68)
Race, n (%)			
Asian	16 (46)	13 (72)	29 (55)
White	19 (54)	5 (28)	24 (45)
Ethnicity, n (%)			
Not Hispanic or Latino	35 (100)	18 (100)	53 (10)
Weight (kg)			
Mean (SD)	73.7 (23.9)	68.8 (26.6)	72.0 (24.7)
Median	69.3	62.9	67.0
Min, Max	47.1, 163.8	36.2, 152.5	36.2, 163.8
Region, n (%)			
Africa	5 (14)	2 (11)	7 (13)
Asia (excluding Japan)	13 (37)	12 (67)	25 (47)
Europe	14 (40)	2 (11)	16 (30)
Japan	1 (3)	1 (6)	2 (4)
United States	2 (6)	1 (6)	3 (6)

[1] Randomized Set (RS): all randomized subjects.
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis); ADSL.xpt

Table 9. Baseline Disease Characteristics (RS[1])

	Spesolimab (N=35)	Placebo (N=18)	Total (N=53)
IL36RN Mutation, n (%)			
Yes	8 (23)	6 (33)	14 (26)
No	21 (60)	11 (61)	32 (60)
Unknown	6 (17)	1 (6)	7 (13)
GPPPGA Total Score, n (%)			
3 – Moderate	28 (80)	15 (83)	43 (81)
4 – Severe	7 (20)	3 (17)	10 (19)
GPPPGA Pustulation Sub-score, n (%)			
2 – Mild	6 (17)	5 (28)	11 (21)
3 – Moderate	16 (46)	7 (39)	23 (43)
4 – Severe	13 (37)	6 (33)	19 (36)
GPPPASI			
Mean (SD)	27.8 (13.4)	24.1 (15.2)	26.5 (14.0)
Median	27.4	20.9	27.2
Min, Max	7.5, 54.2	5.2, 68.8	5.2, 68.8
Pain VAS			
Mean (SD)	76.4 (16.8)	64.6 (27.6)	72.4 (21.6)
Median	79.8	70.0	77.9
Min, Max	20.0, 100.0	0.0, 100.0	0.0, 100.0
PSS Total Score			
Mean (SD)	10.4 (3.6)	10.3 (3.1)	10.4 (3.4)
Median	11.0	10.5	11.0

	Spesolimab (N=35)	Placebo (N=18)	Total (N=53)
Min, Max	3.0, 16.0	2.0, 16.0	2.0, 16.0
FACIT-Fatigue Score			
Mean (SD)	18.1 (14.2)	19.0 (14.9)	18.4 (14.3)
Median	14.0	18.0	15.0
Min, Max	1.0, 49.0	0.0, 49.0	0.0, 49.0
WBC > 12 x 10^9/L, n (%)			
Yes	15 (43)	5 (28)	20 (38)
No	18 (51)	11 (61)	29 (55)
Missing	2 (6)	2 (11)	4 (8)
Temperature, n (%)			
> 38 Celsius	6 (17)	2 (11)	8 (15)
≤ 38 Celsius	29 (83)	16 (89)	45 (85)
WBC > 12 x 10^9/L AND > 38 Celsius, n (%)			
Yes	4 (11)	1 (6)	5 (9)
No	29 (83)	15 (83)	44 (83)
Missing	2 (6)	2 (11)	4 (8)
Prior Biologic Therapy for GPP, n (%)			
Yes	11 (31)	2 (11)	13 (25)
No	24 (69)	16 (89)	22 (75)

[1] Randomized Set (RS): all randomized subjects.
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis); ADSL.xpt

8.1.4 Results of the Primary Efficacy Endpoint

Table 10 presents the results of the primary efficacy endpoint (i.e., proportion of subjects with a GPPPGA pustulation sub-score of 0 [clear] at Day 8). Spesolimab was statistically superior to placebo for the primary efficacy endpoint (one-sided p-value = 0.0004). Prior to the Day 8, a total of 3 subjects (2 spesolimab subjects and 1 placebo subject) received SOC escape. In addition, 1 spesolimab subject discontinued the trial prior to Day 8. These 4 subjects were treated as non-responders for the results presented in Table 10. The results for the PPS (not shown) were very similar to those for the RS.

Table 10. Results of the Primary Efficacy Endpoint (RS[1])

	Spesolimab (N=35)	Placebo (N=18)
GPPPGA Pustulation Score of 0 at Day 8		
n (%)	19 (54.3)	1 (5.6)
Risk Difference (95% CI[2]), %	48.7 (21.5, 67.2)	
P-value[3]	0.0004	

[1] Randomized Set (RS): all randomized subjects. Missing data were imputed using non-responder imputation. Subjects who received SOC escape medication were imputed as non-responders.
[2] Confidence interval based on the Wilson method.
[3] P-value based on the Suissa-Shuster Z-pooled test (1-sided p-value).
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis); ADQSEP.xpt

As discussed in Section 8.1.1, subjects who did not receive SOC escape treatment and who had a GPPPGA total score ≥ 2 at Day 8 and a GPPPGA pustulation sub-score of ≥ 2 at Day 8 were eligible to receive treatment with a single open-label dose of 900 mg of spesolimab. A total of 12 subjects who were randomized to spesolimab received a second dose of spesolimab at Day

8. In these subjects, 5 (41.7%) subjects had a GPPPGA pustulation sub-score of 0 (clear) at Day 15 (i.e., one week after their second dose of spesolimab).

8.1.5 Results of the Secondary Efficacy Endpoints

Table 11 presents the results for the key secondary efficacy endpoint (i.e., proportion of subjects with a GPPPGA total score of 0 or 1 at Day 8). As presented in Figure 9, the GPPPGA total score is the average over the three sign sub-scores (i.e., erythema, pustules, and scaling/crusting) followed by rounding to the whole integer except for a total score of 0, which required all three sub-scores to be equal to 0. Table 47 in Appendix 19.5 presents the GPPPGA sub-scores as well as the average for each subject for Day 1 and Day 8. From this table, we can see that the results for the GPPPGA total score of 0 or 1 is being driven by the pustulation sub-score. For the subjects that had a GPPPGA total score of 0 or 1, all but 1 subject had a pustulation sub-score of 0 at Day 8. In addition, only 2 subjects (1 spesolimab subject and 1 placebo subject) had all three sub-scores ≤ 1 and no subjects had all sub-scores equal to 0.

Table 11. Results of the Key Secondary Efficacy Endpoint (RS[1])

	Spesolimab (N=35)	**Placebo (N=18)**
GPPPGA Total Score of 0 or 1 at Day 8[2]		
n (%)	15 (42.9)	2 (11.1)
Risk Difference (95% CI[3]), %	31.7 (2.2, 52.7)	
P-value[4]	0.0118	

[1] Randomized Set (RS): all randomized subjects. Missing data were imputed using non-responder imputation. Subjects who received SOC escape medication were imputed as non-responders.
[2] The GPPPGA total score is the average over the three sign sub-scores (i.e., erythema, pustules, and scaling/crusting).
[3] Confidence interval based on the Wilson method.
[4] P-value based on the Suissa-Shuster Z-pooled test (1-sided p-value).
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis); ADQSEP.xpt

Table 12 and Table 13 present the secondary efficacy endpoints at Week 4. It should be noted that 15 (42.9%) spesolimab subjects and 16 (88.9%) placebo subjects received SOC escape medication, open-label spesolimab at Day 8, or rescue medication with spesolimab before Week 4. Therefore, it is difficult to draw meaningful conclusions regarding the treatment effect at Week 4.

Table 12. Results of the Secondary Efficacy Endpoint of GPPPASI-75 at Week 4 (RS[1])

	Spesolimab (N=35)	**Placebo (N=18)**
GPPPASI-75 at Week 4		
n (%)	16 (45.7)	2 (11.1)
Risk Difference (95% CI[2]), %	34.6 (5.8, 55.4)	
P-value[3]	0.0081	

[1] Randomized Set (RS): all randomized subjects. Missing data were imputed using non-responder imputation. Subjects who received SOC escape medication, open-label spesolimab at Day 8, or rescue medication with spesolimab were imputed as non-responders.
[2] Confidence interval based on the Wilson method.
[3] P-value based on the Suissa-Shuster Z-pooled test (1-sided p-value).
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis); ADQSEP.xpt

Table 13. Results of the PRO Secondary Efficacy Endpoints at Week 4 (RS[1])

	Spesolimab (N=35)	Placebo (N=18)
Change from Baseline in Pain VAS Score at Week 4		
Median	-22.45	NM[3]
P-value[2]	0.0012	
Change from Baseline in PPS Score at Week 4		
Median	-2.00	NM[3]
P-value[2]	0.0044	
Change from Baseline in FACIT-Fatigue Score at Week 4		
Median	3.00	NM[3]
P-value[2]	0.0012	

[1] Randomized Set (RS): all randomized subjects. Missing data was imputed using LOCF. Subjects who received SOC escape medication, open-label spesolimab at Day 8, or rescue medication with spesolimab were imputed using a worst-case scenario approach.
[2] P-value based on Wilcoxon rank test (1-sided p-value).
[3] The median is not meaningful (NM) as < 50% of the subjects had observed data at Week 4 without receiving open-label spesolimab at Day 8 or receiving SOC escape medication and/or rescue medication with spesolimab prior to Week 4.
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis); ADQSEP.xpt

8.1.6 Findings in Special/Subgroup Populations

Table 14 presents the results of the primary efficacy endpoint by age, sex, race, region, IL36RN mutation status, baseline GPPPGA total score, and baseline GPPPGA pustulation sub-score. Due to the overall small sample size, one cannot reliably determine whether there are differences in response across these subgroups.

Table 14. Results of the Primary Efficacy Endpoint (i.e., Proportion of Subjects with a GPPPGA Pustulation Sub-score of 0 [Clear] at Day 8) by Age, Sex, Race, Region, IL36RN Mutation Status, Baseline GPPPGA Total Score, and Baseline GPPPGA Pustulation Sub-score (RS[1])

	Spesolimab (N=35)	Placebo (N=18)	Difference (95% CI[2])
Age (years)			
< 65 (33, 18)	55%	6%	49% (21%, 68%)
≥ 65 (2, 0)	100%	-	-
Sex			
Male (14, 3)	57%	0%	57% (-19%, 82%)
Female (21, 15)	52%	7%	46% (15%, 69%)
Race			
Asian (16, 13)	63%	8%	55% (17%, 80%)
White (19, 5)	47%	0%	47% (-7%, 72%)
Region			
Africa (5, 2)	80%	0%	80% (-14%, 100%)
Asia (13, 12)	62%	8%	53% (15%, 81%)
Europe (14, 2)	43%	0%	43% (-41%, 73%)
Japan (1, 1)	100%	0%	-
United States (2, 1)	0%	0%	-
IL36RN Mutation			
Yes (8, 6)	88%	17%	71% (13%, 96%)
No (21, 11)	43%	0%	43% (8%, 66%)
Unknown (6, 1)	50%	0%	50% (-61%, 88%)
Baseline GPPPGA Total Score			

	Spesolimab (N=35)	Placebo (N=18)	Difference (95% CI[2])
3 (28, 15)	57%	7%	50% (16%, 71%)
4 (7, 3)	43%	0%	43% (-34%, 82%)
Baseline PGA Score			
2 – Mild (6, 5)	67%	20%	47% (-18%, 87%)
3 – Moderate (16, 7)	50%	0%	50% (6%, 75%)
4 – Severe (13, 6)	54%	0%	54% (7%, 81%)

[1] Randomized Set (RS): all randomized subjects. Missing data were imputed using non-responder imputation. Subjects who received escape medication, open-label spesolimab at Day 8, or rescue medication with spesolimab were imputed as non-responders.
[2] Confidence interval based on the Wilson method.
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis); ADQSEP.xpt

8.2 Review of Safety

8.2.1 Safety Review Approach

The main source of safety data for the safety review derives from trial 1368-0013 with additional safety data informed by trials 1368-0011, 1368-0027 (ongoing), and 1368-0025 (ongoing) (refer to Section 7.1). Given the rarity of GPP, safety was also informed by auxiliary safety cohorts, i.e. exposure of subjects to spesolimab in other developmental programs. The Applicant's summary of safety and safety update include the above trials, trials conducted for other indications, and trials conducted in healthy volunteers. The summary of safety and safety update were reviewed and information will be commented on descriptively in the review. However, the Applicant did not submit SDTM or ADAM datasets for the studies for other indications or for trials 1368-0027 and 1368-0025. Safety data was not pooled by the Applicant or the reviewer due to the heterogeneity in study populations and trial designs across trials, both within the GPP indication and across other diseases.

Of note, there is limited safety data when comparing spesolimab to placebo as the duration for the randomized, double-blind period for trial 1368-0013 was 1 week. At week 1/day 8, all trial participants who had GPPGA total score ≥2 and GPPGA pustulation subscore ≥2 were eligible to receive open-label, single-dose spesolimab 900 mg intravenously. After week 1/day 8 and through week 12, if there was >2 point increase in the GPPPGA score and the pustular component of GPPPGA >2 after achieving a clinical response (GPPPGA 0 or 1) to initial treatment (either with spesolimab at day 1 or placebo at day 1 or escape medication or OL spesolimab at day 8), subjects were eligible to receive rescue treatment with a single-dose spesolimab 900 mg intravenously. A maximum of 3 doses during the trial was allowed. Additional safety data was obtained up to week 12 from randomized treatment or 16 weeks from the last administered dose (residual effect period or REP), however, the data is considered open-label, non-randomized data with no comparative cohort.

8.2.2 Review of the Safety Database

Overall Exposure

Exposure in GPP trials

The total number of subjects with GPP flare who received at least 1 dose of spesolimab intravenously was 64 across trials 1368-0011 (7 subjects), 1368-0013 (51 subjects), and 1368-0027 (6 subjects as of BLA cut-off date, 08 Jan 2021). Of note, all 9 subjects in trial 1368-0025 as of the BLA cut-off date (08 Jan 2021), had rolled over into this open-label, extension trial, from trial 1368-0013, and subsequently not counted in the above exposure count.

In trial 1368-0011, the single dose administered was 10 mg/kg. In trials 1368-0013 and 1368-0027, the single dose administered was 900 mg.

As of the safety update report cut-off date (30 Sep 2021), 16 additional subjects with GPP from trial 1368-0027, for a total of 80 subjects with GPP, were treated with at least 1 dose of spesolimab i.v. as flare treatment.

Exposure in trial 1368-0013

Fifty-three subjects were randomized 2:1 to receive a single 900 mg i.v. dose of spesolimab (35 subjects) or placebo (18 subjects) in trial 1368-0013. On day 8, all trial participants who had GPPGA total score $\geq$2 and GPPGA pustulation subscore $\geq$2 were eligible to receive open-label, single dose spesolimab 900 mg i.v. After day 8 to week 12, all trial participants who had a $\geq$2-point increase in both the GPPGA total score and the GPPGA pustulation subscore after a previous clinical response to treatment (i.e. a GPPGA total score of 0 or 1) were eligible to receive rescue, single dose spesolimab 900 mg i.v. A total maximum of 3 single-doses of spesolimab 900 mg i.v. was allowed throughout the randomized and open-label parts of the trial. Subjects were also allowed to receive escape medication/standard off-label care at the discretion of the investigator.

A total of 27 subjects received an open-label dose of spesolimab on day 8. Of the 35 subjects originally randomized and received spesolimab, 12 subjects received open-label, single, i.v. dose of spesolimab on day 8. Of the 18 subjects originally randomized and received placebo, 15 subjects received open-label, single, i.v. dose of spesolimab on day 8.

A total of 6 subjects received an open-label rescue dose of spesolimab from day 8 to week 12 (see Table 15).

The number of subjects who received 1 dose of spesolimab in trial 1368-0013 was 36. The number of subjects who received 2 doses of spesolimab in trial 1368-0013 was 13. The number

of subjects who received 3 doses of spesolimab in trial 1368-0013 was 2.

Table 15: Treatment Sequence trial 1368-0013

Treatment Sequence 1368-0013	N
Placebo	2
Placebo + OL D8 Speso 900 mg IV	14
Placebo + OL D8 Speso 900 mg IV + Rescue Speso 900 mg IV	1
Placebo + Rescue Speso 900 mg IV	1
Speso 900 mg IV SD	21
Speso 900 mg IV SD + OL D8 Speso 900 mg IV	10
Speso 900 mg IV SD + OL D8 Speso 900 mg IV + Rescue Speso 900 mg IV	2
Speso 900 mg IV SD + Rescue Speso 900 mg IV	2

Source: reviewer table from 1368-0013 ADSL dataset

Exposure in other disease trials

Table 16: Overview of trials with spesolimab in subjects with other diseases

Phase Trial no.	Objective/ Trial design	Treatment duration per protocol	Route of admin.	Trial population	Number of treated patients[1]	Trial status / [Report no.]
Phase II in patients with Palmoplantar Pustulosis (PPP)						
1368-0015	Efficacy (proof of concept), safety, and PK/ Double-blind, randomized, placebo-controlled design	16 weeks	i.v. infusion	Male and female patients with PPP	Placebo (4×): 21 Spesolimab 300 mg q4w (4×): 19 Spesolimab 900 mg q4w (4×): 19	Completed Final CTR [c24420819]
1368-0016	Dose-finding, efficacy, and safety/ Double-blind, randomized, placebo-controlled design	52 weeks	s.c. injection	Male and female patients with PPP	Placebo qw (5×), q4w (3×), then spesolimab 600 mg q4w (9×): 43 Low dose: spesolimab 300 qw (5×), 300 q4w (3×), then 300 q8w (4×): 22 Medium-low dose: spesolimab 300 qw (5×), 600 q4w (3×), then 600 q4w (9×): 21 Medium-high dose: spesolimab 600 qw (5×), 300 q4w (3×), then 300 q4w (9×): 22 High dose: spesolimab 600 qw (5×), 600 q4w (3×), then 600 q4w (9×): 44	Ongoing, Primary Analysis (Week 16) completed / Primary Analysis CTR [c32445633] In addition, interim TFLs [c35847789]
Phase II in patients with Atopic Dermatitis (AD)						
1368-0032	Safety and efficacy/ Double-blind, randomized, placebo-controlled design	Up to 32 weeks	i.v. infusion	Male and female patients with AD	Placebo: 18 Spesolimab 600 q4w (4×): 33 In addition, non-responders were offered additional 600 mg spesolimab q4w i.v. (4×) at Week 16	Completed / Final CTR [c32577607]

[1] For ongoing trials, patients included up to the cut-off date of 08 Jan 2021

Phase Trial no.	Objective/ Trial design	Treatment duration per protocol	Route of admin.	Trial population	Number of treated patients[1]	Trial status / [Report no.]
Phase II in patients with ulcerative colitis (UC)						
1368-0004	Mechanism of action, clinical effect, and safety/ Open-label, single-arm design	12 weeks	i.v. infusion	Patients with moderately to severely active UC	Spesolimab: 1200 mg q4w (3×): 8	Completed / Final CTR [c30128674]
1368-0005	Safety and efficacy/ Double-blind, randomized, placebo-controlled design	Single dose or 12 weeks	i.v. infusion	Patients with moderately to severely active UC	Placebo: 23 Spesolimab 300 mg (1×): 24 Spesolimab 450 mg q4w (3×): 23 Spesolimab 1200 mg q4w (3×): 27	Completed / Final CTR [c31366073]
1368-0010	Safety and efficacy (proof of concept) as add-on treatment to TNF-α inhibitor therapy/ Double-blind, randomized, placebo-controlled	12 weeks	i.v. infusion	Patients with mild to moderately active UC	Placebo: 8 Spesolimab: 1200 mg q4w (3×): 14	Completed / Final CTR [c32073490]
1368-0017	Long-term safety and efficacy/ Open-label design	12 weeks of RI, 336 weeks of MT	i.v. infusion (RI) s.c. injection (MT),	Male and female patients with UC from trials 1368-0005 and -0004	Available interim data for i.v. RI: 57 Available interim data for flare treatment: 16 *Planned to be included for the final analysis: 160 patients: spesolimab 1200 mg i.v. q4w (3×) (RI), spesolimab 300 mg s.c. q4w (up to 84×) (MT),* In addition, patients were offered open-label flare rescue treatment with a single dose spesolimab 1200 mg i.v. The MT schedule after the flare was then 600 mg s.c. q6w (up to 56×) (MT after flare treatment)	Ongoing at the time of submission/ interim TFLs [c35847789]

MT: maintenance treatment; RI: re-induction treatment

[1] For ongoing trials, patients included up to the cut-off date of 08 Jan 2021

Source: Applicant's summary of clinical safety for BLA 761244

Exposure in healthy volunteers

Table 17: Overview of Phase 1 trials with spesolimab in healthy volunteers

Phase Trial no.	Objective/ Trial design	Treatment duration per protocol	Route of admin.	Trial population / Number of treated subjects												Trial status/ [Report no.]
Phase I in healthy volunteers with i.v. administration																
1368-0001	Safety and PK/ Single-blind, partially randomized within dose groups, placebo-controlled	SRD	i.v. infusion	Healthy male volunteers												
				Pbo i.v.	Spesolimab [mg/kg body weight]										Total	Completed / Final CTR [c09985235]
					0.001	0.003	0.010	0.030	0.050	0.100	0.300	1	3	6	10	
				20	6	6	6	6	3	5	4	6	6	6	4	78
1368-0002	Safety and PK/ Partially randomized, placebo-controlled; MRD: Double-blind, parallel-group, SD: Single-blind	MRD: 4 weeks, SD	i.v. infusion	Healthy male volunteers												Completed / Final CTR [c18789185]
				Pbo i.v.	Spesolimab [mg/kg body weight]										Total	
					3 qw (MRD)		6 qw (MRD)		10 qw (MRD)		20 qw (MRD)		20 (SD)			
				10	6		6		6		6		6		40	
1368-0003	Safety and PK/ Open-label, parallel-group	SD	i.v. infusion, s.c. injection	Healthy male and female volunteers												Completed / Final CTR [c21739607]
				Spesolimab [mg]											Total	
				300 i.v.				150 s.c.				300 s.c.				
				12				12				12			36	
1368-0009	Safety and PK/ Double-blind, randomized, placebo-controlled	SRD (i.v.), SD (s.c.)	i.v. infusion, s.c. injection	Healthy Japanese male volunteers												Completed / Final CTR [c22174984]
				Pbo i.v. /s.c.	Spesolimab [mg]										Total	
					300 i.v.			600 i.v.		1200 i.v.			300 s.c.			
				8	6			6		6			6		32	
1368-0043	Safety and PK/ Open-label, parallel-group	SRD (first i.v., then s.c.)	i.v. infusion, s.c. injection	Healthy Chinese male and female volunteers												Ongoing / Interim CTR (i.v. data) [c34784235]
				Spesolimab [mg]											Total	
				450 i.v.			900 i.v.		1200 i.v.			300 s.c.		600 s.c.		
				10			10		10			NA		NA	30	
Phase I in healthy volunteers with s.c. administration only																
1368-0029	Relative bioavailability and safety/ Open-label, matched-group	SD	s.c. injection	Healthy male and female volunteers												Completed / Final CTR [c28472227]
				Spesolimab [mg] s.c.											Total	
				300 (1 pmbl site)			300 (2 pmbl sites)		300 (thigh)			600 (2 pmbl sites)				
				12			12		12			12			48	

MRD: multiple rising dose: pmbl: periumbilical; SD: single dose, SRD: single rising dose

Source: Applicant's summary of clinical safety for BLA 761244

As of the safety update report cut-off date (30 Sep 2021), a total of 80 subjects with GPP, were treated with at least 1 dose of spesolimab i.v. as flare treatment. The total number of subjects

including healthy volunteers, subjects with GPP, and subjects with other diseases treated with spesolimab (i.v. or s.c. at various doses as indicated in the tables above) was 663. During the review cycle, the Applicant submitted safety data regarding reported Guillain-Barre syndrome cases (see section 8.2.5 Analysis of Submission-Specific Safety Issues, Subsection Guillain-Barre syndrome). The Division of Neurology was consulted. At the time of the Division of Neurology consult review, a total number of 750 subjects had been exposed to spesolimab at various doses and methods of administration and for various indications across the development program.

Relevant characteristics of the safety population:

A female preponderance has been reported in some retrospective reviews for GPP.[27] The trial population in trial 1368-0013 was consistent with the female preponderance for GPP with 83% of female subjects. GPP occurs in individuals from all racial backgrounds, with a higher reported prevalence in Asians compared to Caucasians (prevalence in a Japanese population estimated to be 7.46 per million and in a French population, estimated to be 1.76 per million). GPP occurs more frequently in middle-aged adults, with the average age of affected individuals ranging between 40 and 60 years in some reports. In trial 1368-0013, 2 (6%) of SPEVIGO-treated subjects were 65 to 74 years of age and no subjects were 75 years of age or older. The trial did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger adult subjects.

The trial population from trial 1368-0013 overall appears to represent the expected target population. One exception is the exclusion of pregnant subjects which is an important limitation given that pregnancy can trigger the onset of GPP flare. An additional limitation is that geographic regions were not widely represented with a smaller representation from the United States. However, given the rarity of the disease and a higher reported prevalence in Asians compared to Caucasians, the smaller representation from the United States and larger representation from Asia is acceptable.

