13 October 2022
EMA/50357/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Spevigo

International non-proprietary name: spesolimab

Procedure No. EMEA/H/C/005874/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACH	Acrodermatitis continua of Hallopeau
AD	Atopic dermatitis
ADA(-)	Anti-drug antibody (negative)
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BI	Boehringer Ingelheim
BIcMQs	Boehringer Ingelheim customized-MedDRA Query
BSA	Body surface area
Bw	Body weight
CGI-I	Clinical global impression-improvement
CHMP	Committee for Medicinal Products for Human Use (of the EMA)
CI	Confidence interval
CL_{CR}	Creatinine clearance
C_{max}	Maximum measured concentration of the analyte in plasma
CMC	Chemistry, manufacturing, and control
CRF	Case report form
CRP	C-reactive protein
CTP	Clinical trial protocol
CTR	Clinical trial report
DBL	Database lock
DDI	Drug-drug interaction
DLQI	Dermatology quality of life index
DME	Designated medical event
DP	Drug product
DRESS	Drug reaction with eosinophilia and systemic symptoms
EoS	End of study
EQ-5D-5L	EuroQol 5-dimensional quality of life questionnaire (5-level version)
ERASPEN	European Rare And Severe Psoriasis Expert Network
FACIT	Functional assessment of chronic illness therapy
GFR	Glomerular filtration rate
GPP	Generalized pustular psoriasis
GPPASI	Generalized pustular psoriasis area and severity index
GPPGA	Generalized pustular psoriasis physician global assessment
i.v	intravenous
IBD	Inflammatory bowel disease
IL	Interleukin
IMP	Investigational medicinal product
IND	Investigational new drug
ISI	Integrated summary of immunogenicity
ISS	Integrated summary of safety
ITE	Indirect target engagement
JDA	Japanese Dermatological Association
LD	Loading dose
LOCF	Last observation carried forward
MAA	Marketing authorisation application
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities

MHRA	Medicines and Healthcare Products Regulatory Agency of the UK
MIP	Macrophage inflammatory protein
NAb	Neutralising antibody
NC	Not calculable
NR(I)	Non-response (imputation)
OC	Observed cases excluding all values after any use of escape medication, OL spesolimab on Day 8, or spesolimab rescue medication after Day 8
OC-IR	Observed cases including values after any use of escape medication/ OL spesolimab on Day 8/spesolimab rescue medication after Day 8
OL(E)	Open-label (extension)
PCSA	Possibly clinically significant abnormality
PD	Pharmacodynamics
PDCO	Paediatric Committee of the EMA
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Device Agency of Japan
PoC	Proof of concept
PPP	Palmoplantar psoriasis
PRO	Patient-reported outcome
PSS	Psoriasis symptom scale
PT	Preferred term of MedDRA
Q	Quartile
qxw	Once every x weeks
RCTC	Rheumatology common toxicity criteria
REP	Residual effects period
RS	Randomised set
s.c	subcutaneous
SA	Scientific advice
SAE	Serious adverse event
SAF	Safety analysis set
SCE	Summary of clinical efficacy
SCS	Summary of clinical safety
SD	Single dose / standard deviation
SOC	System Organ Class of MedDRA
SoC	Standard of care
TB	Tuberculosis
TFL	Tables, table s, listings
Th	T helper cell
TNF	Tumour necrosis factor
UC	Ulcerative colitis
UDAEC	User-defined adverse event category
ULN	Upper limit of normal
VAS	Visual analogue scale

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Boehringer Ingelheim International GmbH submitted on 6 October 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Spevigo, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No

726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 February 2021.

The applicant applied for the following indication: Spevigo is indicated for the treatment of flares in adult patients with generalised pustular psoriasis.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decisions P/0178/2021 and P/0195/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

1.1. Information relating to orphan market exclusivity

1.1.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Applicant's request(s) for consideration

1.2.1. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.2.2. Conditional marketing authorisation

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

1.2.3. New active substance status

The applicant requested the active substance spesolimab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a

medicinal product previously authorised within the European Union.

1.3. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
22 February 2018	EMEA/H/SA/3721/1/2017/III	*André Elferink, Fernando de Andrés Trelles, Carin Bergquist*
28 March 2019	EMEA/H/SA/3721/1/FU/1/2019/III	*Caroline Auriche, André Elferink, Rune Kjeken*

EMEA/H/SA/3721/1/2017/III: The Scientific advice pertained to the following *quality, non-clinical, and clinical* aspects:

Quality: Acceptability of the analytical comparability approach to support the use of Phase III clinical trial supplies and commercial supplies, the Clinical Trial Supply strategy and the combination product development programme for use of the PFS including design control, risk management and human factors engineering activities.

Non-clinical: The toxicology data to support inclusion of patients of ages 16 and older in the proposed pivotal studies in GPP patients. The non-clinical safety programme to support initiation of study 1368. 13.

Clinical: whether GPP was a seriously debilitating or life-threatening disease, with high unmet medical need

The sufficiency of available clinical safety to support the conduct of the study 1368.13. Acceptability of the proposed patient populations to be included in the two pivotal trials 1368.13 and 1368.27 and the design of study 1368.13, the proposed co-primary endpoints and the key secondary endpoints.

Acceptability of the proposed approach for assessing therapeutic protein-drug interaction.

Acceptability of the proposed safety data base in GPP patients and from other indications.

Acceptability of the overall development programme for the targeted indication including the approach to development in the paediatric population.

EMEA/H/SA/3721/1/FU/1/2019/III: The scientific advice pertained to the following *quality, non-clinical, and clinical* aspects:

Quality: Standards applicable to the pre-filled syringe (PFS)

Non-Clinical: Acceptability of the current nonclinical data to support Phase III trials and MAA submission

Clinical: Acceptability of the available clinical safety data to support the conduct of study 1368.27 in GPP patients. Acceptability of the dosing regimens selected for the Phase III study 1368.27, also the proposed study population in 1368.27, the proposed sample size, the choice of endpoints in 1368.13 and 1368.27, the statistical tests proposed for the analysis of the primary and key secondary endpoints in trial 1368.27, the strategy for controlling the Type I error rate in the trial 1368.27 and the handling of missing data on the primary and key secondary endpoint analyses in trial 1368.27.

Acceptability of the overall approach to assess the effect of immunogenicity, the proposed approach for assessing therapeutic protein-drug interaction and the disposition of BI 655130.

Acceptability of the proposed safety database in GPP patients, and the proposed strategy for the evaluation of safety data.

1.4. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Thalia Marie Estrup Blicher

The appointed CHMP co-rapporteur had no such prominent role in Scientific advice relevant for the indication subject to the present application.

The application was received by the EMA on	6 October 2021
The procedure started on	28 October 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 January 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	27 January 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 February 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 May 2022
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
A GCP inspection at 2 Clinical Investigator sites in Germany and at the Sponsor site in the United States between 1 February and 4 March 2022. The outcome of the inspection carried out was issued on:	12 April 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	27 June 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	07 July 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	21 July 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	12 August 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues	01 September 2022

to all CHMP and PRAC members on	
The CHMP agreed on a second list of outstanding issues to be sent to the applicant on	15 September 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 September 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	28 September 2022
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	11 October 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Spevigo on	13 October 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	13 October 2022
A revised opinion was adopted by the CHMP	20 December 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Generalised pustular psoriasis (GPP) is a rare severe neutrophilic skin disease characterised by episodes of widespread eruption of sterile, macroscopically visible pustules that can occur with systemic inflammation. Flares are characteristic of the clinical course of GPP, with some patients having a relapsing disease with recurrent flares and others having a persistent disease with intermittent flares.

2.1.2. Epidemiology

The prevalence of GPP varies across geographical regions (Table 1). It is more prevalent in females than in males, with a reported female to male ratio of 2:1 and a mean age of onset of about 41 years (range: 21 to 81 years).