Table 18: Demographic Characteristics for subjects in Trial 1368-0013

Subgroup	Placebo (N = 18) n (%)	Speso 900 mg IV SD (N = 35) n (%)	Total (N = 53) n (%)
Sex			

[27] Noe MH, Wan MT, Mostaghimi A, et al. Evaluation of a Case Series of Patients With Generalized Pustular Psoriasis in the United States. *JAMA Dermatol*. 2022;158(1):73-78. doi:10.1001/jamadermatol.2021.4640

Subgroup	Placebo (N = 18) n (%)	Speso 900 mg IV SD (N = 35) n (%)	Total (N = 53) n (%)
Female	15 (83.3)	21 (60.0)	36 (67.9)
Male	3 (16.7)	14 (40.0)	17 (32.1)
Age			
Mean	42.56	43.23	43
Standard Deviation	8.37	12.14	10.92
Minimum	30	21	21
Median	41.5	41	41
Maximum	57	69	69
Age Group			
Age Group 1 (AGE < 65)	18 (100.0)	33 (94.3)	51 (96.2)
Age Group 2 (65 <= AGE)	0 (0.0)	2 (5.7)	2 (3.8)
Race			
Asian	13 (72.2)	16 (45.7)	29 (54.7)
White	5 (27.8)	19 (54.3)	24 (45.3)
Ethnicity			
Not Hispanic or Latino	18 (100.0)	35 (100.0)	53 (100.0)
Region			
Africa	2 (11.1)	5 (14.3)	7 (13.2)
Asia	13 (72.2)	14 (40.0)	27 (50.9)
Europe	2 (11.1)	14 (40.0)	16 (30.2)
United States	1 (5.6)	2 (5.7)	3 (5.7)

Source: reviewer table from MAED demographic tool from Applicant's ADSL dataset

Table 19: Demographic Characteristics for subjects in Trial 1368-0011

Subgroup	Speso 10 mg/kg IV SD (N = 7) n (%)
Sex	
Female	4 (57.1)
Male	3 (42.9)
Age	
Mean	38.57
Standard Deviation	13.78

Subgroup	Speso 10 mg/kg IV SD (N = 7) n (%)
Minimum	22
Median	34
Maximum	58
Age Group	
Age Group 1 (AGE < 65)	7 (100.0)
Age Group 2 (65 <= AGE)	0 (0.0)
Race	
Asian	4 (57.1)
Missing	1 (14.3)
White	2 (28.6)
Ethnicity	
Not Hispanic or Latino	7 (100.0)
Region	
Africa	2 (28.6)
Asia	4 (57.1)
Europe	1 (14.3)

Source: reviewer table from MAED demographic tool from Applicant's ADSL dataset

Adequacy of the safety database:

The exact prevalence of GPP is unknown but estimates have ranged from 1 to 9 per million.[28] Claims based data[29] 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. For rare diseases, a safety database consisting of 1-10% of the existing disease population is preferable for detecting important safety signals.[30] Given the wide range of prevalence estimates, there are limitations to determining the size and adequacy of the safety database.

[28] https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=247353
[29] US Truven MarketScan administrative claims from 01 Oct 2015 to 30 Sep 2016 and Optum US claims database using data from 01 Oct 2015 to 30 Jun 2017
[30] O'Connell and Pariser. Clinical Trial Safety Population Size: Analysis of Drug Approvals for Rare and Common Indications by FDA Center for Drug Evaluation and Research. Exp Opin Orphan Drugs. 2014

Based on a prevalence estimate of 1 per million, the preference for a safety database would range from 78 to 775 subjects (1-10% of 7753 with an estimated 7.753 billion individuals in the worldwide population). Based on an approximate number of individuals with GPP in the United States between 29,000-32,000, the preference for a safety databased would range from 290 to 2,900 subjects (1-10% of 29,000).

The total number of subjects with GPP flare who received at least 1 dose of spesolimab intravenously was 64 across trials 1368-0011 (7 subjects), 1368-0013 (51 subjects), and 1368-0027 (6 subjects). In trial 1368-0011, the single dose administered was 10 mg/kg. In trials 1368-0013 and 1368-0027, the single dose administered was 900 mg. The number of subjects who received 2 doses of spesolimab in trial 1368-0013 was 13. The number of subjects who received 3 doses of spesolimab in trial 1368-0013 was 2.

Table 20: Treatment Sequence trial 1368-0013

Treatment Sequence 1368-0013	N
Placebo	2
Placebo + OL D8 Speso 900 mg IV	14
Placebo + OL D8 Speso 900 mg IV + Rescue Speso 900 mg IV	1
Placebo + Rescue Speso 900 mg IV	1
Speso 900 mg IV SD	21
Speso 900 mg IV SD + OL D8 Speso 900 mg IV	10
Speso 900 mg IV SD + OL D8 Speso 900 mg IV + Rescue Speso 900 mg IV	2
Speso 900 mg IV SD + Rescue Speso 900 mg IV	2

Source: reviewer table from 1368-0013 ADSL dataset

Baseline disease characteristics in trial 1368-0013

At baseline acute flare, 15/18 (83.3%) subjects randomized to placebo vs. 28/35 (80%) subjects randomized to spesolimab had GPPGA scores of 3, and 3/18 (16.7%) subjects randomized to placebo vs. 7/35 (20%) subjects randomized to spesolimab had GPPGA scores of 4.

At baseline acute flare, 5/18 (27.8%) subjects randomized to placebo vs. 6/35 (17.1%) subjects randomized to spesolimab had GPPGA pustulation subscores of 2, 7/18 (38.9%) subjects randomized to placebo vs. 16/35 (45.7%) subjects randomized to spesolimab had GPPGA pustulation subscores of 3, and 6/18 (33.3%) subjects randomized to placebo vs. 13/35 (37.1%) subjects randomized to spesolimab had GPPGA pustulation subscores of 4.

Regarding systemic symptoms, at baseline acute flare, of the subjects with white blood cell count (WBC) assessments, 15/33 (45%) and 5/16 (31%) of subjects in the spesolimab and placebo groups, respectively, had (WBC) >12 x 10^9/L. Six out of 35 (17%) and 2/18 (11%) of subjects in the spesolimab and placebo groups, respectively, had temperature >38^o Celsius. Of the subjects with WBC assessments, 4/33 (12%) and 1/16 (6%) of subjects in the spesolimab and placebo groups, respectively, had both WBC >12 x 10^9/L and temperature >38^o Celsius.

Regarding baseline disease characteristics in trial 1368-0013, randomization appears to be evenly distributed between the two study cohorts, spesolimab and placebo, with a trend towards more severe baseline disease flare in the spesolimab group.

Based on the SUR, a total of 80 subjects with GPP were treated with at least 1 dose of spesolimab i.v. as flare treatment from completed and ongoing trials in GPP.

While a higher number of subjects would improve the adequacy of the safety database, the number of subjects in this application for the safety database is adequate given a precise estimate of GPP prevalence of GPP is unknown. Furthermore, additional safety information is provided in the clinical summary of safety from auxiliary safety cohorts, i.e. exposure of subjects to spesolimab in other developmental programs for different indications and in healthy volunteers (total 663 subjects based on the SUR). Limitations for the additional safety information include different routes of administration (intravenous and subcutaneous), doses, and study populations.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of spesolimab. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

For trial 1368-0013's protocol, the Applicant defined an adverse event (AE) as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. The Applicant defined a serious adverse event (SAE) as any AE which fulfils at least one of the following criteria: results in death, is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe, requires inpatient hospitalization, requires prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly / birth defect, is deemed serious for any other reason if it is an important medical event which, when based on appropriate medical judgement, may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. The Applicant provided accurate definitions of AEs and SAEs in the protocol for trial 1368-0013.

The Applicant defined "treatment emergent" adverse events as all AEs occurring between start of treatment and end of the residual effect period (REP). For trial 1368-0013, the REP was

defined as 16 weeks, which corresponds to approximately 5 half-lives of spesolimab in subjects with GPP, after the last dose of trial medication. Note, in some other trials (e.g. in healthy volunteer trials, where the half-life is longer), a different period of treatment-emergent AE recording (constituting the REP) was used. For the analyses of treatment-emergent AEs on trial level, the REPs as defined in the respective trials were used. For placebo-controlled trials where an open-label dose of spesolimab could be administered as rescue treatment (i.e. 1368-0013), primary safety reporting was censored at the time of open-label spesolimab administration. For subjects who continued into the extension trial, only TEAE up to the first dose in the extension trial were available for display in the current study. Adverse events that started before first drug intake and deteriorated under treatment were also considered as 'treatment-emergent.' The Applicant's definition of TEAEs appears appropriate.

The AEs were coded using the MedDRA coding dictionary. The MedDRA version used to code AEs in trial 1368-0013 was 23.1. For other trials, the MedDRA versions used were 19.0 to 24.0. Studies were not pooled. The grading scale used to assess severity was the Rheumatology Common Toxicity Criteria (RCTC) version 2.0.

The period for AE collection, documentation and reporting started for all subjects from signing the informed consent and lasted 1) for subjects rolling over into the open-label extension trial 1368-0025, until the first dose of trial medication in the extension trial, 2) for subjects not rolling over into the open-label extension trial 1368-0025, until the individual subject's end of trial (after an individual subject's end of trial, an investigator did not have to actively monitor the subject for AEs but should have reported SAEs and Adverse Events of Special Interests (AESIs) of which he/she may have become aware by any means of communication (e.g. phone call) only if assessed as related to the study medication. These AEs should have been reported on the Applicant's SAE form, but not on the electronic case report form (eCRF).

Adverse events were collected at screening, days 1, 2, 3, 4, 5, 6, 7, 8, 15, 22, 29, 57, 85, 92-127 (for subjects who received rescue treatment with OL spesolimab), and 113-197 (timing variable depending on whether subject enrolled in open-label extension trial, 1368-0025). For each AE, the information was provided on the appropriate eCRF pages and, if applicable, the Applicant's SAE form. The following were also recorded as an (S)AE in the CRF and if applicable, the Applicant's SAE form: 1) worsening of the underlying disease or of other pre-existing conditions, 2) changes in vital signs, ECG, physical examination and laboratory test results, if they were judged clinically relevant by the investigator.

All (S)AEs, including those persisting after a subject's end of trial, were followed up until they had resolved, had been assessed as "chronic" or "stable", or no further information was able to be obtained.

The grading scale used to assess severity was the Rheumatology Common Toxicity Criteria (RCTC) version 2.0. Intensity options were grade 1: mild, grade 2: moderate, grade 3: severe, and grade 4: life-threatening. The causality assessment used was medical judgement, considering all relevant factors, including pattern of reaction, temporal relationships, de-

challenge or re-challenge, confounding factors such as concomitant medications, concomitant diseases and relevant history. Arguments that may have suggested that there was a reasonable possibility of a causal relationship could have been: 1) The event is consistent with the known pharmacology of the drug, 2) The event is known to be caused by or attributed to the drug class, 3) A plausible time to onset of the event relative to the time of drug exposure, 4) Evidence that the event is reproducible when the drug is re-introduced, 5) No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications), 6) The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome), 7) An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished). These AE assessment strategies appear adequate and appropriate.

Verbatim terms were included in the data files. Overall, the Applicant translated verbatim terms used by investigators to MedDRA preferred terms appropriately. There were instances where there was incomplete coding to the preferred terms (e.g. verbatim term: “generalized pustular psoriasis worsening with fever [and sinus tachycardia]” where the preferred terms, “pyrexia” and “sinus tachycardia” were not coded). The Applicant’s translation of verbatim terms to preferred terms was reviewed these incomplete coding terms did not appear to significantly alter the outcome of the adverse event data review.

The Applicant’s coding did not appear to significantly diminish safety signals through lumping or splitting of terms.

The Applicant grouped and analyzed the adverse event by primary system organ class (SOC) and preferred terms (PTs).

Adverse events were assessed by frequency. The analysis sets comprised all (randomized) subjects treated with at least 1 dose of trial medication, i.e. the treated set (TS) or the safety analysis set (SAF). In some trials, analyses of AEs adjusted for exposure/time at risk were also presented due to differing exposures in the treatment groups.

For trial 1368-0013, the primary analysis was based on the AE data collected during the first 12 weeks of treatment (i.e. up to Day 85), using the OC-IE method, i.e. patients were censored when they received open-label spesolimab on Day 8 or rescue medication between Day 8 and Week 12. All AE tables were repeated for the data collected during the 1st week of treatment and for the data up to the end of the REP of randomized treatment on Day 1.
The exposure-adjusted incidence rate (per 100 patients-years) of a selected TEAE was defined as:

Number of patients experiencing the AE per treatment group during time at risk /total time of patients at risk in that treatment group to contribute the event to the analysis multiplied by 100 (per 100 patient-years)

Time at risk [patient-years] = (date of onset of TEAE – study drug start date + 1) /365.25.

If, for a patient, the selected TEAE did not occur then the time at risk was censored at min: a) Date of death, b) For patients who did not roll over into the OLE study: last contact date per EoS page, c) For patients who rolled over into the OLE study: the 1st dose in the OLE study, d) Drug stop date + 112 days, e) Date of Day 8 if OL spesolimab was given, f) Date of rescue medication if spesolimab was given.

For each selected TEAE, the exposure-adjusted incidence rate was calculated as: Incidence rate [1/100 patients-years] = 100 × number of patients with AE / Total AE-specific time at risk [patient-years].

Based on knowledge from other compounds in the same class, the following adverse events of special interests were pre-specified in the clinical trial protocol:

-Hepatic injury, defined by the following alterations of hepatic laboratory parameters:
-An elevation of AST and/or ALT and/or AP ≥3×ULN plus 2×baseline value, combined with an elevation of total bilirubin ≥2×ULN plus 1.5×baseline value, measured in the same blood draw sample, or
-ALT and/or AST elevations ≥10×ULN

-Systemic hypersensitivity reactions, including infusion reactions and anaphylactic reaction using the following clinical criteria for diagnosing anaphylaxis.

-Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING

a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF),
b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP (Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg +[2 x age] from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.)
    b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

-Severe infections (according to RCTC grading in the ISF)

-Opportunistic and mycobacterium tuberculosis infections
These included pneumocystis jirovecii BK virus disease including PVAN, CMV, post-transplant lymphoproliferative disorder (EBV), progressive multifocal leukoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis [zygomycosis, rhizopus, mucor, lichtheimia], scedosporium/pseudallescheria boydii, fusarium), legionellosis, listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), HBV reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only), paracoccidioides, penicillium marneffei, sporothrix schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), trypanosoma cruzi infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), HCV progression

Routine Clinical Tests

Safety laboratory tests (clinical chemistry, hematology, coagulation, and urinalysis) and vital signs were obtained at screening, days 1, 2, 3, 4, 5, 6, 7, 8, 15, 22, 29, 57, 85, 92-127 (for subjects who received rescue treatment with OL spesolimab), and 113-197 (timing variable depending on whether subject enrolled in open-label extension trial, 1368-0025).

The laboratory tests were performed at a central laboratory. Local laboratories were used for dosing decisions at visits involving i.v. administration of spesolimab or placebo.

Clinically relevant abnormal findings (e.g. anemia, hypoproteinemia, hypoalbuminemia, hypocalcemia, etc.) were to be reported as baseline conditions or AEs. A clinically relevant value may have been either in- or outside the reference range. Clinically relevant abnormal laboratory test results had to be confirmed using an unscheduled visit laboratory kit and should have been repeated until normalization or stabilization or until an alternative explanation had been found. Abnormal laboratory values were also to be graded for intensity by using RCTC

Version 2.0 criteria.

Regarding vital signs: a) On non-study–drug administration days, vital sign assessments were done prior to blood sampling; b) On study drug administration days, vital signs were assessed at pre-dose, at approximately 5 minutes after the end of infusion, and 120 mins after the end of infusion.

The safety assessment methods and time points that were described in the protocol appear reasonable.

8.2.4 Safety Results

Deaths

No deaths were reported in any GPP trial.

In the ulcerative colitis development program (trial 1368-0017), 1 subject had a fatal AE. The subject was reported with SARS-CoV-2 pneumonia and Guillain-Barre syndrome (including tetraparesis) 20 days after the last administration of trial medication. The subject was hospitalized and died 12 days later.

As of the safety update report (SUR), no deaths were reported in any trial between the BLA cut-off date (08 Jan 2021) and the SUR cut-off date (30 Sep 2021).

Serious Adverse Events

Table 21: Serious Adverse Events in trial 1368-0013*

		Actual Treatment for Period 01				
		Speso 900 mg IV SD		Placebo		
		(N = 35)		(N = 18)		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Total
Skin and subcutaneous tissue disorders	Pustular psoriasis	4	11.4%	3	16.7%	7
	Drug reaction with eosinophilia and systemic symptoms	2	5.7%	.	.	2
Infections and infestations	Urinary tract infection	1	2.9%	.	.	1
Musculoskeletal and connective tissue disorders	Arthritis	1	2.9%	.	.	1
Hepatobiliary disorders	Drug-induced liver injury	1	2.9%	.	.	1

Source: reviewer table created from JMPClinical from Applicant's ADAE dataset;

*Covers treatment phase including residual effect period (REP) (16 weeks after drug administration) of randomized treatment at Day 1 and censored at the time of any non-randomized Spesolimab administration (either OL at day 8 or OL rescue after day 8).

Pustular Psoriasis
In trial 1368-0013, the most frequently reported serious adverse event was pustular psoriasis with the placebo cohort having a greater frequency of pustular psoriasis compared to the study drug cohort. No factors suggest a causal link between pustular psoriasis to the study drug.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
There were two reported cases of drug reaction with eosinophilia and systemic symptoms (DRESS) in trial 1368-0013. One case was also associated with the reported serious adverse events (SAE) of moderate urinary tract infection and moderate drug-induced liver injury (DILI).

Case 1 (Subject ID 1368-0013 (b) (6)): 40-year-old Asian female with reported fever, edema, erythema involving 70% BSA, lymphadenopathy, chills, and ALT elevation, 19 days prior to hospitalization and 22 days prior to study drug administration. Three days prior to study drug administration, the subject received acetaminophen/paracetamol (dose not specified) and 2 days prior to study drug administration, received cefuroxime. One day after study drug administration, cefuroxime was switched to cefepime. Two days after study drug administration, subject had recurrent fever, worsening of skin lesions, new facial lesions, periorbital edema, leg edema, but no new pustulation, and abnormal laboratory values with reported SAEs of DILI and DRESS. Three days after study drug administration, aminotransferases increased > 10-fold ULN. Total bilirubin was normal. Aminotransferases normalized 7 days later. No therapy was documented for DILI and DRESS but antibiotics were discontinued.

This case is less likely a case of DRESS due to the timing of liver enzyme elevation, recurrent fever, and symptoms described as “worsening of skin lesions, new facial lesions, periorbital edema, cheilitis, and severe leg edema with blistering, but no new pustulation, with BSA involvement of 70%,” 2 days after study drug administration (onset too soon for DRESS due to study drug) and Regi-SCAR score of 1 or ‘no case’ (for liver involvement). The subject later revealed a history of allergy to cefuroxime. Regarding DILI, while DILI due to the drug product cannot be entirely ruled out, given the history of allergy to cephalosporins, it is possible that the cephalosporin induced both the drug eruption and liver injury.

Case 2 (Subject ID 1368-0013- (b) (6): 34-year-old White female who developed edema and arthralgia of the ankles 11 days after study drug administration. Paracetamol was administered on the same day as study drug administration. Two days prior to edema and arthralgia, the subject had received spiramycin and paracetamol for tooth pain and infection, which was continued for 5 days. Nineteen days after study drug administration, skin folds remained inflamed, and continued to worsen per the subject and spiramycin was restarted and continued for 6 days. Thirty-five days after study drug administration, subject presented with generalized rash, with both worsening of GPP flare and DRESS documented. Eosinophils were 200/µL. The subject received OL rescue treatment with study drug 36 days after initial study

drug administration. The infusion was stopped after 15 minutes because of abdominal pain. The subject further had pyrexia, diarrhea, upper abdominal pain, oligoarthritis, hypomenorrhea, and dysmenorrhea. The infusion was restarted after 1.5 hours but interrupted because of reported malaise (hypotension [84/44 mmHg] causing syncope), cyanosis, and gastrointestinal symptoms (nausea and vomiting). After 10 minutes of infusion interruption, the blood pressure normalized (115/54 mmHg). After completion of the total infusion volume, the subject recovered from the events with the exception of oligoarthritis, worsening of GPP flare, hypomenorrhea, and dysmenorrhea. One day after second dose of study drug and 37 days after initial study drug administration, the subject developed edema of her feet and subsequent arthralgia. Eosinophils were 650/µL. Four days after the second study drug administration (and 40 days after initial study drug administration), she reportedly recovered from the oligoarthritis and the worsening of GPP flare. Six days after the second study drug administration (and 42 days after initial study drug administration), eosinophils were 1000/µL. She subsequently had further episodes of pustular psoriasis and upper abdominal pain, and pain in extremity. No therapy was documented for the event DRESS which was resolved 41 days after the initial report of the AE. Months later, the subject was re-exposed to spiramycin and developed generalized erythema, scales, and desquamation, lack of pustules and involvement of palms and soles) but without systemic symptoms.

This case has a calculated Regi-SCAR score of 2 or 'possible' case (-1 point for unknown fever of $\geq 38.5^0$ C, 1 point for eosinophilia, 1 point for skin rash suggesting DRESS, 1 point for liver involvement)of DRESS. Both the drug product and spiramycin are possible culprit medications. While it is unusual that upon re-exposure with spiramycin, the subject did not develop systemic symptoms, there have been cases of sensitization to antibiotics during DRESS with cases of drug eruption without systemic symptoms upon re-exposure.[31] Given the 'possible' case of DRESS by Regi-SCAR criteria, recommend labeling DRESS in sections 4 Contraindications, 5 Warnings and Precautions, and 6.1 Clinical Trial Experience/6 Adverse Reactions of the PI.

This subject was also reported to have symptoms during the infusion of a second dose that may represent a hypersensitivity reaction or an infusion reaction. The event was not documented or recorded as anaphylaxis and no treatment for anaphylaxis was documented in the case narrative or case report forms. The hypotension stabilized upon infusion interruption and the subject was able to complete the total infusion volume. Of note, DRESS was reported 3 weeks after the first ADA/Nab positive sample. Refer to Table 3 and Section 6.3.2 Clinical Pharmacology Questions. Based on a single case, however, it is indeterminate whether development of ADAs correlates with hypersensitivity risk. The risk of hypersensitivity reactions will be described in labeling. Recommend that hypersensitivity and infusion reactions continue

[31] Santiago LG, Morgado FJ, Baptista MS, Gonçalo M. Hypersensitivity to antibiotics in drug reaction with eosinophilia and systemic symptoms (DRESS) from other culprits. Contact Dermatitis. 2020;82(5):290-296. doi:10.1111/cod.13462

to be monitored in the ongoing clinical trials/development program and in the postmarket setting. In addition, further evaluation of whether the development of ADAs correlate with hypersensitivity risk will be needed in the postmarket setting.

Arthritis
In trial 1368-0013, there was one reported SAE of severe arthritis starting 6 days after study drug administration and was treated with unspecified antibiotic therapy. Joint aspiration obtained 5 days after antibiotic therapy administration indicated absence of visible bacteria. Urine culture grew streptococcus agalactiae (group B). The investigator assessed the arthritis to be probable septic arthritis to be related to the study treatment.

A causal link between the reported SAE of arthritis and the study drug is inconclusive. An increase risk of infections was observed for common adverse events (see section on treatment emergent adverse events and adverse reactions); thus, there may be a causal link between septic arthritis and the study drug. However, both sepsis and arthritis are associated complications of GPP, potentially confounding the link between the reported SAE and study drug.

In trial 1368-0011, no SAEs were reported.

In trial 1368-0027 (ongoing), one subject had one SAE of viral encephalitis and hypertensive encephalopathy on blinded SC treatment, one subject had one SAE of angioedema on blinded SC treatment and one SAE of erythema and erythrodermic psoriasis three days after IV rescue spesolimab treatment. Although the SAEs occurred on blinded treatment, it is possible for these SAEs to be related to spesolimab treatment given that both infection and hypersensitivity reactions appear to be emerging safety signals with spesolimab that will be labeled and monitored.

In trial 1368-0025 (ongoing), one subject had one SAE of injection site urticaria and two SAEs of application site urticaria after spesolimab 300 mg SC administration, one subject had one SAE of pneumonia and one SAE of rash while receiving spesolimab 300 mg SC q12w administrations, one subject had one SAE of facial paralysis and one SAE of cerebrovascular accident while receiving spesolimab 300 mg SC q6w administrations. Similarly as above, it is possible for the SAEs of urticaria and pneumonia to be related to spesolimab treatment given that both hypersensitivity reactions and infection appear to be emerging safety signals with spesolimab that will be labeled and monitored. It is also possible for the SAE of facial paralysis to be related to spesolimab treatment given the reported cases of Guillain-Barre syndrome with spesolimab that will be labeled and monitored.

Table 22: Serious Adverse Events Reported in other Ongoing Trials

SOC PT	N
Patients with SAEs	24
Infections and infestations	7
COVID-19 pneumonia	2
Staphylococcal bacteraemia	2
Arthritis infective	1
Gastroenteritis	1
Post procedural infection	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2
Colon cancer	1
Squamous cell carcinoma of skin	1
Endocrine disorders	1
Adrenal insufficiency	1
Nervous system disorders	3
Guillain-Barre syndrome	2
Generalised tonic-clonic seizure	1
Eye disorders	1
Glaucoma	1
Vascular disorders	1
Deep vein thrombosis	1
Gastrointestinal disorders	7
Colitis ulcerative	4
Large intestine polyp	1
Pancreatitis	1
Proctalgia	1
Skin and subcutaneous tissue disorders	1
Psoriasis	1
Musculoskeletal and connective tissue disorders	2
Fistula	1
Chondropathy	1
Metabolism and nutrition disorders	1
Obesity	1
Congenital, familial and genetic disorders	1
Hypertrophic cardiomyopathy	1
General disorders and administration site conditions	1
Mass	1
Injury, poisoning and procedural complications	5
Ankle fracture	1
Lower limb fracture	1
Meniscus injury	1
Post procedural haemorrhage	1
Thoracic vertebral fracture	1

Events are included up to the SUR cut-off date (30 Sep 2021)

Trials included: 1368 0024 (PPP), 1368 0037 (AD), 1368-0052 (HS), 1368-0067 (HS) , 1368 0017 double-blind part (UC), 1368-0007 (CD), and 1368-0008 (CD). Treatment allocation still blinded.

Source data: [SUR Appendix 2]

Source: Applicant provided table in SUR

Overall for the ongoing trials for the other indications, there appears to be a higher aggregate number of SAEs of infections, Guillain-Barre syndrome, and ulcerative colitis. The potential risks

for infections identified in the GPP program and Guillain-Barre syndrome will be included in labeling and continued to be monitored in the postmarket setting. Given that the above table includes trials conducted in subjects with ulcerative colitis and Crohns disease, it is inconclusive whether there is a risk of ulcerative colitis with the study drug. There were no reported cases of ulcerative colitis as a SAE in the GPP trials. Recommend continued monitoring of the risk of ulcerative colitis in ongoing trials/development program and the postmarket setting.

Dropouts and/or Discontinuations Due to Adverse Effects

No subjects discontinued the study drug due to TEAEs in trial 1368-0013.

As of the SUR, two subjects discontinued the study drug due to erythema (already reported at time of BLA) and guttate psoriasis (reported after BLA cut-off date) during flare treatment in trial 1368-0027.

One subject discontinued the study drug due to adenocarcinoma in trial 1368-0025 during the first maintenance period.

In trial 1368-0013, protocol specified criteria for withdrawal of subjects included anaphylactic reactions, severe infections, serious infections, opportunistic or mycobacterium tuberculosis infections until the active infection has resolved and the subject has recovered according to investigator's assessment, and malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix if deemed clinically appropriate by the investigator.

The pre-specified safety withdrawal criteria appear reasonable.

Significant Adverse Events

In trial 1368-0013, ten subjects were reported with severe (RCTC grade 3) events across the entire treatment period and one subject was reported with a life-threatening AE (RCTC grade 4). Most of the severe cases and the life-threatening case were also categorized as serious and are further described in the section, Serious Adverse Events.

During Week 1, two subjects in the placebo group (PTs pustular psoriasis and pyrexia) and six subjects in the spesolimab group (PTs anemia, pustular psoriasis, and arthritis) were reported with grade 3 events. These events can be associated complications of GPP. No further events were reported by Week 12 (for subjects who did not receive non-randomized spesolimab).

After non-randomized spesolimab treatment (open-label on Day 8 or as rescue treatment later), in total, six subjects were reported with grade 3 events, but as some of them had already had grade 3 events before, the overall number of patients with severe events was 10. PTs reported after non-randomized spesolimab use were squamous cell carcinoma of skin,

abdominal pain, pustular psoriasis, and psoriasis.

Treatment Emergent Adverse Events and Adverse Reactions

In trial 1368-0013, TEAEs were selected for inclusion in the ADVERSE REACTIONS section of the labeling (see table Table 25). TEAEs that occurred in greater than or equal to 1% frequency, more frequently than the placebo group, after the time of drug exposure, and up to week 1 (placebo-controlled period) were selected.

Infections (urinary traction infection, bacteremia, bacteriuria, cellulitis, herpes dermatitis and oral herpes, upper respiratory tract infection) occurred most frequently during the 1-week placebo-controlled period and were reported in 14% (5/35) of subjects treated with study drug compared with 5.6% of subjects treated with placebo. Serious infection (urinary tract infection) was reported in one subject (2.9%) in the study drug group and no subjects in the placebo group. Infections observed through week 1 with study drug were mild (28.6%) (2/7 infections) to moderate (71.4%) (5/7 infections). Given that the study drug is a humanized antagonistic monoclonal IgG1 antibody that blocks human IL-36, there is a biologic plausibility that the study drug increases the risk of infection.

While fatigue and pruritus are associated with GPP, these AEs occurred more frequently in the study drug cohort compared to the placebo cohort and thus, included as adverse reactions.

While nausea and vomiting and headache are general symptoms commonly observed in the general population, these AEs occurred more frequently in the study drug cohort compared to the placebo cohort and thus, included as adverse reactions.

While the AEs of infusion site hematoma and bruising are consistent with the method of administration of the study drug (i.v.), these AEs occurred more frequently in the study drug cohort compared to the placebo cohort and thus, included as adverse reactions.

Dyspnea, eye edema and urticaria have biologic plausibility as adverse reactions given the drug profile of the study drug as a humanized monoclonal IgG1 antibody having the potential to cause immunologic, hypersensitivity reactions.

Recommend including Table 25 in section 6 Adverse Reactions in labeling.

Table 23: Treatment Emergent Adverse Events (TEAEs) Summary, Safety Population, trial 1368-0013

	Actual Treatment for Period 01			
	Speso 900 mg IV SD (N=35)		Placebo (N=18)	
	N	%	N	%
Subjects with any TEAE	32	91.43	17	94.44
Subjects with severe TEAE	0	0.00	0	0.00
Subjects with any treatment emergent SAE	9	25.71	6	33.33
Subjects with any Treatment Emergent Adverse Events leading to death	0	0.00	0	0.00
Subjects with any Treatment Emergent Adverse Events leading to permanent treatment discontinuation	0	0.00	0	0.00

Source: JMP clinical derived table from Applicant provided ADAE dataset. TEAE: Treatment emergent adverse event, SAE: Serious adverse event
N (%): Number and percentage of subjects with at least one TEAE

Table 24: TEAEs Reported in Treated Subjects through Week 1, trial 1368-0013

		Actual Treatment for Period 01				
		Speso 900 mg IV SD		Placebo		
		(N = 35)		(N = 18)		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Total
Skin and subcutaneous tissue disorders	Pustular psoriasis	13	37.1%	7	38.9%	20
	Dermatitis allergic	.	.	1	5.6%	1
	Drug reaction with eosinophilia and systemic symptoms	1	2.9%	.	.	1
	Pain of skin	.	.	1	5.6%	1
	Prurigo	1	2.9%	.	.	1
	Pruritus	1	2.9%	.	.	1
	Skin ulcer	1	2.9%	.	.	1
	Urticaria	1	2.9%	.	.	1
General disorders and administration site conditions	Pyrexia	2	5.7%	4	22.2%	6
	Oedema peripheral	2	5.7%	1	5.6%	3
	Asthenia	1	2.9%	1	5.6%	2
	Fatigue	2	5.7%	.	.	2
	Chills	1	2.9%	.	.	1
	Infusion site haematoma	1	2.9%	.	.	1
	Injection site bruising	1	2.9%	.	.	1
	Non-cardiac chest pain	1	2.9%	.	.	1
Investigations	C-reactive protein increased	2	5.7%	.	.	2

		Actual Treatment for Period 01				
		Speso 900 mg IV SD		Placebo		
		(N = 35)		(N = 18)		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Total
	Alanine aminotransferase increased	.	.	1	5.6%	1
	Blood creatinine increased	1	2.9%	.	.	1
	Blood pressure increased	1	2.9%	.	.	1
	Eosinophil count increased	.	.	1	5.6%	1
	Eosinophil percentage increased	.	.	1	5.6%	1
	Haematocrit decreased	.	.	1	5.6%	1
	Haemoglobin decreased	.	.	1	5.6%	1
	High density lipoprotein decreased	.	.	1	5.6%	1
	Protein total decreased	.	.	1	5.6%	1
Infections and infestations	Urinary tract infection	2	5.7%	.	.	2
	Bacteraemia	1	2.9%	.	.	1
	Bacteriuria	1	2.9%	.	.	1
	Cellulitis	1	2.9%	.	.	1
	Herpes dermatitis	1	2.9%	.	.	1
	Oral herpes	1	2.9%	.	.	1
	Pustule	1	2.9%	.	.	1
	Streptococcal infection	.	.	1	5.6%	1
	Upper respiratory tract infection	1	2.9%	.	.	1
Musculoskeletal and connective tissue disorders	Pain in extremity	2	5.7%	1	5.6%	3
	Arthralgia	2	5.7%	.	.	2
	Myalgia	1	2.9%	1	5.6%	2
	Arthritis	1	2.9%	.	.	1
Gastrointestinal disorders	Nausea	2	5.7%	.	.	2
	Vomiting	1	2.9%	1	5.6%	2
	Abdominal distension	1	2.9%	.	.	1
	Constipation	1	2.9%	.	.	1
	Diarrhoea	1	2.9%	.	.	1
Nervous system disorders	Headache	3	8.6%	1	5.6%	4
	Dizziness	.	.	2	11.1%	2
	Presyncope	1	2.9%	.	.	1
Metabolism and nutrition disorders	Decreased appetite	.	.	1	5.6%	1
	Dehydration	1	2.9%	.	.	1
	Hypercholesterolaemia	1	2.9%	.	.	1
	Hyperlipidaemia	1	2.9%	.	.	1
	Hyperuricaemia	.	.	1	5.6%	1
Blood and lymphatic system disorders	Anaemia	1	2.9%	1	5.6%	2
	Erythropenia	.	.	1	5.6%	1
Hepatobiliary disorders	Drug-induced liver injury	1	2.9%	.	.	1
	Hepatic function abnormal	.	.	1	5.6%	1
	Hepatocellular injury	1	2.9%	.	.	1
Renal and urinary disorders	Haematuria	1	2.9%	.	.	1
	Leukocyturia	1	2.9%	.	.	1
	Prerenal failure	1	2.9%	.	.	1
Psychiatric disorders	Anxiety	.	.	1	5.6%	1

		Actual Treatment for Period 01				
		Speso 900 mg IV SD		Placebo		
		(N = 35)		(N = 18)		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Total
	Insomnia	.	.	1	5.6%	1
Respiratory, thoracic and mediastinal disorders	Cough	.	.	1	5.6%	1
	Dyspnoea	1	2.9%	.	.	1
Cardiac disorders	Palpitations	.	.	1	5.6%	1
Eye disorders	Eye oedema	1	2.9%	.	.	1
Vascular disorders	Hypotension	.	.	1	5.6%	1

Source: JMP Clinical derived from Applicant provided ADAE dataset, variables: TRT01A, ASPER=1

Table 25: Selected Adverse Reactions Occurring in **≥1%** of the TRADENAME Group and More Frequently than in the Placebo Group through Week 1

Adverse Reaction	**Spesolimab N = 35 n (%)**	**Placebo N = 18 n (%)**
Asthenia and Fatigue*	3 (8.6)	0
Nausea and Vomiting*	3 (8.6)	1 (5.6)
Headache	3 (8.6)	1 (5.6)
Pruritus and prurigo*	2 (5.7)	0
Infusion site hematoma and bruising*	2 (5.7)	0
Urinary tract infection	2 (5.7)	0
Bacteremia	1 (2.9)	0
Bacteriuria	1 (2.9)	0
Cellulitis	1 (2.9)	0
Herpes dermatitis and oral herpes**	1 (2.9)	0
Upper respiratory tract infection	1 (2.9)	0
Dyspnea	1 (2.9)	0
Eye edema	1 (2.9)	0
Urticaria	1 (2.9)	0

Source: reviewer adapted table from Table 24. *=reviewer combined terms, **=same subject, counted as one infection by reviewer

Safety through Week 12: trial 1368-0013

Through Week 12, by randomized treatment (data censored at the time of any non-randomized spesolimab administration, either OL at day 8 or OL rescue after day 8), and by actual treatment for "all" subjects who received at least 1 dose of spesolimab during the randomized and OL phases, adverse events were similar compared to those observed during the first week of randomized spesolimab treatment (see tables Table 26 to Table 28 below). Additional adverse reactions that occurred through Week 12 in subjects treated with 1 single dose of randomized SPEVIGO were mild to moderate infections: device-related infection (3%), subcutaneous abscess (3%), furuncle (3%), and influenza (3%).

Table 26: TEAEs Reported in Treated Subjects Weeks 2-4, trial 1368-0013

		Actual Treatment for Period 01				
		Speso 900 mg IV SD		Placebo		
		(N = 35)		(N = 18)		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Total
Investigations	Alanine aminotransferase increased	1	2.9%	1	5.6%	2
	Aspartate aminotransferase increased	1	2.9%	1	5.6%	2
	Platelet count increased	1	2.9%	1	5.6%	2
	Blood alkaline phosphatase increased	1	2.9%	.	.	1
	Blood creatine phosphokinase increased	1	2.9%	.	.	1
	Blood glucose increased	1	2.9%	.	.	1
	Blood lactate dehydrogenase increased	.	.	1	5.6%	1
	C-reactive protein increased	1	2.9%	.	.	1
	Electrocardiogram PR prolongation	1	2.9%	.	.	1
	Gamma-glutamyltransferase increased	1	2.9%	.	.	1
Skin and subcutaneous tissue disorders	Pustular psoriasis	3	8.6%	.	.	3
	Alopecia	.	.	1	5.6%	1
	Dermatitis	1	2.9%	.	.	1
	Psoriasis	1	2.9%	.	.	1
Musculoskeletal and connective tissue disorders	Arthralgia	1	2.9%	1	5.6%	2
	Joint swelling	.	.	1	5.6%	1
	Myalgia	1	2.9%	.	.	1
	Tendonitis	1	2.9%	.	.	1
Gastrointestinal disorders	Abdominal pain upper	1	2.9%	.	.	1
	Nausea	1	2.9%	.	.	1
	Toothache	1	2.9%	.	.	1
	Vomiting	1	2.9%	.	.	1
Infections and infestations	Device related infection (moderate)	1	2.9%	.	.	1
	Folliculitis	1	2.9%	.	.	1
	Subcutaneous abscess (moderate)	1	2.9%	.	.	1
Blood and lymphatic system disorders	Anaemia	1	2.9%	.	.	1
	Leukocytosis	1	2.9%	.	.	1
Metabolism and nutrition disorders	Hyperglycaemia	1	2.9%	.	.	1
	Hyperlipidaemia	1	2.9%	.	.	1
Nervous system disorders	Headache	1	2.9%	.	.	1
	Paraesthesia	.	.	1	5.6%	1

		Actual Treatment for Period 01				
		Speso 900 mg IV SD		Placebo		
		(N = 35)		(N = 18)		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Total
General disorders and administration site conditions	Asthenia	1	2.9%	.	.	1
Injury, poisoning and procedural complications	Arthropod sting	1	2.9%	.	.	1

Source: JMP Clinical derived from Applicant provided ADAE dataset, variables: ASPER=2 (Week 2-4 analysis sub-period)

Table 27: TEAEs Reported in Treated Subjects Weeks 5-12, trial 1368-0013

		Actual Treatment for Period 01				
		Speso 900 mg IV SD		Placebo		
		(N = 35)		(N = 18)		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Total
Skin and subcutaneous tissue disorders	Pustular psoriasis	6	17.1%	.	.	6
	Drug reaction with eosinophilia and systemic symptoms	1	2.9%	.	.	1
	Psoriasis	1	2.9%	.	.	1
	Urticaria	.	.	1	5.6%	1
Musculoskeletal and connective tissue disorders	Arthralgia	.	.	1	5.6%	1
	Back pain	1	2.9%	.	.	1
	Joint effusion	.	.	1	5.6%	1
	Osteoarthritis	.	.	1	5.6%	1
	Tendonitis	.	.	1	5.6%	1
Infections and infestations	Bacteriuria (mild)*	1	2.9%	.	.	1
	Furuncle (moderate)	1	2.9%	.	.	1
	Influenza (mild)	1	2.9%	.	.	1
	Rhinitis	1	2.9%	.	.	1
Injury, poisoning and procedural complications	Road traffic accident	1	2.9%	.	.	1
	Scratch	1	2.9%	.	.	1
	Skin laceration	1	2.9%	.	.	1
	Tendon injury	.	.	1	5.6%	1
Gastrointestinal disorders	Aphthous ulcer	1	2.9%	.	.	1
	Nausea	1	2.9%	.	.	1
General disorders and administration site conditions	Inflammation	.	.	1	5.6%	1
	Peripheral swelling	1	2.9%	.	.	1
Investigations	High density lipoprotein increased	.	.	1	5.6%	1
Metabolism and nutrition disorders	Hypoglycaemia	1	2.9%	.	.	1
Renal and urinary disorders	Leukocyturia	1	2.9%	.	.	1

Source: JMP Clinical derived from Applicant provided ADAE dataset, variables: ASPER=3 (Week 5-12 analysis sub-period)
*=bacteriuria: same subject as bacteriuria reported in table Table 25, same episode counted twice

Table 28: TEAEs Reported in Treated Subjects Post Week 12, trial 1368-0013

		Actual Treatment for Period 01				
		Speso 900 mg IV SD		Placebo		
		(N = 35)		(N = 18)		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Total
Injury, poisoning and procedural complications	Scratch	1	2.9%	.	.	1
Skin and subcutaneous tissue disorders	Pustular psoriasis	1	2.9%	.	.	1

Source: JMP Clinical derived from Applicant provided ADAE dataset, variables: ASPER=4 (Post Week 12 analysis sub-period)

TEAEs in OL D8 spesolimab and OL rescue spesolimab cohorts in trial 1368-0013

Additional adverse reactions that occurred through Week 17 in subjects treated with a single dose of open-label SPEVIGO at Week 1 (second dose and first dose for subjects in the SPEVIGO and placebo groups, respectively) were mild to moderate infections: otitis externa (7%), vulvovaginal candidiasis (4%), vulvovaginal mycotic infection (4%), and latent tuberculosis (4%), diarrhea (11%), and gastritis (4%). No new adverse reactions were identified for up to 16 weeks in subjects treated with a single dose of open-label rescue SPEVIGO from Week 1 to Week 12 (range 1-3 total doses).

TEAEs by number of doses in trial 1368-0013

The number of subjects who received 1 dose of spesolimab in trial 1368-0013 was 36. The number of subjects who received 2 doses of spesolimab in trial 1368-0013 was 13. The number of subjects who received 3 doses of spesolimab in trial 1368-0013 was 2. While the Applicant determined that the exposure adjusted rates of the adverse reactions did not increase compared to those observed during the first week of randomized spesolimab treatment, this interpretation based on exposure adjusted rates is limited given the small number of subjects in each dose category (i.e. only 2 subjects received 3 doses of spesolimab). No meaningful conclusions can be made based on exposure adjusted rates. Consequently, a statement on exposure adjusted rates in Section 6 Adverse Reactions, Subsection 6.1 Clinical Trial Experience of the PI is not recommended.

Laboratory Findings

For trial 1368-0013, during the controlled period to Week 1, the number of subjects who were within normal range at baseline and then shifted to either below or above limits of normal was generally low. From baseline to end-of-treatment, no marked increases or decreases of mean values were observed for any parameter.

Vital Signs

For trial 1368-0013, at baseline, mean values were generally comparable between the treatment groups. Minimal and maximal changes from baseline on treatment were also comparable across treatment groups during the treatment phase (including REP, but censored at use of any non-randomized spesolimab).

Regarding temperature, baseline mean temperature for placebo group was 37.1 ºC (median 37.1 ºC) and spesolimab group was 37.2 ºC (median 37 ºC) with values decreased from baseline until end of treatment.

Two subjects were reported with AEs related to blood pressure: 1 subject in the placebo group with hypotension and 1 subject in the spesolimab group with increased blood pressure. Based on this single case, it is indeterminate whether this case of increased blood pressure is study drug-related.

Electrocardiograms (ECGs)

In trial 1368-0013, abnormal findings in 12-lead ECG were to be reported as baseline conditions (if identified at screening) or otherwise as AEs if judged clinically relevant by the investigator. One subject, a 21-year old male in the spesolimab group, was reported with an AE related to ECG (PR prolongation).

While prolongation of the PR interval has been associated with increased risks of atrial fibrillation, pacemaker implantation, and all-cause mortality in one study, PR prolongation is a common ECG finding in clinical practice.[32] Based on this single case, it is indeterminate whether this case is related to the study drug.

QT

QT clinical trials were not conducted for spesolimab. The ICH E14 guideline regarding the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs does not specifically address QT assessments for biologic agents. Recent publications, however, indicate a consensus that, because of their large size and high target specificity, monoclonal antibodies such as spesolimab have a very low likelihood for ion channel interactions and therefore thorough QT/QTc studies are not generally needed.

Immunogenicity

See Section 6 Clinical Pharmacology.

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[32] Cheng S, Keyes MJ, Larson MG, et al. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. *JAMA*. 2009;301(24):2571-2577. doi:10.1001/jama.2009.888

8.2.5 Analysis of Submission-Specific Safety Issues

The Applicant conducted safety assessments for Adverse Events of Special Interests (see section Categorization of Adverse Events) and User Defined Adverse Event Category (UDAEC).

Table 29: Definition of UDAEC

UDAEC	Categories
Infections	
Infections all	All of the categories below
Opportunistic infections	Narrow SMQ "Opportunistic infections"
Tuberculosis-related terms	BIcMQ "Infections": Narrow Sub-search 8.2 "Tuberculosis related terms"
Serious infections	SOC "Infections and infestations" – SAEs
Severe infections	SOC "Infections and infestations" – AEs of at least severe RCTC grade
Hypersensitivity	
Hypersensitivity all	All of the categories below
Anaphylactic reaction	Narrow SMQ "Anaphylactic reaction"
Angioedema	Narrow SMQ "Angioedema"
Hypersensitivity	Narrow SMQ "Hypersensitivity"
Malignancies	
Malignant tumours	Narrow Sub-SMQ "Malignant tumours" Narrow Sub-SMQ "Haematological malignant tumours" Narrow Sub-SMQ "Non-Haematological malignant tumours"
Malignant skin tumors	Broad Sub-SMQ "Skin malignant tumours"
Skin melanomas	HLT "Skin melanomas (excl. Ocular)"
Non-melanoma skin cancer (NMSC)	Broad Sub-SMQ "Skin malignant tumours" excluding HLT "Skin melanomas (excl. Ocular)"
Malignancies excluding NMSC	Sub-SMQ "Malignant tumours", excluding NMSC as defined above
3-point MACE	BIcMQ "Major adverse cardiovascular events" in 2 parts with BIcMQ "3-point MACE" Part 1/2 narrow search BIcMQ "3-point MACE" Part 2/2 narrow search associated with a fatal AE
Torsades de pointes	Broad Sub-SMQ "Torsades de pointes/QT prolongation"

Source: Applicant table from 1368-0013 study report body

The Applicant did not conduct additional clinical tests.

Severe, Serious, Opportunistic and Tuberculosis Infections

In trial 1368-0013, there were 3 subjects with reported severe, serious, opportunisitic or tuberculosis infections (PTs urinary tract infection, influenza, and latent tuberculosis).

The subject with the UTI also had reported DILI and DRESS (see section Serious Adverse Events).

Influenza was reported in a subject randomized to spesolimab who also received open-label rescue treatment with spesolimab. The AE was reported 67 days after the first administration of spesolimab and 60 days after the open-label rescue treatment. The AE was reported resolved 19 days later. The AE was classified as serious due to hospitalization. The subject had not received the influenza vaccination. A bacterial superinfection was also reported.

Latent tuberculosis was reported in a subject randomized to placebo who also received open-label rescue treatment with spesolimab, 91 days and 84 days after receiving the placebo and open-label spesolimab, respectively when a planned Quantiferon test during screening for the open-label extension trial 1368-0025 was positive. The AE was classified as non-serious and mild intensity. The subject had no respiratory symptoms or abnormalities on pulmonary function tests and chest X-ray was normal; active tuberculosis was excluded. The subject was treated with isoniazid and rolled over into the open-label extension trial.

In trial 1368-0011, no subject was reported with severe, serious, opportunistic or tuberculosis infections.

In trial 1368-0025 s.c. maintenance, one subject was reported with pneumonia, which was categorized as AESI, and in the UDAEC subsearches severe and serious infections. The subject had rolled over from trial 1368-0013 after 1 randomized 900 mg i.v. spesolimab dose and started maintenance treatment with 300 mg s.c. q12w spesolimab in trial 1368-0025. The pneumonia (reported term: community acquired pneumonia) was reported between the first and second dose (starting 45 days after the first dose and resolved by the second dose on Day 85). It was categorized as serious due to hospitalization and as AESI due to an RCTC grading of 3. The subject continued in the trial and was still ongoing on trial medication (after 5 s.c. doses and approximately 58 weeks).