Table 1. Prevalence of GPP by geographical region

Country	Prevalence	Data source
China	1.4 per 100 000 persons	Urban Employee and Urban Resident Basic Medical Insurance
France	1.76 per 1 000 000 persons	French survey of 121 dermatology clinics
Germany	4.6 per 10 000 persons[1]	German administrative claims database
Japan	0.2 to 0.3 per 10 000 persons	Japanese claims database [data on file]
USA	0.7 to 0.9 per 10 000 persons	US claims databases [data on file]

[1] Based on an ICD-10 code of L40.1 (GPP), with the limitation that the diagnosis might neither have been made nor confirmed by a dermatologist

2.1.3. Biologic features

According to Krueger et al (Krueger et al, 2022) the pathogenic mechanisms of GPP fares are poorly understood. However, recent advances in our understanding of the biology and genetic mechanisms of autoinflammation and autoimmunity have led to the characterisation of critical genetic mutations associated with the incidence and pathogenesis of GPP such as IL36RN loss-of-function mutations resulting in the hyperactivation of IL-36 signaling due to the stimulation of the IL-36 receptor by its ligands, IL-36α, IL36β, and IL-36γ. The increased production of IL-36 induces the production of chemokines by keratinocytes, leading to neutrophil epidermal accumulation, which drives the pathogenesis of GPP, and the formation of the characteristic spongiform pustules (Krueger et al, 2022).

2.1.4. Clinical presentation, diagnosis and prognosis

The classification of GPP is presented in Table 2.

Table 2. Classification of GPP by ERASPEN and the JDA

Consensus definition for the diagnosis of GPP by the European Rare And Severe Psoriasis Expert Network (ERASPEN)	
Primary, sterile, macroscopically visible pustules on non-acral skin (excluding cases where pustulation is restricted to psoriatic plaques)	
Subclassifier	With or without systemic inflammation
Subclassifier	With or without psoriasis vulgaris
Subclassifier	Either relapsing (>1 episode) or persistent (>3 months)
Definition of GPP and the primary signs/parameters required for diagnosis by the Japanese Dermatological Association (JDA)	
A definitive diagnosis of GPP can be made in patients with all of the 4 following features; GPP would be suspected in patients with features 2 and 3	
1	Systemic symptoms, such as fever and fatigue
2	Systemic or extensive flush, accompanied by multiple sterile pustules that sometimes merge to form lakes of pustules
3	Neutrophilic subcorneal pustules histopathologically characterised by Kogoj's spongiform pustules
4	The above clinical and histological features recur repeatedly

A GPP flare consists of the acute onset of rapidly disseminating painful skin manifestations (including aseptic pustules), which can be accompanied by systemic symptoms, such as high fever and extreme fatigue, as well as acute phase response (with increased C-reactive protein). GPP flares may be idiopathic or triggered by external stimuli (e.g. infection, corticosteroid use or withdrawal, stress, or pregnancy). Whilst the severity of GPP flares can vary, GPP flares can lead to failure in multiple organ systems, e.g. lung (acute respiratory distress syndrome), liver/kidney, cardiovascular/shock, and possibly to sepsis increasing the likelihood of hospitalisation for inpatient medical management and monitoring. The all-cause mortality for patients hospitalized with a GPP flare was estimated to be 2.5% within 4 weeks after the flare. The reported mortality rates due to GPP or associated treatment ranged between 2% and 16%.

GPP flares are also associated with significant burden on patient's lives. Based on patient experience data, presented in the dossier, patients living with GPP ranked pustules, pain, and itch as the most burdensome symptoms. In addition to skin symptoms, patients reported fever, poor sleep, general malaise, exhaustion, anxiety, and depression. They described being socially isolated and having negative impacts on their professional life, relationships, and daily activities.