In trials in other diseases, there was 1 case of severe bacterial pneumonia in trial 1368-0016 and 1-3 cases of AESI and/or UDAEC infections in each of the trials in UC.

Per the SUR, new AEs grouped to serious, severe, or opportunistic infections since the BLA cut-off included tuberculosis in trial 1368-0016, which was based on positive Quantiferon test results without clinical symptoms.

Overall, the Applicant reports a higher proportion of mild to moderate and non-serious but not severe, serious, or opportunistic infections noted after spesolimab than placebo treatment. There were no reported opportunistic infections. There were two reported cases of tuberculosis, two reported cases of pneumonia, one reported case of influenza, and one reported cases of urinary tract infection.

Given the likely causal link between the study drug and general infection risk, it is plausible that the study drug could potentially increase the risk of severe, serious, or opportunistic infections. The risk of infections is an important consideration given that sepsis is a known, potentially life-threatening complication that occurs in GPP. It is recommended that the risk of infections is conveyed in labeling and that severe, serious, and opportunistic infections are evaluated in the post-market setting through pharmacovigilance measures. Additonal information on spesolimab and the risk for infection may also be further characterized in ongoing clinical trials.

Hypersensitivity Reactions

For trial 1368-0013, the systematic UDAEC searches for hypersensitivity and infusion reactions included PTs from 3 SMQs (hypersensitivity, anaphylactic reactions, angioedema). One subject had reported DRESS (see Serious Adverse Events section), one subject had reported urticaria, and one subject had reported eye edema in the spesolimab group up to week 1 (see Treatment Emergent Adverse Events section). An additional one subject had reported DRESS (see Serious Adverse Events subsection), one subject had reported urticaria, and one subject had reported dermatitis post any spesolimab. No cases in the grouping of anaphylactic reactions were reported.

In trial 1368-0011, two subjects had reported eczema and one subject had reported infusion-related reaction.

In trial 1368-0027, per the SUR, two subjects had reported rash and urticaria during the s.c. maintenance period after the BLA cut-off date.

In 1368-0025, no subjects had reported any hypersensitivity events during the i.v. flare treatment period. Four subjects had reported application site urticaria, injection site urticaria, rash, and allergic rhinitis during the s.c. maintenance period. No cases in the groupings of angioedema, infusion reactions, or anaphylactic reactions were reported.

In trial 1368-0025, per the SUR, four subjects had reported acneiform dermatitis, allergic dermatitis, contact dermatitis, and urticarial dermatitis during the first s.c. maintenance period after BLA cut-off date.

In trials in other diseases, AEs grouped to UDAEC systemic hypersensitivity were reported in all non-GPP trials, mostly with nonspecific PTs like rash or eczema per the Applicant's summary of clinical safety.

Overall, there were no reported cases of anaphylactic reactions across the various trials. There was one reported case of angioedema in a subject on blinded treatment (trial 1368-0027; see Section 8.2.4 Safety Results, Subsection Serious Adverse Events). There were two reported cases of DRESS ('no case' and 'possible' under the Regi-SCAR criteria) in trial 1368-0013. There was one reported case of infusion-related reaction in trial 1368-0011 and one case with reported symptoms that may represent an infusion-related reaction (not reported as an AE as an infusion-related reaction) in trial 1368-0013 (this subject also had the reported case of DRESS; see Serious Adverse Events subsection). There were several reported cases of urticaria across the various trials. Otherwise, there were nonspecific reported terms of rash, dermatitis, and eczema across the various trials.

In the general population, DRESS is estimated to occur in 0.9 to 2 per 100,000 patients per year.[33,34] Given the biologic plausible causal link between the study drug and hypersensitivity events, the small amount of pre-market safety data due to the rarity of the disease, and the two reported DRESS cases (one "no case" and one "possible case" under the Regi-SCAR cristeria) in trial 1368-0013, recommend the risk of systemic hypersensitivity be evaluated further in the post-market setting through pharmacovigilance measures. Additional information on spesolimab and the risk for hypersensitivity reactions may also be further characterized in ongoing clinical trials. Additionally, given the one 'possible' case of DRESS by Regi-SCAR criteria, recommend that the risk of DRESS be conveyed in labeling in sections 4 Contraindications, 5 Warnings and Precautions, and 6.1 Clinical Trial Experience/6 Adverse Reactions of the PI (see section SAEs).

Hepatic Injury

In trial 1368-0013, there was one subject with reported drug induced liver injury (DILI) who also had reported DRESS and UTI (see section Serious Adverse Events), 2 days and 1 day after receiving study drug and cefuroxime (which was switched to cefepime the same day for 2 days), respectively. Given the history of prior reaction to cephalosporins, and onset of the AE 1-3 days after dosing, it is more likely that cefuroxime caused both an acute drug eruption and a DILI rather than the study drug.

Liver laboratory parameters were also reviewed by the Applicant for relevant elevations. Six subjects were identified with markedly elevated ALT or AST values, all of them during the controlled period before any open-label spesolimab use: 3 subjects (16.7%) in the placebo group (all with an elevation of ≥3x ULN but <5x ULN) and 3 subjects (8.6%) in the spesolimab group (2 with an elevation of ≥3x ULN but <5x ULN and 1 with an elevation ≥10x ULN). The subject with the ALT elevation of >10x ULN also had reported DRESS ('no case' under the Regi-SCAR criteria) and concomitant cephalosporin use and later reported to have a cephalosporin allergy (see subsection Serious Adverse Events for details). None of these subjects had a marked elevation in AP or total bilirubin, and no subject was categorized as a potential Hy's law case. Of note, laboratory findings in GPP include elevated liver enzymes.

In trial 1368-0011, no subject was reported within AESI hepatic injury or had significant laboratory abnormalities for hepatic laboratory parameters.

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[33] Wolfson AR, Zhou L, Li Y, Phadke NA, Chow OA, Blumenthal KG. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome Identified in the Electronic Health Record Allergy Module. *J Allergy Clin Immunol Pract*. 2019;7(2):633-640. doi:10.1016/j.jaip.2018.08.013

[34] Muller P, Dubreil P, Mahé A, et al. Drug Hypersensitivity Syndrome in a West-Indian population. *Eur J Dermatol*. 2003;13(5):478-481.

In trial 1368-0025 s.c. maintenance, no subject was reported within AESI hepatic injury or had significant laboratory abnormalities for hepatic laboratory parameters.

In trials in other diseases, the Applicant reported a few subjects (1-3 per treatment group) with elevated ALT or AST values (mostly with an elevation of ≥3x ULN but <5x ULN), and mostly in similar frequencies across treatment groups in the placebo-controlled trials. None of these subjects had a reported marked elevation in AP or total bilirubin, and no subject was categorized as a potential Hy's law case.

Based on the available safety data thus far, a causal link between the study drug and hepatotoxic effects is indeterminate at this time.

Cardiac

In trial 1368-0013, one subject in the spesolimab group had reported PT syncope of UDAEC torsades de pointes (reflecting the broad scope of the respective SMQ) following open-label spesolimab administration (i.e. after 2 doses of spesolimab). The event was reported during an open-label rescue treatment on Day 36 (i.e. second dose of spesolimab). The AE was accompanied by hypotension and occurred during study drug infusion. The blood pressure normalized after 10 minutes of infusion interruption and without therapy. This subject also had 'possible' DRESS and symptoms described may be related to an infusion related or hypersensitivity reaction rather than cardiac (see subsection Serious Adverse Events for further details).

In trials 1368-0011 and 1368-0025 s.c. maintenance, no subject had reported events captured under the UDAEC torsades de pointes.

In trials in other diseases, there were 1 or 2 cases per trial in trials 1368-0015, 1368-0016, and 1368-0005 of AEs grouped to torsades de pointes category in which all of the cases the PT was non-serious syncope. Given these cases of syncope reported across various trials for other indications and the case reported in the GPP trial 1368-0013, recommend continued monitoring for the risk of syncope in the ongoing trials and the postmarket setting. In trial 1368-0016, there was a serious case grouped to 3-point MACE (PT cerebral infarction). The subject reported with the serious cerebral infarction was hospitalized for dizziness about 11 weeks after first trial medication administration (spesolimab medium-high dose (600 mg s.c. weekly 5x, 300 mg s.c. q4weeks 3x). During the hospital stay, an MRI scan revealed subacute ischemia lesion and old bilateral multiplex ischemic vascular lesions on both sides in the cranium. The subject did not remember any symptoms which could be associated with these lesions. Both parents of the subject had a history of stroke. The event was treated with piracetam and vinpocetine.

Based on the available safety data thus far, a causal link between the study drug and cardiac effects is indeterminate at this time.

Guillain-Barre Syndrome

On April 25, 2022, the Applicant submitted information on 3 reported Guillain-Barre syndrome (GBS) cases from three non-GPP clinical trials (ulcerative colitis (b) (4) palmoplantar psoriasis [IND 131311] and hidradenitis suppurativa [IND 131311]), (b) (4) The information constituted a major amendment to this BLA. The Division of Neurology (DN1) was consulted and concluded of the 3 reported/submitted GBS cases by the Applicant, there were "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 [from the ulcerative colitis and hidradenitis suppurativa clinical trials]. 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" (see consult review by Dr. Daniel Foster, DO, MPH, MS, dated June 17, 2022). From the consult review:

"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."

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.

DN1 consultant 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.

DN1 consultant 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[35,36]. 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[37]. 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)."

DN1 recommended that the Applicant include the statement, "Among 750 patients exposed to spesolimab during clinical development, two cases of Guillain-Barre syndrome occurred" in Section 6, and remove the Applicant's proposed statement, (b) (4)

[redacted]

[35] Caress, J., Castoro, R., & Simmons, Z. (2020, July). COVID-19-Associated Guillaine-Barre Syndrome: The Early Pandememic Experience. Muscle & Nerve, 62(4), 485-491.
[36] Keddie, S., Pakpoor, J., & Mousele, C. (2021, March). Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. Brain, 144(2), 682-693.
[37] Awong, I., Dandurand, K., & Keeys, C. (1996). Drug-associated Guillain-Barre Syndrome: a literature review. Annals of Pharmacotherapy, 30(2), 173-180.

(b) (4)
and remove the Applicant's proposed statement (b) (4) DN1 also recommended consideration of enhanced pharmacovigilance (PV) in the post-market setting (see section 12 postmarketing requirements and commitments).

For the probable GBS case 1, prior to the AE onset, the subject with hidradenitis suppurativa received spesolimab 1200 mg i.v. weekly (3 doses total) in the parent trial 1368-0052 and 600 mg s.c. (1 dose) followed by 600 mg s.c. every 2 weeks (6 doses total) in the OLE trial 1368-0067. For the probable GBS case 2, prior to the AE onset, the subject with ulcerative colitis received spesolimab 450 mg i.v. every 4 weeks (3 doses total) in the parent trial 1368-0005 and 1200 mg i.v. every 4 weeks (3 doses total) in the OLE trial 1368-0017.

Given that the proposed dosing for GPP will be a single dose of 900 mg administered intravenously, with an option for a second single dose at Week 1 for persistent flare symptoms which differs from the various doses, frequency of dosing, and methods of administration that the two subjects with probable GBS received in clinical trials for the different unapproved indications, it is reasonable to include a description of the two cases of probable GBS in section 6 of the PI rather than section 5 as recommended by DN1 with a plan for enhanced PV (see section 13 Postmarketing Requirements and Commitment).

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

8.2.7 Safety Analyses by Demographic Subgroups

Trial 1368-0013 did not include sufficient numbers of subjects to determine if there are differences in response according to biological sex, age, race, baseline GPPPGA pustulation sub score, baseline GPPPGA total score, and mutation status in IL-36RN.

8.2.8 Specific Safety Studies/Clinical Trials

8.2.9 No specific safety studies outside of the clinical trials were conducted. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Nonclinical data did not identify any suggestive carcinogenic or immunosuppressive potential with spesolimab (see section 5.5.3).

In trial 1368-0013, one subject, who had been randomized to spesolimab, was reported with a malignancy (PT squamous cell skin carcinoma) following open-label spesolimab administration

(i.e. after 2 doses of spesolimab).

The event started 71 days after the first administration of spesolimab on Day 1 and 64 days after open-label treatment on Day 8 and was considered resolved 14 days later following several biopsies. Due to its medical significance, it was considered serious. The patient had a history of acrodermatitis continua of Hallopeau (ACH) covering the entire left hand. Squamous cell carcinoma has been reported to arise in ACH lesions[38] and is less likely to be study drug-related.

In trial 1368-0011, there were no subjects reported with the adverse event of special interest of malignancies.

In trial 1368-0025, one subject was reported with a malignancy (PT adenocarcinoma). The subject had rolled over from trial 1368-0013 and started maintenance treatment with 300 mg s.c. q12w spesolimab in trial 1368-0025. The lung adenocarcinoma (reported term: microinvasive adenocarcinoma) was reported after the first dose (starting 32 days after the first dose and reported as resolved 4 days later). It was categorized as serious due to hospitalization and with RCTC grade 1. The patient had an enlarging pulmonary mass at the time of randomization into 1368-0013. Thus, the malignancy is less likely to be study drug-related. In the SAE report, a smoking history was also mentioned, which had been unknown to the investigator at screening. The patient discontinued treatment because of this AE.

Trials in other diseases: There was 1 case of prostate cancer in trial 1368- 0016 in a subject with PPP randomized to placebo and 1 case of adenocarcinoma of colon in trial 1368-0010 in a subject with ulcerative colitis randomized to spesolimab. The two malignancies are less likely to be study drug-related.

As of the SUR, in trial 1368-0016 for PPP, three subjects had serious malignant tumors (PTs basal cell carcinoma, breast cancer, and colon cancer) which are less likely to be study drug-related.

As of the SUR, in trial 1368-0017 for ulcerative colitis, one subject had adenocarcinoma of colon which is less likely to be study drug-related.

As of the SUR, in trial 1368-0024 for PPP (extension of trial 13686-0016), one subject had squamous cell carcinoma of the right ulnar dorsal hand which is less likely to be study drug-related.

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[38] Sehgal VN, Verma P, Sharma S, et al. Acrodermatitis continua of Hallopeau: evolution of treatment options. *Int J Dermatol*. 2011;50(10):1195–1211. doi:10.1111/j.1365-4632.2011.04993.x

Overall, there were two reported cases of squamous cell carcinoma, two reported cases of adenocarcinoma of colon (both cases in subjects with ulcerative colitis) and one reported case of colon cancer (in a subject with PPP), one reported case of lung adenocarcinoma, one reported case each of basal cell carcinoma and breast cancer.

Based on the available safety data thus far, a causal link between the study drug and human carcinogenicity or tumor development is indeterminate at this time.

Human Reproduction and Pregnancy

Pregnant individuals were excluded from clinical trials across the development program with spesolimab. There were three pregnancies reported across the development program with spesolimab. One resulted in a miscarriage (atopic dermatitis trial 1368-0032), the second, the outcome was a healthy female newborn (palmoplantar pustulosis trial 1368-0016), and the third, the outcome was not available (ongoing double blind GPP trial, 1368-0027, to study GPP flare prevention).

DPMH was consulted for labeling recommendations. Refer to the DPMH consult review by Jean Limpert, MD, dated March 2, 2022. DPMH recommends removal of the Applicant's proposed statement, (b) (4) from section 8.1 Pregnancy of the PI given the available nonclinical data and lack of clinical data do not provide evidence to make this recommendation. Dr. Limpert states in the review, "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." Dr. Limpert also states in the review, "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 (PMR) 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 (https://www.fda.gov/media/124746/download)."

Given the 1) rarity of GPP, 2) anticipated approval for use of spesolimab as a GPP flare treatment, 3) variability in the frequency of flare and remission periods among individuals with GPP, and 4) difficulty assessing or attributing causality to the drug product in the setting of potential use of other off-label therapy as maintenance treatment for stable GPP disease (i.e. methotrexate, acitretin, biologics), some of which are known to be teratogenic (i.e. methotrexate and acitretin), the feasibility and utility of a pregnancy PMR were considered in consultation with DEPI and DPMH. It was determined that it is unlikely that a pregnancy PMR would be feasible and would not be completed within a reasonable timeframe with a sufficient number of subjects to inform any decisions on any potential future regulatory actions. As such, the division will not request a pregnancy PMR.

However, it is important to evaluate the pregnancy outcomes upon exposure to spesolimab given that pregnancy can trigger a GPP flare and untreated pregnant individuals undergoing a GPP flare can have complications from the disease. Thus, recommend enhanced pharmacovigilance to monitor for adverse events in pregnant patients and pregnancy-related outcomes with spesolimab use (see Section 13 Postmarketing Requirements and Commitment, Subsection Pharmacovigiliance and Enhanced Pharmacovigilance (EPV) Plan Memorandum by Dr. Kelly Harbourt, PharmD, BCCP from the Division of Pharmacovigilance I dated August 15, 2022).

Pediatrics and Assessment of Effects on Growth

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

Because this drug product for the GPP indication has an orphan drug designation, the application is exempt from these requirements.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Based on the pharmacodynamic properties of spesolimab, no drug abuse is to be expected and a Controlled Substance Staff (CSS) consultation was not obtained.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable as the drug product has not yet been marketed in any country.

Expectations on Safety in the Postmarket Setting

One important subpopulation not adequately represented in the safety database is pregnant individuals. In the development program for the drug product, pregnant or nursing women or women who planned to become pregnant while in the clinical trials were excluded.

Pregnancy can trigger GPP (impetigo herpetiformis) and the drug product may potentially be used in the postmarket setting in pregnant individuals. Impetigo herpetiformis is associated with an increased risk in morbidity and mortality for both the mother and fetus.[39] The main obstetric risk in impetigo herpetiformis is placental insufficiency, with an increased risk of stillbirth, neonatal death, and fetal abnormalities.[40]

Of note, the IL-36 pathway may have physiological and pathological roles in pregnancy.[41]

See above subsection Human Reproduction and Pregnancy for discussion on evaluation of safety in the postmarket setting.

One additional potential safety issue that could cause concern when considering how the drug may be used in the postmarket setting is the risk of DRESS and other systemic hypersensitivity events. During trial 1368-0013, two cases of DRESS were reported (see Serious Adverse Events section), one case classified as "no case" and the other case classified as "possible" under the Regi-SCAR criteria. DRESS is estimated to occur in 0.9 to 2 per 100,000 patients per year,[42,43] The mortality rate among patients with DRESS is estimated to be between 2 and 10%.[44,45,46,47]

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[39] Oumeish OY, Parish JL. Impetigo herpetiformis. *Clin Dermatol*. 2006;24(2):101-104. doi:10.1016/j.clindermatol.2005.10.009

[40] Lotem, M., Katzenelson, V., Rotem, A., et al. Impetigo herpeti-formis: a variant of pustular psoriasis or a separate entity?, J. Am. Acad. Dermatol. 1989; 20: 338–341.

[41] Murrieta-Coxca JM, Rodríguez-Martínez S, Cancino-Diaz ME, Markert UR, Favaro RR, Morales-Prieto DM. IL-36 Cytokines: Regulators of Inflammatory Responses and Their Emerging Role in Immunology of Reproduction. Int J Mol Sci. 2019;20(7):1649. Published 2019 Apr 3. doi:10.3390/ijms20071649

[42] Wolfson AR, Zhou L, Li Y, Phadke NA, Chow OA, Blumenthal KG. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome Identified in the Electronic Health Record Allergy Module. *J Allergy Clin Immunol Pract*. 2019;7(2):633-640. doi:10.1016/j.jaip.2018.08.013

[43] Muller P, Dubreil P, Mahé A, et al. Drug Hypersensitivity Syndrome in a West-Indian population. *Eur J Dermatol*. 2003;13(5):478-481.

[44] Kardaun SH, Sekula P, Valeyrie-Allanore L, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *Br J Dermatol*. 2013;169(5):1071-1080. doi:10.1111/bjd.12501

[45] Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. *Arch Dermatol*. 2010;146(12):1373-1379. doi:10.1001/archdermatol.2010.198

[46] Cacoub P, Musette P, Descamps V, et al. The DRESS syndrome: a literature review. *Am J Med*. 2011;124(7):588-597. doi:10.1016/j.amjmed.2011.01.017

[47] Chiou CC, Yang LC, Hung SI, et al. Clinicopathological features and prognosis of drug rash with eosinophilia and systemic symptoms: a study of 30 cases in Taiwan. *J Eur Acad Dermatol Venereol*. 2008;22(9):1044-1049. doi:10.1111/j.1468-3083.2008.02585.x

Another potential safety issue that could cause concern when considering how the drug may be used in the postmarket setting is the risk of serious infections. An increased risk of infections was noted in trial 1368-0013 (see Treatment Emergent Adverse Events and Adverse Reaction section).

One other emerging safety signal is the risk of GBS that was identified in the other trials for other indications.

Finally, one potential important difference in how the drug was administered and used in the clinical trial (i.e. rescue treatment with study drug could be administered up to 12 weeks with a limit of 3 total doses during the trial) versus its expected use in the postmarket setting that could lead to increased risk, is the potential for multiple, repeat dosing for GPP reoccurrence and the unknown effect of immunogenicity on efficacy and safety (see immunogenicity section).

See section 13 Postmarketing Requirements and Commitment for further discussion.

8.2.11 Integrated Assessment of Safety

Important safety issues and limitations regarding safety identified during the review of this application include the unknown effects of immunogenicity on safety (and efficacy) upon subsequent repeat dosing, the small number of trial participants with GPP who received i.v. flare treatment due to the rarity of the disease limiting the safety database (80 subjects total which includes subjects from the open-label section of the trial/trials), the short duration of the randomized, placebo-controlled period (i.e. 1 week) for trial 1368-0013 limiting the comparison between AE rates between the study drug and the placebo groups, the lack of dose-ranging evaluation for the i.v. flare treatment of GPP throughout the development program, and the unknown risks of the study drug in pregnancy, on systemic hypersensitivity, on serious infections, and on GBS.

There are no other therapies approved for the treatment of GPP flares in adults. Most of the safety issues identified is based on the remaining uncertainties that exist with the study drug. However, based on the available safety data, no significant safety concerns were identified that would preclude the approval of the study drug for the treatment of GPP flares in adults, particularly given the demonstration of efficacy of the study drug on a serious disease such as GPP (see section Integrated Assessment of Effectiveness). Risk mitigation strategies to address these safety concerns can be utilized through labeling and in the post-market setting.

8.3 Conclusions and Recommendations

To establish the effectiveness of spesolimab, the Applicant submitted data from one adequate and well-controlled trial [Trial 1368-0013 (Effisayil-1)]. The trial's key inclusion criteria included

subjects 18 to 75 years of age who had a diagnosis of GPP based on the consensus diagnostic criteria defined by the European Rare and Severe Psoriasis Expert Network (ERASPEN) (see Section 8.1.1 Study Design and Endpoints), subjects with a GPPPGA score of 0 or 1 and a known and documented history of GPP (per ERASPEN criteria) regardless of IL36RN mutation status, and in addition with previous evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leucocytosis with peripheral blood neutrophilia (above ULN) OR subjects with 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 IL36RN mutation status, and in addition with previous evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leucocytosis with peripheral blood neutrophilia (above ULN) OR subjects with 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 leucocytosis with peripheral blood neutrophilia (above ULN). For these subjects, the diagnosis was to be confirmed retrospectively by a central external expert/committee. The Effisayil-1 trial assessed the changes from baseline flare to Week 1 compared to placebo in the primary efficacy endpoint: the proportion of subjects with a GPPPGA pustulation sub score of 0 (indicating no visible pustules) at Week 1 after treatment. Spesolimab was statistically superior to placebo for the primary efficacy endpoint (one-sided p-value = 0.0004).

Clinically, supportive evidence derived from trials 1368-0011 (phase 1, completed), 1368-0025 (phase 2, ongoing), and 1368-0027 (phase 2, ongoing) (see 7.1 Table of Clinical Studies). In Trial 1368-0011, although not defined as an efficacy endpoint in trial 1368-0011, the proportion of subjects with a GPPPGA pustulation subscore of 0 at Week 1was 71.4% (5/7 subjects). In trial 1368-0025, of the 9 subjects who received i.v. flare treatment, 5 subjects (55.6%) achieved a GPPPGA pustulation subscore of 0 on Day 8 in their first flare treatment period. In trial 1368-0027, of the 6 subjects who received i.v. flare treatment, 5 subjects (83.3%) achieved a GPPPGA pustulation subscore of 0 on Day 8.

The Applicant conducted an acceptable assessment of the safety of spesolimab in the target population for the limited indication of GPP flare. The size of the safety database and the safety evaluations were adequate, particularly given the context of the rarity of the disease.

Submitted safety and efficacy data support approval of this BLA for spesolimab for the treatment of generalized pustular psoriasis flares in adults, a potentially life-threatening, painful and debilitating rare disease with an unmet medical need.

9 Advisory Committee Meeting and Other External Consultations

The application was not presented to an Advisory Committee or other external consult.

10 Pediatrics

The application included data from studies of spesolimab in the treatment of GPP flare conducted in adults. Orphan drug designation was granted to the Applicant for this product for the treatment of generalized pustular psoriasis on October 03, 2018; this application is therefore exempt from the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c).