Information on the natural course of GPP flares from the patient perspective are presented in the dossier. Of the 66 respondents, 41% experienced 2 to 3 flares and 46% experienced ≥4 flares in the previous year. A total of 76% of respondents indicated their flares were severe in nature; 23% of patients surveyed visited an emergency department, and 12% were admitted to the hospital because of their GPP flare. After the flares have resolved, 77% of respondents still expected some residual symptoms when their condition is "under control".

2.1.5. Management

To date, there are no approved therapies specifically indicated for the treatment of GPP flares. There is limited evidence of the efficacy and safety for the use of the non-targeted immunomodulatory therapies (e.g. methotrexate, ciclosporin, retinoids, systemic corticosteroids). Most of therapies used in clinical practice are associated with toxicities. The limitation in efficacy and safety data also applies to the use of biologic treatment options in GPP, including TNF inhibitors (adalimumab, infliximab, and certolizumab pegol), IL-17 inhibitors (secukinumab, brodalumab, and ixekizumab), and IL-23 inhibitors (risankizumab and guselkumab). The approval of these biologics in Japan for the treatment of GPP is based on evidence from endpoints assessing any improvement (without the need for complete pustular

clearance) at late time points (e.g. 12 to 16 weeks) in small (<12 patients), open-label, single-arm trials. Data on the impact of these biologics on flare treatment (e.g. time to pustular clearance and sustainability) are lacking.

In a recent publication (Kromer et al, 2020) on the treatment response of 86 patients with GPP receiving 201 treatment courses for their disease in dermatology centres in Germany, the most frequently administered drugs were methotrexate (20.9% of treatment courses), acitretin (13.9%), fumaric acid esters (9.5%), etanercept and infliximab (9.0% each), as well as adalimumab and ciclosporin (8.5% each). Overall, in nearly 60% of all treatment series, no response (27.3%) or only partial response (31.4%) was achieved, while excellent response was reached in 41.3% of all treatment courses. According to the authors, these 3 qualitative categories of response were used for this retrospective study because the parameters of disease severity GPPGA and GPP Area and Severity Index (GPPASI) had only recently been established.

Most of the participants in the applicant's survey reported trying multiple treatments over the years either consecutively and/or in combination, due to limited efficacy or loss of efficacy over time or side effects. Given these limitations of current treatments, patients emphasized the high unmet need for new treatments that rapidly and completely resolve the symptoms associated with GPP flares and prevent the reoccurrence of flares, with an acceptable safety profile. Patient-relevant treatment goals are to reduce or eliminate pustules, reduce or eliminate flares, clear crust and scaling, and reduce pain.

In summary, there is a high need for treatments that rapidly resolve the symptoms associated with GPP flares and prevent reoccurrences of flares with an acceptable safety profile.

2.2. About the product

Spesolimab (BI 655130) belongs to the pharmacotherapeutic group Immunosuppressants, Interleukin inhibitors. The ATC code is: L04AC22.

Spesolimab is a humanized antagonistic monoclonal IgG1 antibody that binds to IL-36R and blocks human IL-36α-, IL-36β-, and IL-36γ-induced IL-36R activation, leading to suppressed pro-inflammatory and pro-fibrotic pathways in inflammatory skin diseases. In patients with GPP, blockade of IL-36R signalling is a novel, targeted therapeutic approach. IL-36R inhibition with spesolimab has been shown to lead to normalisation of inflammatory blood biomarkers (CRP, neutrophils, leukocytes), the gene expression profile of lesional skin in patients with GPP, and the downregulation of biomarkers correlated with decreases in clinical disease severity.

The recommended dose of Spevigo is a single dose of 900 mg (2 x 450 mg/7.5 mL vials) administered as an intravenous infusion. If flare symptoms persist, an additional 900 mg dose may be administered 1 week after the initial dose. Following dilution with 0.9% sodium chloride solution, Spevigo should be administered as a continuous intravenous infusion over 90 minutes.