11 Labeling Recommendations

11.1 Prescription Drug Labeling

Prescribing information
The Applicant submitted proposed Prescribing Information (PI) and carton/container labels for SPEVIGO (spesolimab) injection. The Applicant's PI that was reviewed was received by the Agency on January 3, 2022. The review team provided recommendations regarding the PI which are provided throughout this review and summarized in the table below. The Division of Pediatric and Maternal Health (DPMH) reviewed and provided comments regarding the PI (Refer to the DPMH review by Jean Limpert, MD, dated March 2, 2022). The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the PI (Refer to the OPDP review by Laurie Buonaccorsi, PharmD, dated March 28, 2022). The Division of Medical Policy Programs (DMPP) Patient Labeling reviewed and provided comments regarding the Applicant's proposed Medication Guide (MG) and PI (Refer to the OPDP and DMPP review by Ruth Mayrosh, PharmD, and Laurie Buonaccorsi, PharmD, dated March 29, 2022). These comments are reflected in final labeling. Labeling negotiations are currently ongoing and final agreed upon labeling will be attached to the action letter.

Summary of Significant High Level Labeling Changes	
Section	Additional Comments
2 Dosage and Administration	-Refer to section 8.1.2. Study Results, Subsection Additional Analyses Conducted on the Individual Trial of this review. -Added recommendation for evaluation of active tuberculosis and test for latent tuberculosis before drug initiation given such information is critical to the safe and effective use of the drug.
4 Contraindications	-Given that a "possible" case of DRESS by Regi-SCAR criteria was reported in trial 1368-0013 and given that DRESS is a severe or life-threatening hypersensitivity, included the specific hypersensitivity reaction (i.e. DRESS) that was observed in the clinical trials to 4 Contraindications and cross-referenced to a more detailed discussion in section 5 of the PI per the W&P guidance. Refer to sections 8.2.4 Safety Results, Subsection Serious Adverse Events and 8.2.5 Analysis of Submission-Specific Safety Issues, Subsection Hypersensitivity Reactions of this review.

5 Warnings and Precautions	-Refer to section 8.2.4. Safety Results, subsection Treatment Emergent Adverse Events and Adverse Reactions of this review for discussion on subsection 5.1 Infections of the PI. -Recommend inclusion of description of two reported cases of DRESS from trial 1368-0013 under subsection 5.3 Hypersensitivity and Infusion-Related Reactions of the PI. Refer to sections 8.2.4. Safety Results, Subsection Serious Adverse Events and 8.2.5. Analysis of Submission-Specific Safety Issues, Subsection Hypersensitivity Reactions of this review. -Regarding section 5.4 Vaccination of the PI: 1) Considered recommending addition of the statement, "Consider completing all age-appropriate vaccinations as recommended by current immunization guidelines prior to initiating treatment with SPEVIGO" to the Applicant, however, given that the indication is for GPP flare, and the drug would be given on an immediate/urgent basis as flare treatment, this consideration is less practical or applicable. Could consider addition of such a statement in the future if the indication were to change. 2) No formal drug-drug interaction studies were conducted. No specific studies were conducted in spesolimab-treated patients who had recently received live viral or live bacterial vaccines. Recommend omission of the Applicant's proposed (b) (4) [redacted] -Refer to section 8.2.5 Analysis of Submission-Specific Safety Issues, subsection Guillain-Barre syndrome.
6 Adverse Reactions	-Refer to section 8.2.2. Review of the Safety Database, Subsection Overall Exposure and

	section 8.2.4 Safety Results, Subsection Treatment Emergent Adverse Events and Adverse Reactions of this review for discussion on subsection 6.1 Clinical Trial Experience of the PI. -Refer to section 8.2.5 Analysis of Submission-Specific Safety Issues, subsection Guillain-Barre syndrome.
7 Drug Interactions	-Given that no formal drug interactions studies were conducted with the drug product, recommended omission of this section. Refer to section 6.3.2. Clinical Pharmacology Questions of this review.
8 Use in Specific Populations	-Refer to section 8.2.9 Additional Safety Explorations, Subsection Human Reproduction and Pregnancy of this review. -DPMH recommends removal of the Applicant's proposed statement, (b) (4) from section 8.1 Pregnancy of the PI. -Refer to subsection 19.3.2 Nonclinical labeling of this review for discussion on section 8.1 Pregnancy of the PI. -Refer to section 8.2.2 Review of the Safety Database, Subsection Relevant characteristics of the safety population of this review for discussion on section 8.5 Geriatric Use of the PI.
10 Overdosage	-Given that no specific overdosage data were available in the application or identified in the literature, recommended omission of this section per the labeling tool.
12 Clinical Pharmacology	-Refer to section 6 of this review.
14 Clinical Studies	-Added a description of the number of trial subjects in trial 1368-0013 who had systemic symptoms according to WBC and temperature at flare/randomization. Refer to section 8.1.2 Study Results, Subsection Other Baseline characteristics (e.g. disease characteristics, important concomitant drugs) of this review.

	-Given that the GPPPPGA total score is a calculated mean score of erythema, pustulosis, and scaling/crusting and was mainly driven by the one component, pustulosis, results for GPPPGA total score will not be included in labeling. -Given that starting at Week 1, subjects in trial 1368-0013 were eligible to receive OL spesolimab at Week 1 or OL rescue spesolimab after Week 1 to Week 12, interpretation of the analyses after Week 1 is limited and results for GPPPASI and PROs at Week 4 will not be included in labeling. -The trial 1368-0013 did not include sufficient numbers of subjects to determine if there are differences in response according to biological sex, age, race, baseline GPPPGA pustulation sub score, baseline GPPPGA total score, and mutation status in IL-36RN. -Removed Applicant's proposed statements (b) (4)
17 Patient Counseling Information	-Recommend omission of the Applicant's proposed (b) (4) -Refer to section 8.2.5 Analysis of Submission-Specific Safety Issues, subsection Guillain-Barre syndrome.

12 Risk Evaluation and Mitigation Strategies (REMS)

Risk mitigation measures beyond professional labeling and a Medication Guide are not warranted at this time. Under 21CFR208.1, the Medication Guide is required to help prevent serious adverse effects. See Section 11 Labeling Recommendations. As no additional risk management strategies are required, this section is not applicable for this review.

13 Postmarketing Requirements and Commitment

Clinical postmarketing requirements are intended to characterize the risks of spesolimab use and address the long-term safety of this novel biologic product in the target population.

(b) (4)

Based on review of the data in the submission, the following postmarketing requirements (PMRs) were conveyed to the Applicant:

POSTMARKETING REQUIREMENTS UNDER 505(o)
PMR 1:

1. Conduct an open label safety study to assess the effect of immunogenicity on pharmacokinetics (PK), safety, and efficacy on re-treatment of flares that occur after the first flare incidence has been treated and resolved.

PMR 2:

1. Submit the final study reports with safety results from ongoing trials 1) Effisayil-2 (clinicaltrials.gov identifier: NCT04399837, other study ID number: 1368-0027): Multi-center, Randomized, Parallel Group, Double Blind, Placebo Controlled, Phase IIb Dose-finding Study to Evaluate Efficacy and Safety of BI 655130 (Spesolimab) Compared to Placebo in Preventing Generalized Pustular Psoriasis (GPP) Flares in Patients With History of GPP and 2) Effisayil-ON (clinicaltrials.gov identifier: NCT03886246, other study ID number: 1368-0025): An Open-label, Long Term Extension Study to Assess the Safety and Efficacy of BI 655130 Treatment in Patients With Generalized Pustular Psoriasis (GPP).

PMR 3:

1. Submit the final study report for the planned voluntary European Post-Authorization Safety Study (PASS).

Pharmacovigilance Plan

DDD requested assistance from the Division of Pharmacovigilance (DPV) to develop a pharmacovigilance plan for AESIs of serious infection and hypersensitivity (including DRESS, anaphylaxis, and infusion related reactions). Options considered for postmarketing surveillance include enhanced pharmacovigilance vs. routine pharmacovigilance.

1) The proposed plan for enhanced pharmacovigilance includes the following:

Proposed Enhanced Pharmacovigilance Plan (EPV)
Adverse events of special interest (AESIs):

- Serious infections and hypersensitivity events including DRESS (drug reaction with eosinophilia and systemic symptoms)

EPV Activities:
"We request enhanced pharmacovigilance (EPV) to monitor the safety of SPEVIGO beyond routine pharmacovigilance. Provide the following in each quarterly periodic report for the first 3 years post approval then reevaluate the need to continue EPV thereafter:

A summary, assessment, and listing of cases of all serious infections and hypersensitivity events including DRESS in your global safety data system from the time of approval through the end of the reporting time.

The summary should include the following:

- Total number of unique cases of serious infection and hypersensitivity events, including DRESS by time period covered by periodic report and cumulative since approval
- Patient outcome
    - For fatal cases, provide cause of death
    - For non-fatal cases, provide the following:
        - Admitted to hospital, prolonged hospitalization or required medical intervention but not hospitalized (i.e., visit to the emergency department)
        - Include any medical intervention(s) required
- Age (Mean, Range)
- Sex
- Indication for SPEVIGO, including date of onset of signs/symptoms and date of diagnosis
- Dosage of SPEVIGO
- Route of administration of SPEVIGO
- Dates of administration of SPEVIGO
- Number of doses of SPEVIGO administered prior to AESI in question
- Time to AESI after SPEVIGO administration
- Concurrent and past medical history
- Concomitant medications (list all, including prescription medications [indication, dosage], non-prescription medications, and illicit substances)
- Action taken with SPEVIGO (including, but not limited to, dose modifications, discontinuation, pause in therapy)
- Include outcome after action taken, i.e., dechallenge/rechallenge information

In addition to the summary and assessment in each periodic report, provide narrative of report and above data including the respective manufacturer control number for each case, in .xlsx format.

In addition to submitting adverse experience reports per the requirements set forth in 21 CFR 314.80, we request that you report each case of serious infection or hypersensitivity events including DRESS to the FDA within 15 days from your initial receipt of the information (i.e., expedited reporting). Every effort should be made to obtain thorough and complete follow-up, assessments, or evaluations of patients with any events related to serious infections or hypersensitivity events, including DRESS. 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."

2) The option for routine pharmacovigilance includes the following activities:

- monitoring the FDA Adverse Event Reporting System (FAERS) inbox for new adverse event reports received by the FDA in the past 7 days (weekly);
- reviewing scheduled weekly queries for medical literature publications (weekly);

- reviewing periodic safety reports for select products (i.e., NMEs, new BLAs) (periodically);
- conducting disproportionality analysis (i.e., datamining) in Empirica Signal (periodically);
- reviewing potential safety signals or recent actions taken by foreign regulatory agencies (periodically)

DPV recommends that routine pharmacovigilance activities would suffice to detect additional cases of the AESIs per above and DDD concurs with DPV's recommendations for routine pharmacovigilance for these AESIs.

On April 25, 2022, the Applicant submitted information on Guillain-Barre syndrome (GBS) cases from three non-GPP clinical trials. The information constituted a major amendment to this BLA. See Section 8.2.5 Analysis of Submission-Specific Safety Issues, Subsection Guillain-Barre syndrome. Enhanced pharmacovigilance for GBS was recommended by the consultant reviewer from the Division of Neurology and DDD concurs with DN1's recommendations for enhanced pharmacovigilance for GBS. DPV provided the following enhanced pharmacovigilance plan language for the Applicant (see Enhanced Pharmacovigilance (EPV) Plan Memorandum by Dr. Kelly Harbourt, PharmD, BCCP from the Division of Pharmacovigilance I dated August 15, 2022):

> 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.*

It will also be important to evaluate pregnancy outcomes upon exposure to spesolimab given that pregnancy can trigger a GPP flare and untreated pregnant individuals undergoing a GPP

flare can have complications from the disease. Thus, recommend enhanced pharmacovigilance to monitor for adverse events in pregnant patients and pregnancy-related outcomes with spesolimab use (see Enhanced Pharmacovigilance (EPV) Plan Memorandum by Dr. Kelly Harbourt, PharmD, BCCP from the Division of Pharmacovigilance I dated August 15, 2022). DPV provided the following enhanced pharmacovigilance plan language for the Applicant:

> 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.

DDD agrees with the plan for enhanced pharmacovigilance as provided by DPV to evaluate pregnancy outcomes upon exposure to spesolimab in the postmarket setting.

14 Division Director (DPT-IIHOT) Comments

Not applicable.

15 Division Director (OCP) Comments

Not applicable.

16 Division Director (OB) Comments

Not applicable.

17 Division Director (Clinical) Comments

BLA 761244 was submitted through the 351(a) regulatory pathway by the applicant for SPEVIGO (spesolimab) intravenous product in support of an indication for the treatment of flares in adult patients with generalized pustular psoriasis (GPP). Spesolimab is a humanized monoclonal immunoglobulin G1 antibody that inhibits interleukin-36 (IL-36) signaling by specifically binding to the IL-36 receptor (IL36R). Binding of spesolimab to IL36R prevents the subsequent activation of IL36R by cognate ligands (IL-36 α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways.

Generalized pustular psoriasis (GPP) is a rare, potentially life-threatening dermatological disease that presents with widespread sterile pustules with or without systemic symptoms and with or without a history of psoriasis. The clinical course is mostly chronic with unpredictable relapsing and remitting periods of flares over several years. Life-threatening complications can occur and include sepsis, neutrophilic cholangitis, neutrophilic pneumonitis, acute respiratory distress syndrome, renal abnormalities, and death. No approved treatments for GPP are currently available in the United States, although several treatments are used off-label.

In support of this application, the sponsor conducted 4 phase 1 clinical pharmacology studies in healthy subjects and 3 studies in GPP patients. Study 1368-0011 was a proof-of-concept study in (N=7) GPP patients. Pivotal efficacy was evaluated in a Phase 2 study (1368-0013) in (N=53) GPP patients. Study 1368-0025 is an ongoing open-label extension evaluating spesolimab for flare prevention that voluntarily enrolled subjects from Study 1368-0013.

Study 1368-0013, the primary study supporting efficacy, was a randomized, multicenter, double-blind, placebo-controlled trial to evaluate the safety, efficacy, and tolerability of a single 900 mg intravenous dose of spesolimab (BI 655130) compared with placebo in subjects with GPP presenting with an acute flare. At the Day 8 visit, the primary and key secondary efficacy

endpoints were assessed. Subjects who did not receive escape treatment for worsening of disease between Days 1 and 8, and who had a GPPPGA total score ≥ 2 at Day 8 and a GPPPGA pustulation sub-score of ≥ 2 at Day 8 were eligible to receive treatment with a single open-label i.v. dose of 900 mg of spesolimab.

Spesolimab was statistically superior to placebo for the primary efficacy endpoint of proportion of subjects with GPPPGA Pustulation Score of 0 at Day 8 (54.3% versus 5.6%, p-value=0.0004). Subjects who did not receive standard-of-care escape treatment and who had a GPPPGA total score ≥ 2 at Day 8 and a GPPPGA pustulation sub-score of ≥ 2 at Day 8 were eligible to receive treatment with a single open-label dose of 900 mg of spesolimab. A total of 15 (83%) subjects treated with placebo on Day 1 received open-label spesolimab on Day 8 and 12 (34%) subjects treated with spesolimab on Day 1 received open-label spesolimab on Day 8. Secondary endpoints were generally supportive of the primary efficacy finding. Due to the small trial size, differences in response across subgroups could not be reliably assessed.

The primary safety database which consisted of data from trial 1368-0013, was considered adequate to characterize the safety profile of SPEVIGO (spesolimab) injection. Of note, there is limited safety data when comparing spesolimab to placebo as the duration for the randomized, double-blind period for trial 1368-0013 was 1 week. At week 1/day 8, all trial participants who had GPPGA total score ¬>2 and GPPGA pustulation subscore >2 were eligible to receive open-label, single-dose spesolimab 900 mg intravenously. Given the rarity of GPP and the limitations of safety data from trial 1368-0013, safety was also informed by auxiliary safety cohorts, i.e. exposure of subjects to spesolimab in other developmental programs for other diseases and healthy volunteers at various doses and dosage forms (subcutaneous and intravenous). Based on the analysis of the submitted data, treatment with spesolimab did not appear to increase the risk of mortality. No deaths were reported in the trials for GPP. Serious adverse events included a case of drug reaction with eosinophilia and systemic symptoms (DRESS) in a subject exposed to spesolimab in trial 1368-0013 and two probable cases of Guillain-Barre syndrome reported in other spesolimab development programs. The risk of DRESS and GBS will be conveyed in product labeling. Infections such as urinary tract infections, bacteremia, bacteriuria, cellulitis, herpes dermatitis and oral herpes, and upper respiratory infection occurred more frequently in subjects who received spesolimab compared to subjects who received placebo (14% vs 6% through Week 1). Other adverse reactions, occurring in >1% and observed more frequently in subjects receiving spesolimab through Week 1, included asthenia and fatigue, nausea and vomiting, headache, pruritis and prurigo, infusion site hematoma and bruising, dyspnea, eye edema, and urticaria. These identified adverse reactions will be conveyed in product labeling.

In GPP patients treated with IV spesolimab, anti-drug antibodies (ADAs) were formed in 46% of patients by Week 12-17 with a median onset of 2.3 weeks. Among ADA-positive patients, those with ADA titer values greater than 4000 (24%), were observed to have significantly decreased plasma spesolimab concentrations from Week 3 onward. In patients with ADA titers below 4000, spesolimab PK was similar to ADA negative patients. ADA development did not impact the efficacy or safety of treatment of a first flare in Study 1368-013 as ADAs generally did not

develop until after treatment and resolution of a flare. The impact of ADAs on safety or efficacy for subsequent flares that are treated with spesolimab is unknown due to the limited number of patients (N=9) who experienced a recurrent flare in Study 1468-0025 to-date.

In Study 1368-0025, 39 patients were rolled-over from Study 1368-0013. Of 39 patients that were rolled over, 9 patients experienced a recurrent flare and were treated with IV spesolimab as of the time of BLA submission. Upon re-exposure to spesolimab, ADA+ patients experienced mean reductions in AUC and Cmax of approximately 75% and 10%, respectively, compared to their mean exposures in Study 1368-0013. The sponsor will be required to conduct a postmarketing study to assess the effects of immunogenicity on retreatment of GPP flares.

I concur with the review team's recommendation to approve spesolimab for the treatment of flares in adults with GPP. Spesolimab will provide a treatment option for patients with this chronic, serious and potentially life-threatening disease.

18 Office Director Comments

I concur with the recommendation of the Division of Dermatology and Dentistry to approve BLA 761244 for SPEVIGO (spesolimab-sbzo) injection for the treatment of flares in adults with generalized pustular psoriasis (GPP), a rare and potentially life-threatening dermatologic condition. Spesolimab is a humanized monoclonal immunoglobulin G1 antibody that inhibits interleukin-36 signaling thereby preventing subsequent activation of pro-inflammatory and pro-fibrotic pathways thought to be responsible for disease flares. The recommended dose is a single 90-minute intravenous infusion of 900 mg. If flare symptoms persist, an additional intravenous 900 mg dose may be administered 1 week after the initial dose. Spesolimab is a new molecular entity and was granted Breakthrough Designation. It represents the first drug approved in the U.S. for this condition.

The efficacy of spesolimab was demonstrated in Trial 1368-0013, a randomized, multicenter, double-blind, placebo-controlled trial conducted in 53 adults with GPP presenting with an acute flare. Spesolimab was statistically superior to placebo for the primary efficacy endpoint of the proportion of subjects with a Physician's Global Assessment for Generalized Pustular Psoriasis (GPPPGA) Pustulation Score of 0 (clear) at Day 8 (54.3% versus 5.6%). There were 12 non-responding spesolizumab-treated subjects who met protocol-specified criteria to receive a second 900 mg dose at Day 8. Of these, 5 (or 41.7%) subjects had a GPPPGA Pustulation Score of 0 at Day 15. Secondary endpoint findings were generally supportive of the primary efficacy finding. The application also included supportive efficacy data from a small number subjects achieving a GPPPGA Pustulation Score of 0 at Day 8 in a completed Phase 1 trial and in two ongoing Phase 2 trials of spesolimab.

Assessment of the safety of spesolimab in GPP subjects was supplemented by information on exposures to the drug in other trial populations, including ulcerative colitis and hidradenitis suppurativa. Spesolimab was generally well tolerated; common adverse reactions were asthenia and fatigue, nausea and vomiting, headache, pruritus and prurigo, infusion site hematoma and bruising, and urinary tract infection. A possible case of drug reaction with eosinophilia and systemic symptoms (DRESS) was reported in a spesolimab-treated subject in Trial 1368-0013. In addition, there were two probable cases of Guillain-Barre syndrome in spesolimab-treated subjects receiving other regimens for other conditions. Although the occurrence of two cases among 750 exposed subjects represents an unexpected finding, the regimens in these cases differed substantially from that recommended for GPP flares.

The applicant has agreed to conduct enhanced pharmacovigilance post-approval to better describe the occurrence of serious infections, hypersensitivity events including DRESS, and Guillain-Barre syndrome, and of possible exposure to spesolimab in pregnant patients, patients who are lactating, and infants exposed through breastmilk or infants who were exposed while in utero. In addition, the applicant will be required to conduct a clinical study to assess the effect of immunogenicity on the pharmacokinetics, safety, and efficacy on re-treatment of GPP flares that occur after the first flare has been treated and has resolved.

19 Appendices

19.1 References

The majority of the references are included in footnotes.

19.2 Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical studies for spesolimab. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 32 CFR 54.4(a)(3)(i-iv).

The covered clinical studies as defined in 21 CFR 54.2(e) were trials 1368-0013 and 1368-0011, which provided the primary data to establish effectiveness and safety of this product for the proposed indication. Refer to Section 8.1.1 for the trial designs and Section 8.2.1 for the safety review approach.

Covered Clinical Study (Name and/or Number): 1368-0013

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: 37		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not applicable (N/A) Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in S Sponsor of covered study: N/A		
Is an attachment provided with details	Yes ☐	No ☐ (Request details from

of the disclosable financial interests/arrangements: N/A		Applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 1368-0011

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: 6		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not applicable (N/A) Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in S Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

19.3 Nonclinical Pharmacology/Toxicology

19.3.1 Calculations for multiples of exposures

The pivotal studies including the 6-month repeat-dose intravenous toxicity study in mice and reproductive and developmental toxicology studies were conducted with the mouse surrogate antibody BI 674304. Therefore, calculations for multiples of exposures for spesolimab are not appropriate.

19.3.2 Nonclinical labeling

Recommended changes to nonclinical information in sections 8.1, 12.1, and 13.1 of the Applicant's proposed labeling are provided below. The pharmacologic class for spesolimab is Interleukin-36 receptor antagonist. Although the Applicant provided nonclinical data to factually support statements made in section 12.1, several portions are of unclear relevance to the mechanism of action and should be removed. Reviewer-recommended deletions and additions are indicated by ~~strike through~~ and <u>underlined</u> text, respectively.

(b) (4)

(b) (4)

19.4 OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1 Bioanalytical Methods to Assess Spesolimab Plasma Concentrations

The methodologies used in the analysis of biological samples were sensitive, robust, and fully validated. A first-generation PK assay using an ELISA method was developed and validated by (b) (4) was used to measure the concentration of spesolimab in Study 1368-001. The lower limit of quantification of the ELISA method was 10 ng/mL in neat human plasma. Subsequently, the PK method was re-developed based on the FDA Bioanalytical Method Validation Guidance for Industry (2018). The updated GyroLab PK assay used a blocking anti-spesolimab monoclonal antibody capture and detection GyroLab method to determine spesolimab concentration in all other clinical studies. Overall, the incurred sample reanalysis (ISR) was conducted on 90 plasma samples with 78 of the 90 samples (86.7%) passing acceptance criteria.