2.3. Type of application and aspects on development

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004. Although it was agreed that an unmet medical need exists and that the results from study 1368-0013 indicate that spesolimab induces rapid pustular clearance in patients with GPP flares, it was considered that the small number of subjects would make the safety assessment difficult. In addition, it was noted that very limited data would be available for the administration of additional spesolimab doses and therefore, it was not considered that it had been sufficiently demonstrated that spesolimab

constitutes a major interest from the point of view of public health and from the viewpoint of therapeutic innovation.
Based on these limitations, the CHMP did not agree to the applicant's request for an accelerated assessment.

The applicant applied for a full marketing authorisation, but during the assessment, in response to CHMP concerns on the comprehensiveness of the data, requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above Regulation, based on the following criteria:

- The benefit-risk balance is positive in the target population of adult patients with GPP flares, as discussed in section 3.7.2. The available data demonstrates a clear benefit, as a significantly larger proportion of patients in the spesolimab arm achieved pustular clearance at week 1 as well as relevant response in the GPPGA total score, evaluating also erythema and scaling /crusting. It is acknowledged by CHMP that long-term efficacy data is scarce and more information on safety is required. However, the demonstrated risk to patients is manageable. Therefore, the benefits of treatment of adult patients with GPP flares with spesolimab outweigh the risk inherent to the absence of comprehensive data on flares re-treatment at time of opinion.

- It is likely that the applicant will be able to provide comprehensive data.

  - Data from the planned additional interventional post-authorisation trial 1368-0120 in approximately 40 patients treated with spesolimab i.v. will evaluate the efficacy and safety as well as the impact of immunogenicity on efficacy, safety, and PK of spesolimab i.v. for the treatment of recurrent, new flares after initial flare treatment with spesolimab i.v. The primary endpoint of trial 1368-0120, the achievement of a GPPGA pustulation subscore of 0 one week after treatment of the first recurrent flare with spesolimab i.v., is in line with the primary endpoint of the pivotal trial 1368-0013. The trial aims to confirm the positive benefit-risk balance of the approved indication "Treatment of flares in adult patients with generalised pustular psoriasis as monotherapy" and to provide comprehensive data on efficacy, safety, immunogenicity, and PK data on the treatment of subsequent GPP flares. A feasibility assessment of the study 1368-0120 was provided. Based on the current feasibility, the final clinical trial report is planned by January 2028. Study 1368-0120 is considered to be feasible within the proposed timeframe.

- Unmet medical needs will be addressed, as this is the first targeted therapy for GPP flare/s. Most of the systemic non-targeted immunomodulatory therapies used in GPP (e.g. methotrexate, ciclosporin, retinoids, systemic corticosteroids) are associated with toxicities and have only limited evidence of efficacy. Some biologics, including TNF-, IL-17, and IL-23 inhibitors, are approved for treatment of GPP in Japan based on small, open-label, single-arm trials that did not specifically evaluate response to flares. Thus, even though some products are used for the treatment of GPP (including off-label use), none is specifically indicated and documented for (re-)treatment of GPP flares, and their effectiveness is considered suboptimal by dermatologists and patients. In pivotal trial 1368-0013, spesolimab was shown to improve GPP pustulation in comparison to placebo and to have beneficial effects on other (systemic) symptoms and efficacy endpoints (including patient-reported outcomes) associated with GPP flares, while showing an acceptable safety profile. Hence, spesolimab addresses the unmet medical need for the treatment of GPP flare. The planned clinical trial 1368-0120 will focus on treatment of subsequent flares to provide comprehensive data to address the unmet need for subsequent flare treatment.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.
  - While the severity of GPP flares can vary, any individual GPP flare can lead to failure in multiple organ systems, e.g. lung (acute respiratory distress syndrome), liver/kidney, cardiovascular/shock, and possibly to sepsis. All GPP flares have the potential to progress to a life-threatening status, requiring hospitalisation and potentially intensive care unit treatment. GPP flares have a substantial mortality; the all-cause mortality for patients hospitalised with a GPP flare was estimated to be 2.5% within 4 weeks after the flare. Aside from the potential risk of hospitalisation and mortality, GPP flares are also associated with significant burden on patients' lives. Based on patient experience data, patients living with GPP ranked pustules, pain, and itch as the most burdensome symptoms. In addition to skin symptoms, patients reported fever, poor sleep, general malaise, exhaustion, anxiety, and depression. They described being socially isolated and having negative impacts on their professional life, relationships, and daily activities.

  - Spesolimab improves GPP pustulation while having beneficial effects on other (systemic) symptoms and patient-reported outcomes relevant for GPP flares, with manageable risks. Considering that spesolimab is effective and based on assessment of available data no serious safety issues have been identified in the treatment of GPP flares, which are associated with significant impairment of the quality of life of patients and their families, hospitalisation with/without intensive care, disability, and potential mortality, the benefits to public health of the immediate availability of spesolimab outweigh the risks inherent in the fact that more comprehensive efficacy and safety data are still required.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a concentrate for solution for infusion containing 450 mg of spesolimab as active substance.

Other ingredients are: sodium acetate trihydrate (E262), glacial acetic acid (E260) (for pH adjustment), sucrose, arginine hydrochloride, polysorbate 20 (E432) and water for injections.

The product is available in a colourless 10 mL glass vial (type I glass), with a coated rubber stopper and aluminium crimp cap with blue plastic button.

2.4.2. Active Substance

2.4.2.1. General information

The active substance (international non-proprietary name spesolimab) is a recombinant IgG1 antibody directed against the human IL-36 receptor. Spesolimab is composed of two heterodimers. Each of the heterodimers is composed of a heavy and a light polypeptide chain. Each heavy chain (HC) is composed of 449 amino acids and each light chain (LC) contains 215 amino acids. The four polypeptide chains of the antibody molecule are covalently linked together by disulfide bonds. The two HCs are connected within the hinge region by two inter-chain disulfide bonds. The antibody molecule contains a total of 12 intra-chain disulfide bonds, four within each of the two HCs and two within each of the two LCs.

The antibody has been engineered to contain two mutations in the Fc region to reduce potential effector functions.

2.4.2.2. Manufacture, characterisation and process controls

Description of manufacturing process and process controls

Spesolimab active substance is manufactured by Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany. Good Manufacturing Practice (GMP) compliance for the site has been confirmed.

The active substance manufacturing process has been adequately described. The active substance is produced in a Chinese Hamster Ovary (CHO) cell line. The purification process consists of chromatography steps, virus inactivation, virus filtration, as well as concentration and buffer exchange by ultrafiltration/diafiltration and final formulation. The batch numbering system is described in the dossier and it is considered acceptable.

Flow charts of the cell culture, harvest and purification processes are provided including the assignment of critical process parameters and associated in process controls (IPCs) to each unit operation. The process has been sufficiently described and in-process controls are adequately set to control the process.

Information on column dimensions (diameter and bed height) are listed in tables with process parameters. The column lifetimes are covered by validation studies and limited to the anticipated validated number of product or regeneration cycles. This is found acceptable.

Virus filtration reprocessing and bioburden reduction filtration reprocessing can be performed, controlled in the same manner as initially performed. This approach can be considered as acceptable.

The active substance is stored in portable stainless steel cryo vessels.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. No human or animal derived materials are used in the active substance manufacturing process. During manufacturing of one raw material which is used as a media component in cell line development, in master cell bank (MCB) and working cell bank (WCB) generation as well as in early stages of cell culture process, an animal derived component was used as secondary raw material. A risk assessment has been provided on the indirect use of animal origin components in the production process for said raw material and it demonstrates that there is no concern that Transmissible Spongiform Encephalopathy/ Bovine Spongiform Encephalopathy (TSE/BSE) or viral contamination could affect the finished product. Acceptable documents have been provided for raw materials of biological origin used.