Summary of GyroLab Bioanalytical Validation Method

Method Description	GyroLab™	
Reference standard used for calibration curve and QCs	DS02 concentration: 20.0 mg/mL DS03 concentration: 59.9 mg/mL PRS01 concentration: 60.1 mg/mL	
Validated Assay Range	20 ng/mL -10,000 ng/mL	
Minimum Required Dilution	1:20	
Source and Lots of Critical Reagents	Capture Reagent: Lot# V170105VF-01, Radix Detection Reagent: Lot# 10949:038A and Lot# 400024-Alexa647, Boehringer Ingelheim	
Regression Model and weighting	5 parameter marquardt, $1/Y^2$	
Validation	Method Validation Summary	
Standard Calibration Curve Performance during accuracy	# Number of standard Calibrators from LLOQ and ULOQ	8

and precision runs	Overall Range of accuracy (% RE) from LLOQ and ULOQ	-2.0 to 4.4
	Overall Range of precision (% CV) from LLOQ and ULOQ	2.2 to 7.6
Performance of QCs during accuracy and precision runs	Overall Range of accuracy (% RE) in 5 QCs	4.0 to 16.0
	Overall Range of Inter-batch precision (%CV)	6.1 to 9.5
	Overall Range Total Error (%TE)	10.6 to 24.8
Selectivity (10 normal/healthy volunteer (HV) lots spiked at 20.0 and 10000 ng/mL)	100% unspiked lots tested BQL, 100% lots tested within 100±25.0% Recovery for the LLOQ and 100% lots tested within 100±20.0% for the ULOQ	
Selectivity (10 GPP lots spiked at 20.0 and 10000 ng/mL)	100% unspiked lots tested BQL, 80% lots tested within 100±25.0% Recovery for the LLOQ and 100% lots tested within 100±20.0% for the ULOQ	
Selectivity (10 PPP lots spiked at 20.0 and 10000 ng/mL)	90% unspiked lots tested BQL, 90% lots tested within 100±25.0% Recovery for the LLOQ and 100% lots tested within 100±20.0% for the ULOQ	
Selectivity (10 UC lots spiked at 20.0 and 10000 ng/mL)	100% unspiked lots tested BQL, 85% lots tested within 100±25.0% Recovery for the LLOQ and 100% lots tested within 100±20.0% for the ULOQ	
Selectivity (10 AD lots spiked at 20.0 and 10000 ng/mL)	90% unspiked lots tested BQL, 89.5% lots tested within 100±25.0% Recovery for the LLOQ and 100% lots tested within 100±20.0% for the ULOQ	

Interference and Specificity	No interference observed up to 1000 µg/mL with Humira®, Remicade® and Dupixent®, Entyvio®, Simponi® and Stelara®
Target (IL36R) Interference[a]	No interference at the blank up to 1000 ng/mL of IL36R. Interference at LLOQ was observed at 10.0 ng/mL up to 1000 ng/mL of IL36R.
Assessment for potential ADA interference using three monoclonal and one polyclonal antibodies generated against Spesolimab which block the binding of Spesolimab to IL-36R.	Anti-spesolimab antibody interference was tested at various ratios concentrations of 1:1 to 1:16 (20 to 320 ng/mL) at the spesolimab LLOQ QC (20 ng/mL) and matrix blank samples (negative control). Regardless of the anti-spesolimab antibody concentrations tested, all matrix blank samples were below the limit of quantitation (BLQ) which demonstrated an absence of non-specific interference with the anti-spesolimab antibody controls in the PK method. For the spesolimab LLOQ QC spiked samples, interference, in the form of % Recovery > 25%, was observed in the majority of anti- spesolimab antibody concentrations.

Hemolysis Effect	100% unspiked lots tested BQL, 100% lots tested within 100±25.0% Recovery for the LLOQ and 100% lots tested within 100±20.0% for the ULOQ
Lipemic Effect	100% unspiked lots tested BQL, 100% lots tested within 100±25.0% Recovery for the LLOQ and 100% lots tested within 100±20.0% for the ULOQ
Dilution Linearity and Hook Effect	200,000 ng/mL diluted 5, 10, 20, 200, 1000, 2000, 10000, 20000, and 100000 –fold. Maximum in range dilution: 10000. No hook effect observed
Bench-top Stability	48 hours at Room Temperature
Freeze-Thaw Stability	8 Cycles at -20°C and -70°C
Long-Term Storage Stability	1106 Days at -20°C 1106 Days at -70°C
Parallelism	Parallelism established, all incurred samples met acceptance criteria (%CV < 30%)
Carry Over	No carryover observed

Summary of in-study PK method performance results used to support submission trials

	1368-0001	1368-0002	1368-0009	1368-0043	1368-0011	1368-0013
Method	ELISA	GyroLab				
Overall Assay Passing Rate	100%	95%	88%	97%	100%	96%
Overall Standard Curve Performance	%RE: -1.4 to 6.6 %CV: 2.8 to 7.1	%RE: -1.8 to 3.5 %CV:2.1 to 5.9	%RE: -2.6 to 3.5 %CV: 1.5 to 7.4	%RE: -3.0 to 6.5 %CV: 1.9 to 6.9	%RE: -1.6 to 2.8 %CV: 1.1 to 2.9	%RE: -3.6 to 5.0 %CV: 2.0 to 5.4
Overall QC Performance	%RE: -2.5 to 0.8 %CV: 6.3 to 7.6	%RE: 0.3 to 1.5 %CV: 4.2 to 8.9	%RE: -3.8 to -3.1 %CV: 4.3 to 6.9	%RE: 0.3 to 4.6 %CV: 2.9 to 6.5	%RE: -2.8 to 0.3 %CV: 1.7 to 2.3	%RE: 6.5 to 8.3 %CV: 3.1 to 5.4
ISR	5.8% non-placebo samples analyzed, 86.7% passed criteria	11.1% nonplacebo analyzed, 95.6% passed criteria	11.0% nonplacebo analyzed, 94.4% passed criteria	10.7% nonplacebo analyzed, 96.3% passed criteria	23.1% non-placebo analyzed, 100%	10.4% nonplacebo analyzed, 100% passed criteria
Study Sample Analysis Stability	Within the validated 12 months of LTS	350 days and within the 1106 days of LTS	240 days and within the 1106 days of LTS	244 days and within the 1106 days of LTS	256 days and within the 1106 days of LTS	595 days and within the 1106 days of LTS

Source: Modified from Summary of Biopharmaceutics and Associated Analytical Methods, table 10, page 28

19.4.2 Population PK Analysis

Population PK Summary Table

General Information		
Objectives of PPK Analysis		Characterize spesolimab' s PK profile by population PK analysis Characterize the effect of pre-specified covariates on PK parameters of spesolimab
Study Included		7 Phase I studies: 1368-0001, 1368-0002, 1368-0009, 1368-0043, 1368-0003, 1368-0029, 1368-011. 8 Phase II studies: 1368-0015, 1368-0016, 1368-0032, 1358-0004, 1368-0005, 1368-0010, 1368-013 and 1368-025. (GPP studies: 1368-011, 1368-013 and 1368-025) Table 30
Dose(s) Included		Table 30
Population Included		HV: 182, UC: 96, PPP: 183, AD:36 ITT(GPP): 58
Population Characteristics (Table 31 & Table 32)	General	Age median: 44 yr (range: 18 -76), (35, 6.3% subj >=65 yr) Weight median: 71.4 kg (range: 42.2, 164.2) 258 (46.5%) male patients Race: 393 (71%) White, 12 (2%) Black, 136 (25%) Asian, 14 (2%) Other ADA: 371 (66.8%) absents, 184 (33%) presents.
	Organ Impairment	Hepatic Impairment (NCI): Normal: 526 (94.8%) Mild: 26 (4.7%) Moderate: 3 (0.5%) Renal Impairment (eGFR): Normal: 416 (74.9%) Mild: 127 (22.9%) Moderate: 12 (2.2%)
No. of Patients, PK Samples, and BLQ		6631 observations from 557 subjects: 6369 samples had quantifiable spesolimab concentrations, 262 BLQ samples (4.1%) and three were missing. 503 samples from 58 GPP patients (382 and 67 observations following IV and SC dosing) were involved in the analysis dataset.

		(Table 33)	
Sampling Schedule	Rich Sampling	4002 observations from 189 subjects	
	In ITT Population	84 observations from 7 GPP patients	
covariates Evaluated	Static	Baseline demographics, body weight, etc	
	Time-varying	ADA	
Final Model		Summary	Acceptability [FDA's comments]
Software and Version		PK analyses were conducted via nonlinear mixed effects modeling with the nonlinear mixed effects modeling (NONMEM®) software, Version 7.4. Pre- and post-processing of model inputs, outputs and analysis scripting was programmed using version 3.6 or above of R	Acceptable
Model Structure		Two-compartment population PK model with parallel linear and nonlinear clearance. The absorption phase following SC dosing was characterized with a sequential zero-order, first-order absorption model. (D1, ka, CL, Q, volume of distribution of the central compartment (V2), volume of distribution of the peripheral compartment (V3), Vmax, Km and F1 for SC dosing)	Acceptable
Model Parameter Estimates		Table 34 and Table 35	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)		Estimates of IIV (CV%) were 34.2% on CL, 47.2% on V2, 105% on ka, 5060% on VmaxADA and 23000% on KmADA. The estimated shrinkage of interindividual random effects on CL and V2 were low (8.43 and 22.9%, respectively. The shrinkage on absorption parameters, ka and F1, were 53.1% and 68.5%, respectively. Similarly, shrinkage on the nonlinear CL terms, VmaxADA and KmADA, were 67.3 and 76.9%, respectively	The high IIV on VmaxADA and KmADA could not be used to extrapolate or simulate variability in ADA effects. Individual empirical bayes estimates should be interpreted

		with caution for ka, F1, VmaxADA and KMADA due to the high shrinkage.
BLQ for Parameter Accuracy	BLQ samples were ignored in the analysis.	Acceptable as the low proportion of BLQ samples.
GOF, VPC	Figure 14 and Figure 15	Acceptable
Significant Covariates and Clinical Relevance	The covariate effects were shown in Figure 16. When the maximum ADA titer > 3600, AUC decreased about 50%, which indicating large increases in maximum ADA titer might have a clinically meaningful effect on AUC. No clear effect on AUC was observed for the site of SC administration (periumbilical area) and the UC or AD subjects. Subjects with lighter bodyweight may have a higher AUC. Similar trends of covariate effects were observed on C_{max} for site of SC administration, subject type on clearance, and weight effects. While there does not appear to be a difference in the C_{max} based on the ADA titer.	Acceptable
Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	A population pharmacokinetic model was developed based on data collected from healthy subjects, patients with GPP, and patients with other diseases. After a single intravenous dose of 900 mg TRADENAME, the population PK model estimated $AUC_{0-\infty}$ (95% CI) and C_{max} (95% CI) in a typical ADA-negative patient with GPP were 4750 (4510, 4970) mcg□day/mL and 238 (218, 256) mcg/mL, respectively.	In general, the labeling language is acceptable, while minor edits were suggested for labeling language.

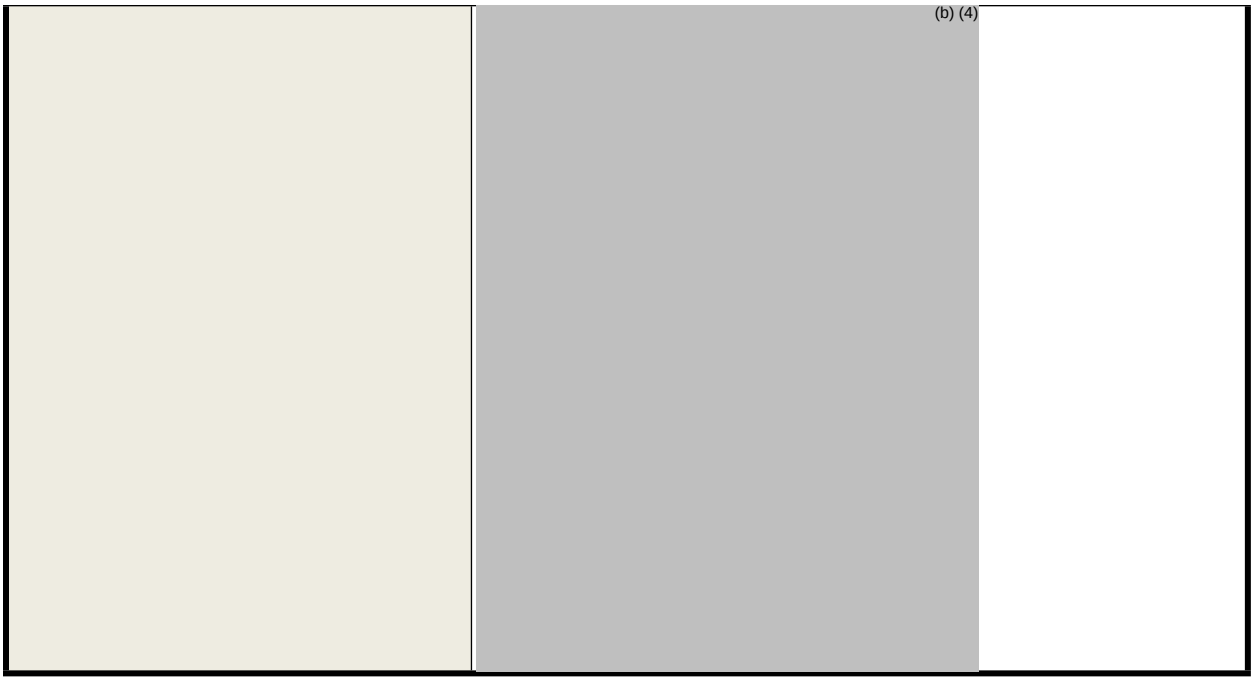

(b) (4)

Table 30. overview of clinical trials with PK data within the clinical development program for spesolimab

Study No./ Status/ [Report]	Description/ Design	Route of admin.	Treatment duration	Dosing regimen of investigational product and control	No. of subjects treated
Trials in HV					
1368-0001 Phase I Completed [c09985235]	SRD Single-blind, partially randomized within dose groups, placebo-controlled	i.v. infusion	Single dose	Placebo	20
				0.001 mg/kg	6
				0.003 mg/kg	6
				0.01 mg/kg	6
				0.03 mg/kg	6
				0.05 mg/kg	3
				0.1 mg/kg	5
				0.3 mg/kg	4
				1 mg/kg	6
				3 mg/kg	6
				6 mg/kg	6
				10 mg/kg	4
1368-0002 Phase I Completed [c18789185]	MRD Partially randomized, placebo-controlled; MRD: Double-blind, parallel-group SD: Single-blind	i.v. infusion	MRD: 4 weeks: SD: Single dose	Placebo	10
				3 mg/kg q1w x 4	6
				6 mg/kg q1w x 4	6
				10 mg/kg q1w x 4	6
				20 mg/kg q1w x 4	6
				20 mg/kg (single dose)	6
1368-0003 Phase I Completed [c21739607]	Bioavailability of s.c. administration Open-label, matched-group	i.v. infusion s.c. injection	Single dose	150 mg (s.c.) (periumbilical (pmbl))	12
				300 mg (s.c.) (pmbl)	12
				300 mg (i.v.)	12

Study No./ Status/ [Report]	Description/ Design	Route of admin.	Treatment duration	Dosing regimen of investigational product and control	No. of subjects treated
1368-0009 Phase I Completed [c22174984]	PK in Japanese volunteers Double-blind, randomized, placebo-controlled	i.v. infusion s.c. injection	Single dose	Placebo (i.v., s.c.) (pmbl)	8
				300 mg (i.v.)	6
				600 mg (i.v.)	6
				1200 mg (i.v.)	6
				300 mg (s.c.) (pmbl)	6
1368-0029 Phase I Completed [c28472227]	Relative bioavailability Open-label, matched-group	s.c. injection	Single dose	300 mg s.c. (1 x 2mL, 1 pmbl site)	12
				300 mg s.c. (1 x 2mL, thigh)	12
				300 mg s.c. (2 x 1mL, 2 pmbl sites)	12
				600 mg s.c. (2 x 2mL 2 pmbl sites)	12
1368-0043 Phase I Ongoing Interim CTR (i.v.) [c34784235]	PK in healthy Chinese volunteers Open-label, parallel-group	i.v. infusion s.c. injection	Single dose	450 mg i.v.	10
				900 mg i.v.	10
				1200 mg i.v.	10
				300 mg s.c. (pmbl)	10
				600 mg s.c. (pmbl)	10
Trials in Patients with GPP					
1368-0011 Phase I Completed [c17444370] Biomarker Report: [c32294014]	Proof of concept (POC) in GPP patients Open-label, single-arm design	i.v. infusion	Single dose	10 mg/kg i.v.	7

Study No./ Status/ [Report]	Description/ Design	Route of admin.	Treatment duration	Dosing regimen of investigational product and control	No. of subjects treated
1368-0013 Phase II Completed [c31523813] Biomarker Report: [c34018597]	Efficacy and safety in GPP flare treatment Double-blind, randomized, placebo-controlled design	i.v. infusion	Single dose	900 mg i.v. Placebo i.v. In addition, all patients were offered up to 2 further open-label flare rescue treatments with single dose spesolimab 900 mg i.v.	35 18
1368-0025 Phase II Ongoing Interim TFLs[1] [c35917894] [c36360406] [c36415824]	Open label extension study Open label design	s.c. injection i.v. infusion as rescue treatment	up to 252 weeks	300mg s.c. q12w; 300mg s.c. q6w if patients had received spesolimab i.v. rescue in the previous trial; Flare rescue treatment: spesolimab single dose 900 mg i.v.	39[1]
Trials in Patients with other Dermatologic Indications (PPP or AD)					
1368-0015 Phase IIa Completed [c24420819]	POC in PPP Double-blind, randomized, placebo-controlled design	i.v. infusion	16 weeks	900 mg i.v. q4w x 4	19
				300 mg i.v. q4w x 4	19
				Placebo i.v. q4w x 4	21
1368-0016 Phase IIb Ongoing Wk16 primary analysis CTR [c32445633] And interim TFLs[1] [c35303719] [c35303750] [c35303749] [c35303753]	Dose-ranging in PPP Double-blind, randomized, placebo-controlled design	s.c. injection	52 weeks	600 mg q1w x 5 +600 mg q4w x 12	44
				600 mg q1w x 5 +300 mg q4w x 12	22
				300 mg q1w x 5 +600 mg q4w x 12	21
				300 mg q1w x 5 +300 mg q4w x 2 + 300 mg q8w x 5	22
				Placebo q1w x5 + placebo q4w x 2 + 600 mg q4w x 10	43

Study No./ Status/ [Report]	Description/ Design	Route of admin.	Treatment duration	Dosing regimen of investigational product and control	No. of subjects treated
1368-0032 Phase IIa Completed [c32577607]	POC in AD Double-blind, randomized, placebo-controlled design	i.v. infusion	Up to 32 weeks	600 mg q4w x 4 Placebo q4w x4 In addition, non-responders were offered additional 600 mg spesolimab q4w i.v.(4×) at wk 16	33 18
Trials in Ulcerative Colitis (UC)					
1368-0004 Phase IIa Completed [c30128674]	Mechanism of action in UC Open-label, single-arm design	i.v. infusion	12 weeks	1,200 mg i.v. q4w x 3	8
1368-0005 Phase II Completed [c31366073]	POC in UC Double-blind, randomized, placebo-controlled design	i.v. infusion	Single dose Or 12 weeks	300 mg i.v. single-dose	24
				450 mg i.v. q4w x 3	23
				1200 mg i.v. q4w x 3	27
				Placebo i.v. q4w x 3	23
1368-0010 Phase IIa Completed [c32073490]	POC as add-on treatment to TNF-α inhibitor therapy Double-blind, randomized, placebo-controlled	i.v. infusion	12 weeks	1,200 mg i.v. q4w x 3	14
				Placebo i.v. q4w x 3	8

Source: Summary of clinical pharmacology studies (c34409862-01), Page 12-14, Table 1.

Table 31. Continuous baseline covariate summary by subject type and population total

Variable	n	Mean	Median	SD	Min / Max
Subject Type: HV					
Weight (kg)	184	72.7	71.8	11.8	50.6 / 110
Height (cm)	184	173	172	9.12	153 / 205
Age (year)	184	35.5	35.0	7.89	18.0 / 51.0
Albumin (g/L)	138	44.4	44.3	3.06	36.3 / 54.3
Total bilirubin (mcmol/L)	184	11.3	10.3	5.61	1.71 / 44.5
C-Reactive Protein (mg/L)	184	3.75	3.00	3.84	0.100 / 36.1
eGFR (mL/min/1.73m^2)	184	108	109	12.9	77.0 / 136
Subject Type: GPP					
Weight (kg)	58	71.6	67.5	23.5	42.2 / 164
Height (cm)	58	163	163	9.73	142 / 187
Age (year)	58	42.2	40.5	11.3	21.0 / 69.0
Albumin (g/L)	58	40.4	41.0	5.36	24.0 / 51.0
Total bilirubin (mcmol/L)	58	9.55	7.90	6.13	2.00 / 36.0
C-Reactive Protein (mg/L)	58	61.2	23.0	74.8	0.200 / 277
eGFR (mL/min/1.73m^2)	58	104	108	18.1	53.3 / 127
Subject Type: UC					
Weight (kg)	96	77.3	76.0	20.4	43.2 / 157
Height (cm)	96	174	174	10.8	150 / 200
Age (year)	96	42.6	44.0	14.4	19.0 / 76.0
Albumin (g/L)	96	41.3	42.0	3.65	28.0 / 48.0
Total bilirubin (mcmol/L)	96	6.27	6.00	3.26	3.00 / 20.0
C-Reactive Protein (mg/L)	96	11.5	4.30	22.1	0.200 / 161
eGFR (mL/min/1.73m^2)	96	101	102	19.2	55.0 / 137

Variable	n	Mean	Median	SD	Min / Max
Subject Type: PPP					
Weight (kg)	183	73.1	69.0	17.7	47.2 / 129
Height (cm)	183	165	163	9.34	130 / 189
Age (year)	183	53.7	55.0	10.8	22.0 / 75.0
Albumin (g/L)	183	45.2	45.0	2.55	39.0 / 52.0
Total bilirubin (mcmol/L)	183	6.79	6.00	3.50	3.00 / 21.0
C-Reactive Protein (mg/L)	183	4.69	2.07	10.2	0.200 / 121
eGFR (mL/min/1.73m^2)	183	92.2	93.8	15.5	39.9 / 132
Subject Type: AD					
Weight (kg)	36	79.1	78.8	19.5	51.9 / 135
Height (cm)	36	166	168	9.57	148 / 185
Age (year)	36	40.5	39.0	15.6	19.0 / 69.0
Albumin (g/L)	36	44.6	45.0	4.00	34.0 / 54.0
Total bilirubin (mcmol/L)	36	8.39	8.00	3.74	3.00 / 17.0
C-Reactive Protein (mg/L)	36	3.35	1.96	4.44	0.280 / 23.5
All data					
Weight (kg)	557	73.9	71.3	17.5	42.2 / 164
Height (cm)	557	169	168	10.5	130 / 205
Age (year)	557	43.7	44.0	13.4	18.0 / 76.0
Albumin (g/L)	511	43.7	44.0	3.86	24.0 / 54.3
Total bilirubin (mcmol/L)	557	8.57	7.00	5.04	1.71 / 44.5
C-Reactive Protein (mg/L)	557	11.3	3.00	31.5	0.100 / 277
eGFR (mL/min/1.73m^2)	557	101	103	17.5	39.9 / 145

Source: Population PK report (c35520225), Page 56-57, Table 10.

Table 32. Summary of the subjects' ADA measurements (present/absent) mean anti-drug antibody (ADA, titer), after scaling factor applied when appropriate, stratified by subject type, study and population total.

		ADA per Subject	
Study	n	Absent	Present
Subject type: HV			
1368.1	44	38(86.3)	6(13.6)
1368.2	30	28 (93.3)	2 (6.7)
1368.3	36	23 (63.9)	13 (36.1)
1368.9	24	19 (79.2)	5 (20.8)
1368.29	48	31 (64.6)	17 (35.4)
Subject type: GPP			
1368.11	7	4 (57.1)	3 (42.9)
1368.13/25	51	21 (41.2)	30 (58.8)
Subject type: UC			
1368.5	74	66 (89.2)	8 (10.8)
1368.4	8	6 (75.0)	2 (25.0)
1368.10	14	12 (85.7)	2 (14.3)
Subject type: PPP			
1368.15	37	20 (54.1)	17 (45.9)
1368.16	146	80 (54.8)	66 (45.2)
Subject type: AD			
1368.32	36	23 (63.9)	13 (36.1)
All data	555	371(66.8)	184(33.3)

		ADA (titer)			
Study	n	Mean	Median	SD	Min / Max
Subject type: HV					
1368.1	6	324	34.7	668	1.19 / 1680
1368.2	2	360	360	213	209 / 510
1368.29	17	1520	599	1740	18.3 / 5190
1368.3	13	1310	751	1430	169 / 4990
1368.9	5	617	527	482	112 / 1310
Subject type: GPP					
1368.11	3	598	422	391	326 / 1050
1368.13	29	62700	906	1.49e+05	32.5 / 5.86e+05
1368.25	1	893	893	-	893 / 893
Subject type: UC					
1368.10	2	133	133	136	37.5 / 229
1368.4	2	132	132	36.5	106 / 158
1368.5	8	1390	100	3570	55.0 / 10200
Subject type: PPP					
1368.15	17	11600	289	35200	20.0 / 1.47e+05
1368.16	66	9680	1050	42100	32.3 / 3.36e+05
Subject type: AD					
1368.32	13	49600	421	1.47e+05	180 / 5.31e+05
All data					
All data	184	18300	616	77900	1.19 / 5.86e+05

Source: Modified based on population PK report (c35520225), Page 68-71, Table 21-24.

Table 33. Data summary with subjects (number) and observations (number and percent) by study and population total

		Number			Percent	
Study	SUBJ	MISS	OBS	BQL	OBS	BQL
1368.1	(b) (6)	0	736	136	11.6	2.1
1368.2		0	801	1	12.6	0.0
1368.3		3	830	21	13.0	0.3
1368.9		0	469	0	7.4	0.0
1368.29		0	1088	13	17.1	0.2
1368.11		0	78	6	1.2	0.1
1368.13		0	285	17	4.5	0.3
1368.25		0	86	31	1.4	0.5
1368.15		0	356	14	5.6	0.2
1368.16		0	972	1	15.3	0.0
1368.32		0	237	9	3.7	0.1
1368.5		0	289	8	4.5	0.1
1368.4		0	55	0	0.9	0.0
1368.10		0	87	5	1.4	0.1
All data	557	3	6369	262	100.0	4.1

Source: Population PK report (c35520225), Page 50, Table 6.

Table 34. Summary of fixed effect parameter estimates in final model..

			Final model	Non-parametric bootstrap	
			Estimate	Median	95% CI
Structural model parameters					
CL (L/day)	$\exp(\theta_1)$	Clearance	0.184	0.184	0.175, 0.194
V2 (L)	$\exp(\theta_2)$	Plasma volume of central	3.77	3.73	3.46, 4.08
Q (L/day)	$\exp(\theta_3)$	Intercompartmental clearance	0.617	0.625	0.545, 0.747
V3 (L)	$\exp(\theta_4)$	Plasma volume of peripheral	2.69	2.68	2.53, 2.82
KA (1/day)	$\exp(\theta_5)$	Absorption rate constant	0.229	0.243	0.192, 0.311
D1 (day)	$\exp(\theta_6)$	Duration of zero order absorption	0.130	0.134	0.107, 0.166
$F1_{SC,notPeri}$	$\exp(\theta_7)/(1+\exp(\theta_7))$	Bioavailability - SC dosing	0.980	0.978	0.934, 0.996
$F1_{SC,peri}$	$\exp(\theta_7+\theta_{10})/(1+\exp((\theta_7+\theta_{10}))$	Bioavailability - SC dosing into the periumbilicum	0.880	0.874	0.803, 0.940
Covariate effect parameters					
VmaxADA (L/day)	$\exp(\theta_8)$	MM max effect parameter for ADA effect on NL CL	0.140	0.0489	0.00576, 0.339
KmADA (titer)	$\exp(\theta_9)$	MM conc at half max effect parameter for ADA effect on NL CL	31400	41100	960 , 506000
$CL_{UC\&AD}$	$\exp(\theta_{11})$	Fold increase on CL for UC and AD patient	1.39	1.41	1.30, 1.50
$VmaxADA_{GPP}$	$\exp(\theta_{12})$	Fold increase on VmaxADA for GPP patient	9.49	15.7	4.94, 71.9

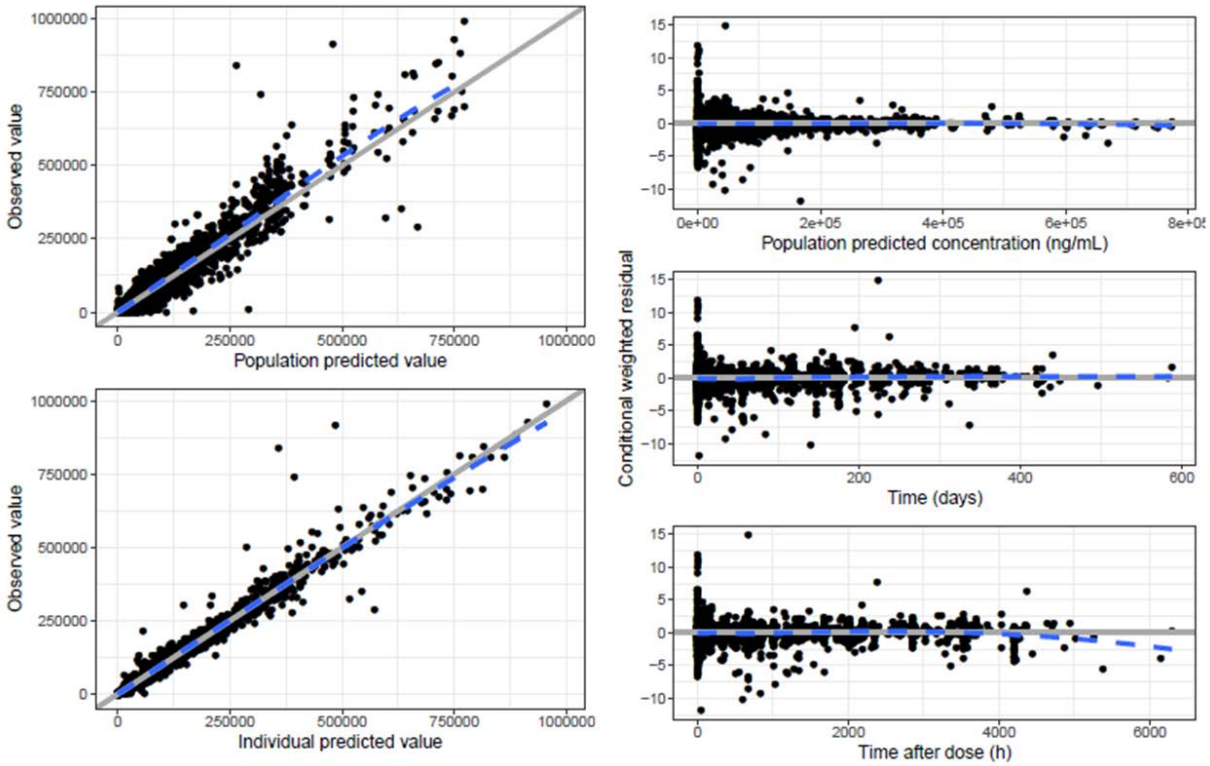
Source: Population PK report (c35520225), Page 42, Table 4.

Table 35. Summary of random effect parameter estimates in final model.

		Final Model		Non-parametric bootstrap	
		Estimate	Shrinkage (%)	Median	95% CI
Interindividual variance parameters					
IIV-CL	$\Omega_{(1,1)}$	0.110 [CV%=34.2]	8.43	0.109	0.0780, 0.153
IIV-V2	$\Omega_{(2,2)}$	0.201 [CV%=47.2]	22.9	0.198	0.111, 0.302
IIV-KA	$\Omega_{(5,5)}$	0.748 [CV%=105]	53.1	1.21	0.540, 1.95
IIV-F1	$\Omega_{(7,7)}$	1.13 [SD=0.0387]	68.5	1.07	0.0610, 2.67
IIV-VmaxADA	$\Omega_{(8,8)}$	7.85 [CV%=5.06e+03]	67.3	13.9	5.84, 34.4
IIV-KmADA	$\Omega_{(9,9)}$	10.9 [CV%=2.30e+04]	76.9	16.4	0.506, 80.2
Interindividual covariance parameters					
CL-V2	$\Omega_{(2,1)}$	0.0871 [Corr=0.584]	-	0.0793	0.0446, 0.140
VmaxADA-KmADA	$\Omega_{(9,8)}$	4.51 [Corr=0.488]	-	9.85	-1.48, 44.8
Residual variance					
Proportional residual error	$\Sigma_{(1,1)}$	0.0552 [CV%=23.5]	6.06	0.0567	0.0441, 0.0743

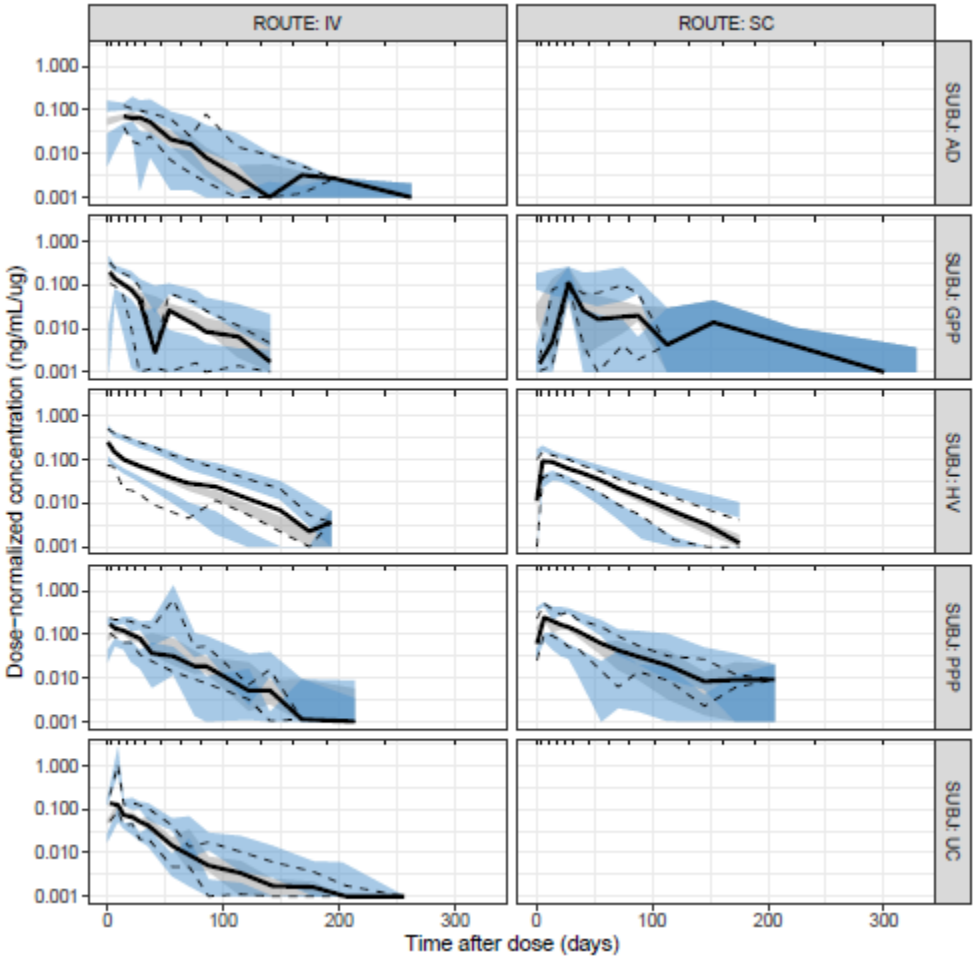
Source: Population PK report (c35520225), Page 43, Table 5.

Figure 14. Goodness of fit plots for final model.



Source: Population PK report (c35520225), Page 151, Figure 73 & Page 158, Figure 80.

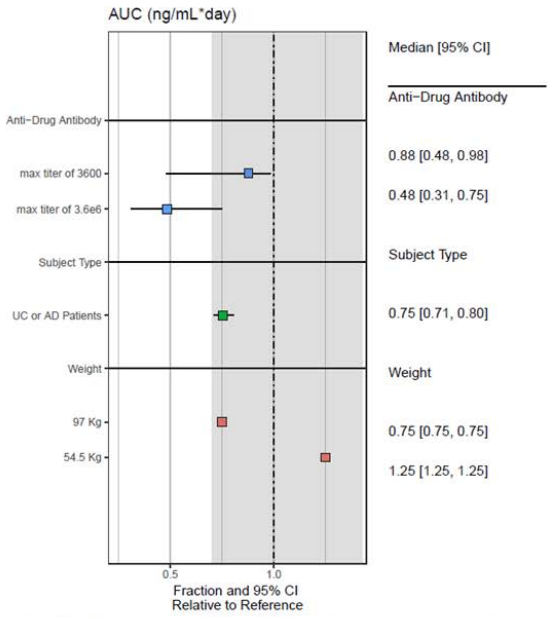
Figure 15. Final Model: Visual predictive check (VPC) of the dose-normalized spesolimab concentration versus time after dose (Observation points removed).



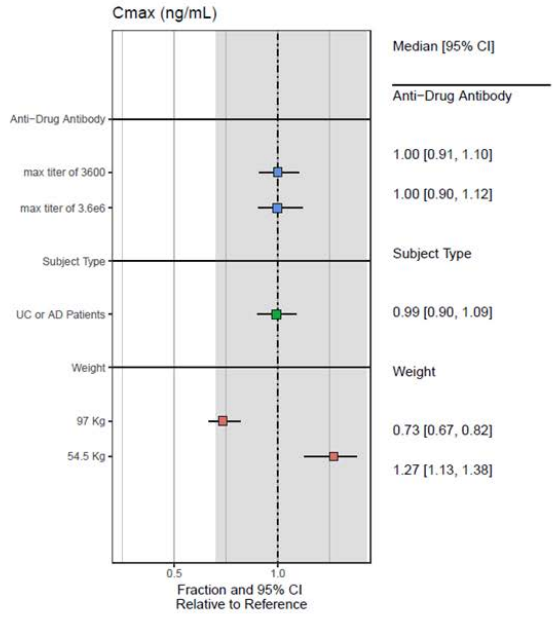
Source: Population PK report (c35520225), Page 203, Figure 125.

Figure 16. Effects of mean 12-week ADA (titer), subject type and weight on the spesolimab normalized maximum concentration (C_{max}) and area under the curve (AUC).

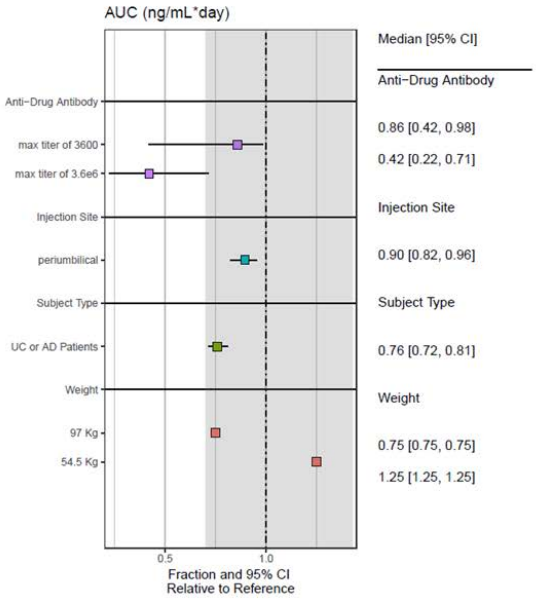
The reference subject was a 70 kg, GPP subject, receiving a single IV dose, with no ADA measured. Solid black squares represent the median and the solid horizontal lines represent the 95% confidence interval. The grey shaded area is the reference range with a lower bound of 0.70 and an upper bound of 1.43.



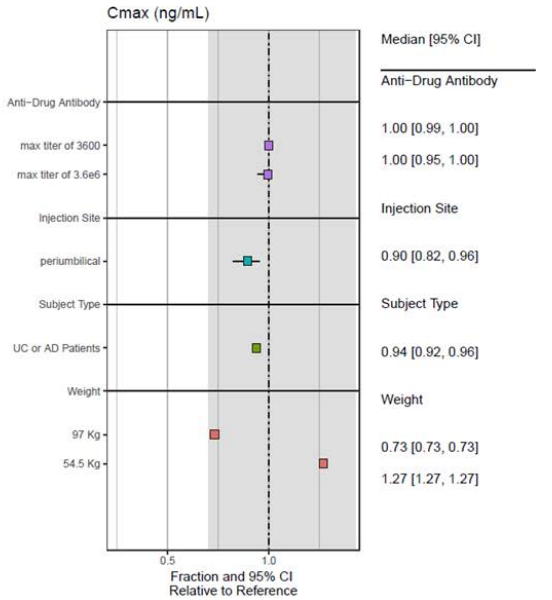
The reference subject was a 70 kg, GPP subject, receiving a single IV dose, with no ADA measured. Solid black squares represent the median and the solid horizontal lines represent the 95% confidence interval. The grey shaded area is the reference range with a lower bound of 0.70 and an upper bound of 1.43.



The reference subject was a 70 kg, GPP subject, receiving a single SC dose (to a site other than the periumbilicum), with no ADA measured. Solid black squares represent the median and the solid horizontal lines represent the 95% confidence interval. The grey shaded area is the reference range with a lower bound of 0.70 and an upper bound of 1.43.



The reference subject was a 70 kg, GPP subject, receiving a single SC dose (to a site other than the periumbilicum), with no ADA measured. Solid black squares represent the median and the solid horizontal lines represent the 95% confidence interval. The grey shaded area is the reference range with a lower bound of 0.70 and an upper bound of 1.43.



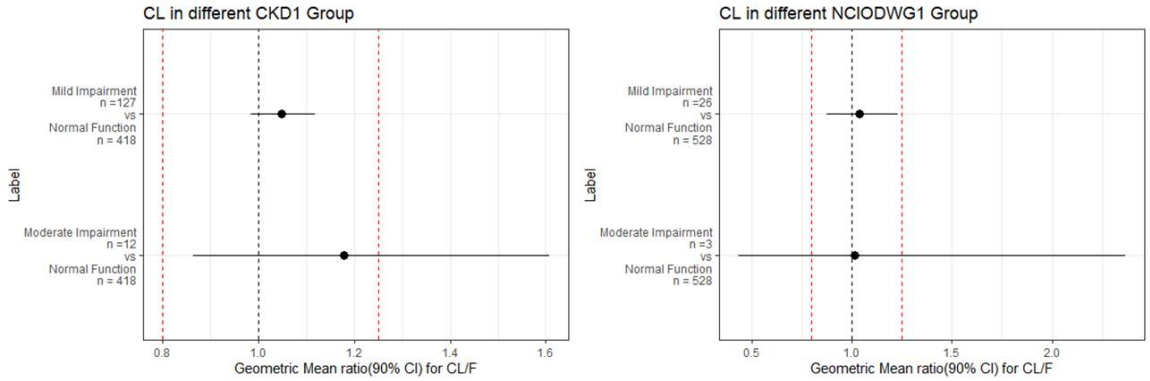
Source: Population PK report (c35520225), Page 198-201, Figure 120-123.

The FDA's Assessment:

The population PK model was checked by the reviewer. In general the population PK model is acceptable due to the agreement of prediction and observation. %). In population PK analysis,

418 subjects with normal renal function, 127 subjects with mild renal impairment and 12 subejcts with moderate renal impairment were involved in the analysis. And there were 528 subjects with normal hepatic function (NCIODWG), 26 subjects with mild hepatic impairment and 3 subejcts with moderate hepatic impairment in the analysis. The results showed that mild, moderate renal impairment or mild hepatic impairment did not impact the clearance of spesolimab. (Figure 17) Due to the limited number of subjects involved in the analysis, the effect of moderate hepatic impairment was not evaluated. No subjects with severe renal or hepatic impairment were involved in the analysis. Although the presence of concomitant medication, including immunosuppressant or oral corticosteroids were involved in the covariate analysis in the population PK model. Evaluation of the influence of concomitant medication on PK with population PK result were not appropriate as there was not sufficient information (detailed dose given, the time of drug administration and the time of drug discontinuation during the treatment) recorded. ADA effect on clearance was described by saturable Michaelis Menten kinetics model. (Equation 1) Based on Applicant's final model, higher ADA titer could spesolimab $AUC_{0\text{-}1wk}$, while the influence of ADA effect on C_{max} is relatively smaller (Figure 16). While the high IIV on VmaxADA and KmADA indicated the final population PK model could not be used to extrapolate or simulate variability in ADA effects.

Figure 17. Comparison of empirical bayes estimates of spesolimab clearance in different renal and hepatic function groups.



Source: Reviewer's analysis.

Equation 1.

$$totalCL_i = CL_i + \frac{VmaxADA_i \cdot \frac{ADA_i}{1000}}{KmADA_i + \frac{ADA_i}{1000}}$$

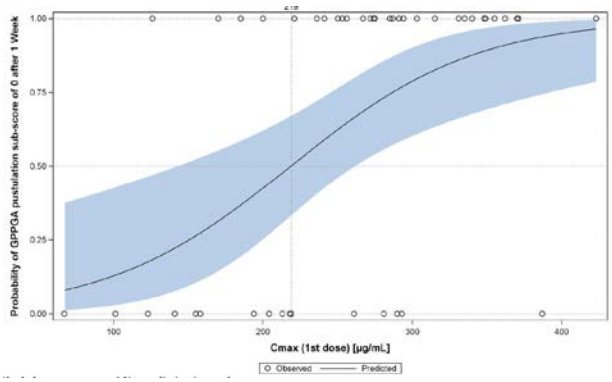
19.4.3 Exposure-Response Analysis for Efficacy

ER Efficacy Summary Table

General Information		
Goal of ER analysis		Explore the exposure-response (E-R) relationship between spesolimab exposure metrics and efficacy endpoints using data from Study 1368-0013.
Study Included		Study 1368-0013
Endpoint		At Week 1 Primary endpoint: GPPGA pustulation sub-score of 0 (binary); Secondary endpoint: GPPGA pustulation sub-score of 0 or 1 (binary); GPPGA score of 0 or 1 (binary); GPPGA pustulation sub-score; Mean of GPPGA sub-scores (continuous)
No. of Patients		53 Patients
Population Characteristics	General	Age median (range): 41 year (21-69) Weight median (range): 68 kg (42.2 – 164.2) Gender: 17 (32%) male Race: White: 24 (45%) Asian: 27 (55%)
	Pediatrics (if any)	Not applicable
Dose(s) Included		One dose: 900 mg IV
Exposure Metrics Explored (range)		$AUC_{0\text{-}wk1}$: 1967 – 12149 mg/L*day $C_{max,1st\ dose}$: 67 – 423 mg/L

Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	Logistic regression analysis for binary endpoints (GPPGA pustulation sub-score of 0; GPPGA pustulation sub-score of 0 or 1; GPPGA score of 0 or 1) Linear regression for Mean of GPPGA sub-scores or change from baseline in mean of GPPGA sub-scores	Acceptable
Model Parameter Estimates	Table 36 - Table 40	Acceptable
Visualization of E-R relationships	Figure 18 - Figure 23	Acceptable

Figure 18. Logistic regression of probability of achieving GPPGA pustulation subscore of 0 vs spesolimab $C_{max,1st\ dose}$ after first active dose.



Source: c36321904, Page 1167, Figure 2.2.1.63.

Table 36. Parameter estimates of logistic regression of probability of achieving GPPGA pustulation subscore of 0 vs spesolimab $C_{max,1st\ dose}$ after first active dose.

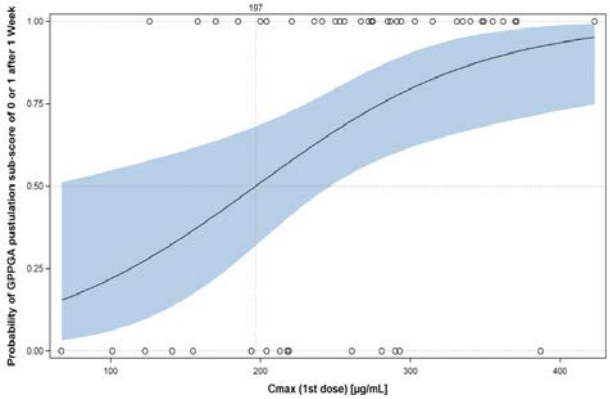
The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq	Exp(Est)
INTERCEPT	1	-3.5275	1.3264	7.0731	0.0078	0.029
EXPOSURE	1	0.0161	0.00531	9.2383	0.0024	1.016

Source: c36321904, Page 1169, Table 2.2.1.64

Figure 19. Logistic regression of probability of achieving GPPGA pustulation subscore of 0 or 1 vs spesolimab $C_{max,1st\ dose}$ after first active dose.



Source: c36321904, Page 1203, Figure 2.2.1.87.

Table 37. Parameter estimates of logistic regression of probability of achieving GPPGA pustulation subscore of 0 or 1 vs spesolimab $C_{max,1st\ dose}$ after first active dose.

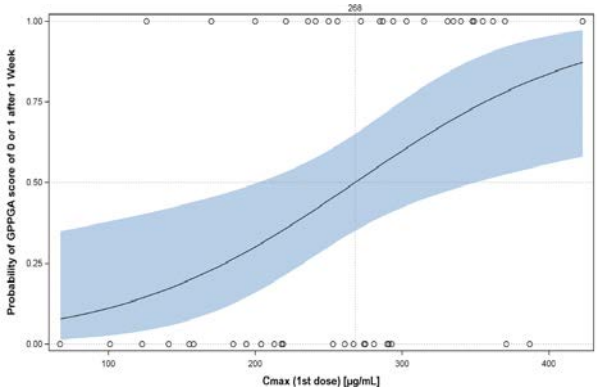
The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq	Exp(Est)
INTERCEPT	1	-2.5848	1.2003	4.6376	0.0313	0.075
EXPOSURE	1	0.0131	0.00486	7.3109	0.0069	1.013

Source: c36321904, Page 1205, Table 2.2.1.88.

Figure 20. Logistic regression of probability of achieving GPPGA score of 0 or 1 vs spesolimab $C_{max,1st\ dose}$ after first active dose.



Source: c36321904, Page 1185, Figure 2.2.1.75.

Table 38. Parameter estimates of logistic regression of probability of achieving GPPGA pustulation subscore of 0 or 1 vs spesolimab $C_{max,1st\ dose}$ after first active dose.

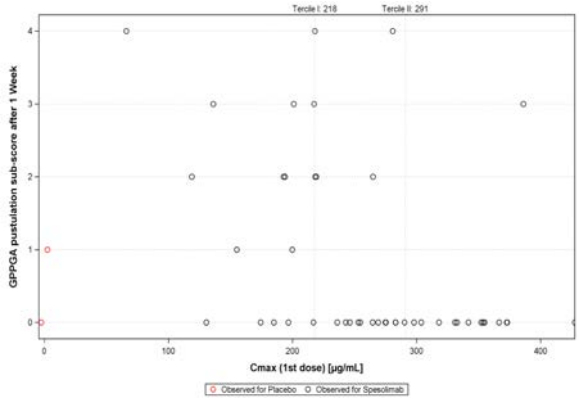
The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq	Exp(Est)
INTERCEPT	1	-3.3229	1.2509	7.0563	0.0079	0.036
EXPOSURE	1	0.0124	0.00464	7.1351	0.0076	1.012

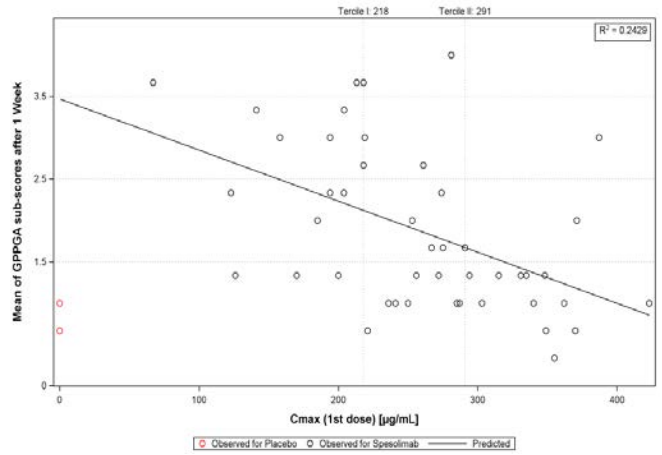
Source: c36321904, Page 1187, Table 2.2.1.76.

Figure 21. Scatterplot of spesolimab $C_{max,\ 1st\ dose}$ exposure vs. GPPGA pustulation sub-score.



Source: c36321904, Page 1110, Figure 2.2.1.21.

Figure 22. Scatterplot of spesolimab $C_{max, 1st dose}$ exposure vs. mean of GPPGA sub-scores.



Source: c36321904, Page 1118, Figure 2.2.1.27.

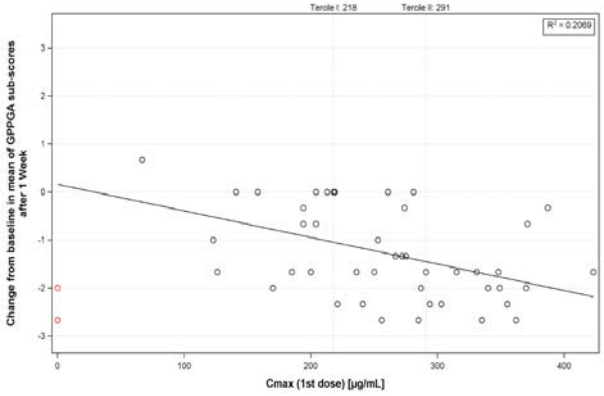
Table 39. Parameter estimates of linear regression of spesolimab $C_{max, 1st dose}$ exposure vs. mean of GPPGA sub-scores.

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	95% Confidence Limits	
Intercept	Intercept	1	3.46760	0.44982	7.71	<.0001	2.56046	4.37474
EXPOSURE	Analysis Value	1	-0.00617	0.00166	-3.71	0.0006	-0.00953	-0.00282

Source: c36321904, Page 1119, Table 2.2.1.28.

Figure 23. Scatterplot of spesolimab $C_{max, 1st dose}$ exposure vs. change from baseline in mean of GPPGA sub-scores.



Source: c36321904, Page 1132, Figure 2.2.1.35.

Table 40. Parameter estimates of linear regression of spesolimab $C_{max, 1st dose}$ exposure vs. change from baseline in mean of GPPGA sub-scores.

Parameter Estimates

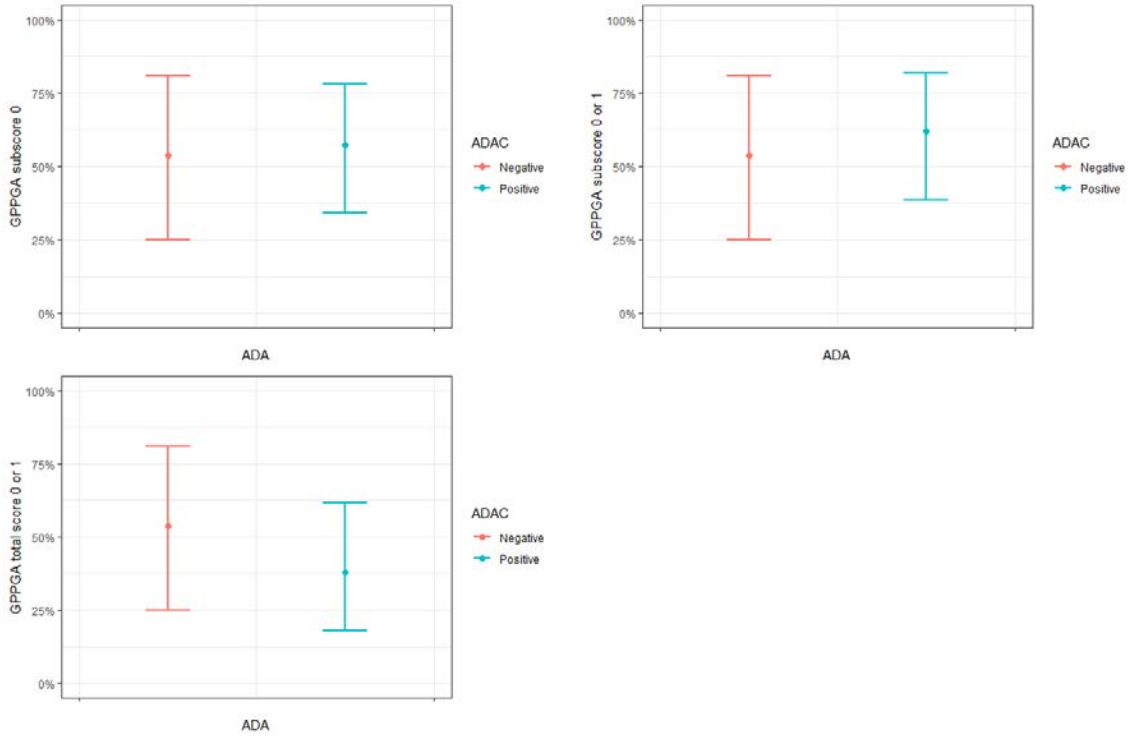
Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	95% Confidence Limits	
Intercept	Intercept	1	0.15979	0.44675	0.36	0.7223	-0.74115	1.06074
EXPOSURE	Analysis Value	1	-0.00553	0.00165	-3.35	0.0017	-0.00886	-0.00220

Source: c36321904, Page 1133, Table 2.2.1.36.

The FDA's Assessment:

The ER efficacy analysis was evaluated by the reviewer. Positive relationships between model predicted spesolimab $C_{max,1st\ dose}$ and GPPGA pustulation sub-score of 0 and 0 or 1 and GPPGA total score of 0 or 1 were observed in the logistic regression analysis for binary endpoints. Negative relationship was identified for spesolimab exposure and mean of GPPGA sub-scores or change from baseline in mean of GPPGA sub-scores in linear regression analysis. In the first week after treatment, maximum ADA titer in patients treating with spesolimab is 180. It's not expected to have a strong effect on spesolimab PK. No significant difference on efficacy were observed between the ADA positive and negative groups. While due to the very limited patients from a single dose level of spesolimab treatment, the ER efficacy relationship observed for spesolimab is inconclusive and should be treated with caution.

Figure 24. GPPGA pustulation sub-score of 0 and 0 or 1 and GPPGA total score of 0 or 1 in patients with negative and positive ADA.



Source: Reviewer's analysis

19.4.4 Exposure-Response Analysis for Safety

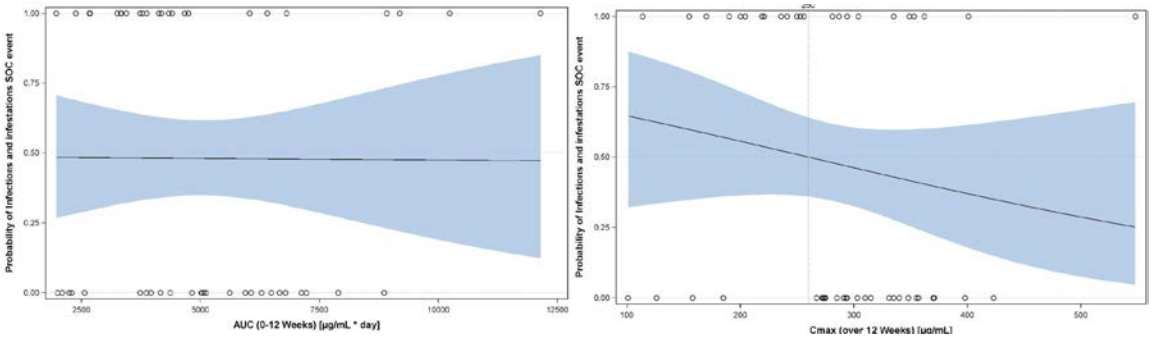
ER Safety Summary Table

General Information

Goal of ER analysis		Explore the E-R relationship between spesolimab exposure metrics and safety endpoints using data in tislelizumab treated patients in study 1368-0013.
Study Included		Study 1368-0013
Population Included		53 Patients
Endpoint		Infection-related AE, liver enzymes (ALT, AST and total bilirubin)
No. of Patients (total, and with individual PK)		53 Patients
Population Characteristics	General	Age median (range): 41 year (21-69) Weight median (range): 68 kg (42.2 – 164.2) Gender: 17 (32%) male Race: White: 24 (45%) Asian: 27 (55%)
	Organ impairment	-Hepatic (NCI, Child-Pugh, etc): n (%) in each category -Renal (CrCL, etc): n (%) in each category
	Pediatrics (if any)	Not applicable
	Geriatrics (if any)	2, 4% subj >=65 yr
Dose(s) Included		One dose: 900 mg IV
Exposure Metrics Explored (range)		$AUC_{0\text{-}wk1}$: 1967 – 12149 mg/L*day $C_{max,1st\ dose}$: 67 – 423 mg/L

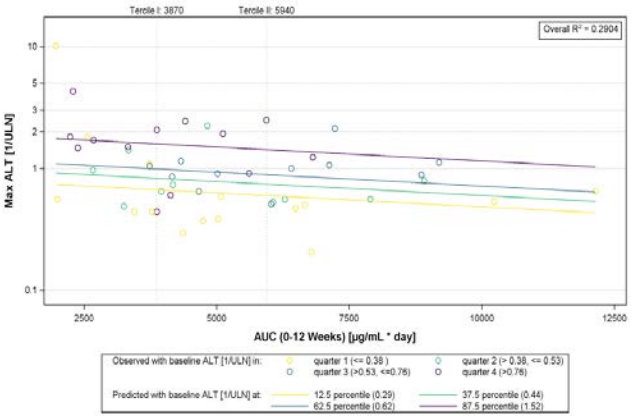
Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	Infection-related AE: logistic regression Live enzymes: linear regression	Acceptable
Model Parameter Estimates	Table 41 - Table 46	Acceptable
Visualization of E-R relationships	Figure 25 - Figure 31	Acceptable
Overall Clinical Relevance for ER	No significant correlation between spesolimab exposure ($AUC_{0\text{-}12wk}$) and infection-related events or liver enzyme evaluation	The result of ER analysis be interpreted with caution due to the limited number of patients.

Figure 25. Logistic regression of probability of occurrence of an infection related AE vs spesolimab exposures



Source: c34409862-01, Page 80-81, Figure 17-18.

Figure 26. Scatter plot of maximum ALT vs spesolimab AUC_{12wk}



Source: c36321904, Page 11, Figure 1.1.1.7.

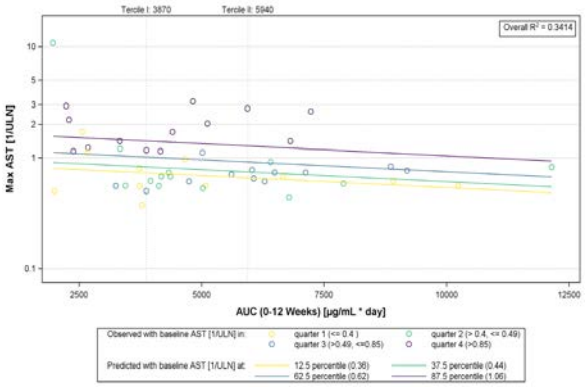
Table 41. Parameter estimates of linear regression model of maximum ALT vs spesolimab AUC_{12wk}

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	95% Confidence Limits	
Intercept	Intercept	1	0.44866	0.22426	2.00	0.0514	-0.00275	0.90007
EXPOSURE	AUC0-84	1	-0.00005267	0.00004204	-1.25	0.2166	-0.00013730	0.00003196
L_ALT_BASE		1	0.52854	0.14618	3.62	0.0007	0.23430	0.82278

Source: c36321904, Page 12, Table 1.1.1.8.

Figure 27. Scatter plot of maximum AST vs spesolimab AUC_{12wk}



Source: c36321904, Page 106, Figure 1.1.1.9.

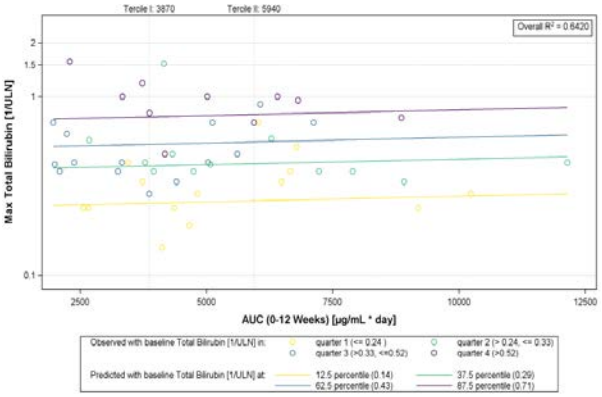
Table 42. Parameter estimates of linear regression model of maximum AST vs spesolimab AUC_{12wk}

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	95% Confidence Limits	
Intercept	Intercept	1	0.50626	0.19444	2.60	0.0124	0.11486	0.89765
EXPOSURE	AUC0-84	1	-0.00005003	0.00003457	-1.45	0.1545	-0.00011961	0.00001954
L_AST_BASE		1	0.61472	0.14087	4.36	<.0001	0.33117	0.89828

Source: c36321904, Page 1107, Table 1.1.1.10.

Figure 28. Scatter plot of maximum total bilirubin vs spesolimab AUC_{12wk}



Source: c36321904, Page 201, Figure 1.1.1.11.

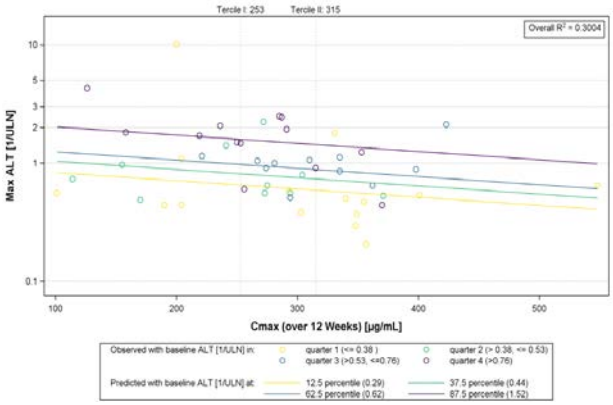
Table 43. Parameter estimates of linear regression model of maximum bilirubin vs spesolimab AUC_{12wk}

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	95% Confidence Limits	
Intercept	Intercept	1	-0.08351	0.12879	-0.65	0.5199	-0.34261	0.17559
EXPOSURE	AUC0-84	1	0.00001439	0.00002055	0.70	0.4873	-0.00002695	0.00005573
L_TBILI_BASE		1	0.69117	0.07551	9.15	<.0001	0.53927	0.84307

Source: c36321904, Page 202, Table 1.1.1.12.

Figure 29. Scatter plot of maximum ALT vs spesolimab C_{max}



Source: c36321904, Page 315, Figure 1.2.1.7.

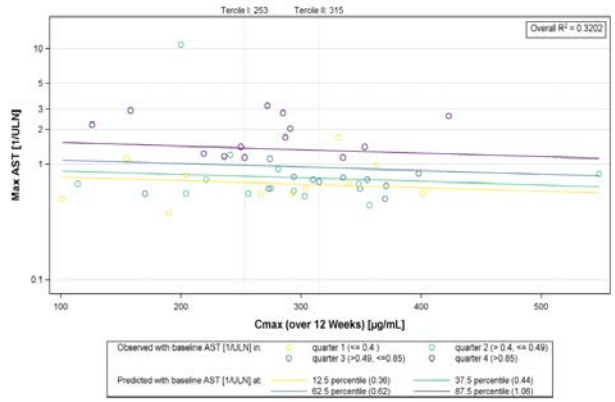
Table 44. Parameter estimates of linear regression model of maximum ALT vs spesolimab C_{max}

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	95% Confidence Limits	
Intercept	Intercept	1	0.64135	0.31095	2.06	0.0448	0.01543	1.26727
EXPOSURE	CMAX0-84	1	-0.00160	0.00107	-1.50	0.1404	-0.00375	0.00054736
L_ALT_BASE		1	0.54217	0.14140	3.83	0.0004	0.25755	0.82679

Source: c36321904, Page 316, Table 1.2.1.8.

Figure 30. Scatter plot of maximum AST vs spesolimab C_{max}



Source: c36321904, Page 410, Figure 1.2.1.9.

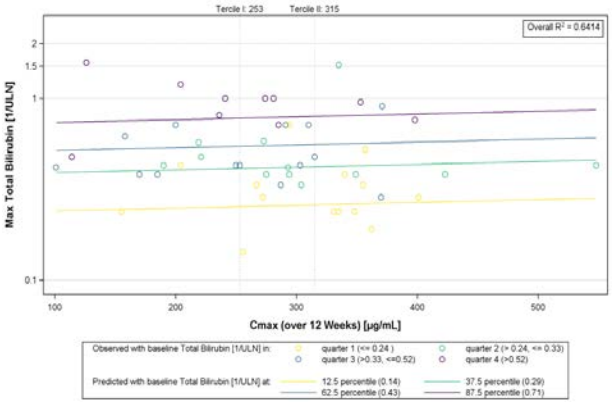
Table 45. Parameter estimates of linear regression model of maximum AST vs spesolimab C_{max}

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	95% Confidence Limits	
Intercept	Intercept	1	0.46428	0.27502	1.69	0.0982	-0.08931	1.01786
EXPOSURE	CMAX0-84	1	-0.00070350	0.00091131	-0.77	0.4441	-0.00254	0.00113
L_AST_BASE		1	0.64157	0.14144	4.54	<.0001	0.35686	0.92628

Source: c36321904, Page 411, Table 1.2.1.10.

Figure 31. Scatter plot of maximum total bilirubin vs spesolimab C_{max}



Source: c36321904, Page 201, Figure 1.1.1.11.

Table 46. Parameter estimates of linear regression model of maximum bilirubin vs spesolimab C_{max}

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	95% Confidence Limits	
Intercept	Intercept	1	-0.10648	0.16270	-0.65	0.5160	-0.43378	0.22083
EXPOSURE	CMAX0-84	1	0.00035831	0.00055595	0.64	0.5224	-0.00076011	0.00148
L_TBILI_BASE		1	0.69634	0.07744	8.99	<.0001	0.54055	0.85212

Source: c36321904, Page 202, Table 1.1.1.12.

The FDA's Assessment:
Applicant's ER safety analysis was verified by the reviewer. No significant correlation between model predicted spesolimab $C_{max,1st\ dose}$ and pustule clearance. While due to the very limited patients from a single dose level of spesolimab treatment, the ER efficacy relationship observed for spesolimab is inconclusive, which should be interpreted with caution. Additional ER safety analysis was performed among patients with other diseases.

19.5 Clinical/Biostatistics

Table 47. GPPPGA at Day 1 (Randomization) and Day 8 by Individual Components (RS[1])

Subject ID	Treatment Group	Day 1 GPPPGA (Baseline/Randomization)				Day 8 GPPPGA				GPPPGA Total Score of 0 or 1	Comment
		Pustules	Erythema	Scaling	Average	Pustules	Erythema	Scaling	Average		
(b) (6)	Spesolimab	2	3	3	2.67	0	1	1	0.67	Yes	
	Placebo	4	3	3	3.33	1	0	1	0.67	Yes	
	Placebo	2	4	3	3.00	0	2	1	1.00	Yes	
	Spesolimab	3	3	2	2.67	0	2	1	1.00	Yes	
	Spesolimab	3	3	2	2.67	0	2	1	1.00	Yes	
	Spesolimab	3	3	3	3.00	0	1	2	1.00	Yes	
	Spesolimab	4	3	3	3.33	0	2	1	1.00	Yes	
	Spesolimab	3	3	2	2.67	0	2	1	1.00	Yes	
	Spesolimab	4	4	3	3.67	0	1	2	1.00	Yes	
	Spesolimab	4	3	3	3.33	0	1	2	1.00	Yes	
	Spesolimab	4	4	4	4.00	0	2	2	1.33	Yes	
	Spesolimab	2	3	4	3.00	0	2	2	1.33	Yes	
	Spesolimab	4	3	2	3.00	0	2	2	1.33	Yes	
	Spesolimab	3	3	3	3.00	0	2	2	1.33	Yes	
	Spesolimab	2	3	3	2.67	0	1	3	1.33	Yes	
	Spesolimab	3	3	4	3.33	0	1	3	1.33	Yes	
	Spesolimab	4	3	2	3.00	0	3	1	1.33	Yes	
	Spesolimab	3	4	2	3.00	0	3	2	1.67	No	
	Placebo	3	3	2	2.67	2	2	2	2.00	No	
	Spesolimab	3	3	3	3.00	0	3	3	2.00	No	
	Spesolimab	4	4	3	3.67	0	3	3	2.00	No	
	Placebo	3	3	3	3.00	2	3	2	2.33	No	
	Spesolimab	3	3	2	2.67	2	3	2	2.33	No	
	Spesolimab	2	4	2	2.67	0	4	3	2.33	No	
	Spesolimab	3	3	3	3.00	1	3	3	2.33	No	
	Spesolimab	2	4	4	3.33	2	3	2	2.33	No	
	Placebo	3	3	3	3.00	2	3	3	2.67	No	
	Spesolimab	2	4	2	2.67	2	4	2	2.67	No	
	Spesolimab	3	3	2	2.67	2	3	3	2.67	No	
	Placebo	4	4	3	3.67	2	4	2	2.67	No	

Subject ID	Treatment Group	Day 1 GPPPGA (Baseline/Randomization)				Day 8 GPPPGA				GPPPGA Total Score of 0 or 1	Comment
		Pustules	Erythema	Scaling	Average	Pustules	Erythema	Scaling	Average		
(b) (6)	Placebo	3	3	3	3.00	2	3	3	2.67	No	
	Placebo	4	3	3	3.33	3	2	4	3.00	No	
	Placebo	2	3	3	2.67	3	3	3	3.00	No	
	Placebo	2	4	3	3.00	2	4	3	3.00	No	
	Spesolimab	4	3	3	3.33	3	3	3	3.00	No	
	Spesolimab	4	4	3	3.67	2	4	3	3.00	No	
	Placebo	3	3	3	3.00	3	3	3	3.00	No	
	Placebo	3	2	3	2.67	3	3	3	3.00	No	
	Spesolimab	4	4	2	3.33	3	4	3	3.33	No	
	Placebo	2	3	3	2.67	3	4	3	3.33	No	
	Placebo	3	3	3	3.00	4	3	3	3.33	No	
	Placebo	4	4	3	3.67	4	3	3	3.33	No	
	Spesolimab	3	4	3	3.33	3	4	3	3.33	No	
	Placebo	2	3	3	2.67	3	3	4	3.33	No	
	Spesolimab	3	4	4	3.67	3	4	4	3.67	No	
	Spesolimab	4	3	2	3.00	4	3	4	3.67	No	
	Spesolimab	4	4	3	3.67	4	4	3	3.67	No	
	Spesolimab	4	4	4	4.00	4	4	4	4.00	No	
	Placebo	4	4	4	4.00	4	4	4	4.00	No	
	Spesolimab	3	3	3	3.00	9999	9999	9999	9999	No	Discontinued
	Spesolimab	3	3	3	3.00	9999	9999	9999	9999	No	Escape SOC (Day 3)
	Placebo	4	3	2	3.00	9999	9999	9999	9999	No	Escape SOC (Day 2)
	Spesolimab	3	3	2	2.67	9999	9999	9999	9999	No	Escape SOC (Day 4)

[1] Randomized Set (RS): all randomized subjects.
Source: Statistical Reviewer's Analysis; ADQSEP.xpt

19.6 Additional Clinical Outcome Assessment Analyses

The Division of Clinical Outcome Assessment (DCOA) was consulted and provided the following review conclusions. Refer to DCOA review by Dr. Julia Ju, PharmD., PhD., dated April 04, 2022.

"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)."

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/

AMY S WOITACH
08/31/2022 01:47:12 PM

YONGCHENG HUANG
08/31/2022 01:53:43 PM

BARBARA A HILL
08/31/2022 01:57:57 PM

ANDREW C GOODWIN
08/31/2022 02:00:55 PM

CHINMAY SHUKLA
08/31/2022 02:05:05 PM
Signing on behalf of Priya Brunsdon and myself.

YANGBING LI
08/31/2022 02:29:13 PM

YOUWEI N BI
08/31/2022 02:30:44 PM

OLUSEYI A ADENIYI
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MICHAEL A PACANOWSKI
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SURESH DODDAPANENI
08/31/2022 03:25:48 PM

MATTHEW W GUERRA
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MOHAMED A ALOSH
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JULIE G BEITZ
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