Sufficiently detailed descriptions of the development of the expression vectors, origin of cells and development of cell banks have been provided.

A two tiered cell banking system is used and sufficient information is provided regarding testing (sterility, mycoplasma, identity of CHO cells and adventitious agents) of Master Cell Bank (MCB) and Working Cell Bank (WCB) and release of future WCBs. Genetic sequence and genetic consistency were investigated, confirming the cDNA sequence of LC- and HC-chains. Genetic stability with regards to copy number was also confirmed. Satisfactory information has also been provided on storage and stability of cell banks.

Prior to transfection and start of cell line development, Host Cell Bank (HCB) and Master Host Cell Bank MHCB) are used as the starting point for the MCB.

Tests for bovine and porcine viruses were not performed on the MCB with the justification that these tests had already been conducted on the host cell bank. This approach is acceptable. Testing for mouse minute virus (MMV) is controlled by Polymerase chain reaction (PCR) or via inclusion of the MMV-susceptible cell line 324K in the adventitious virus *in vitro* test. This approach is acceptable.

Genetic sequence and genetic consistency were investigated, confirming the cDNA sequence of LC- and HC-chains. Genetic stability with regards to copy number was also confirmed. Satisfactory information has also been provided on storage and stability of cell banks.

Genetic heterogeneity in the heavy chain gene was found in the cell banks through Southern blot analysis. Data provide demonstrated that the heterogeneity is reproducible and consistent.

Data from process performance and product quality analysis show no impact on quality of the product. The cell banks can therefore be accepted.

Detailed information on establishment of future WCBs has been provided, including tests that will be performed and acceptance criteria.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the spesolimab active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

The hold times for process intermediates are stated in the dossier and found acceptable.

Process validation

The spesolimab active substance manufacturing process has been validated adequately. Consistency in production has been demonstrated. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces spesolimab active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Validation of the active substance manufacturing process was conducted using a lifecycle approach, consisting of three stages: a) Process Design, b) Process Performance Qualification (PPQ) and c) Continuous Process Verification (CPV).

<u>PPQ batches</u>

PPQ of the manufacturing process has been performed at commercial scale, with consecutive batches executed under nominal manufacturing conditions, according to pre-approved validation protocols and with approved batch records, related test methods and established quality systems.

The PPQ was successfully completed by demonstrating process consistency, as well as by meeting all validation requirements.

The release acceptance criteria were met for the active substance for the PPQ batches.

Hence, it is agreed that the in-process test data, control of process parameters and active substance release testing data demonstrate that the process can be controlled effectively, to reproducibly yield active substance that meets its pre-determined quality criteria.

Removal of impurities

It has been acceptably demonstrated during PPQ that the Process related impurities (PRI) can be reduced to acceptable levels.

In-process hold times

Hold time limits were established for the process intermediates of the manufacturing process, based on both the chemical stability and microbial control of the process intermediates in the individual hold tanks. The hold times are summarised by the applicant. The information provided is found acceptable.

Concurrent validations

A number of concurrent validations are described:

- Resin lifetime and resin cleaning validation
- Membrane lifetime and membrane cleaning validation
- Reprocessing of the virus filtration
- Reprocessing of the formulation and the active substance filtrations

The content and approach of the concurrent validations presented in Module 3.2.R are found acceptable.

Continuous process verification (CPV)

The CPV stage will be initiated and will continue concurrently with commercial manufacturing in order to ensure that the manufacturing process remains in a state of control during commercial manufacture. Data of process parameters, quality influencing indicators and release tests will be continuously reviewed and reported at least on an annual basis, as part of the product quality review. This approach is considered acceptable.

Manufacturing process development

Process history and comparison

Different processes have been used throughout development. Overviews of the active substance batches produced, including process type and their intended use, have been provided.

CQAs

A quality target product profile (QTPP) was compiled for spesolimab describing fundamental requirements of the product to be developed, and active substance critical quality attributes (CQAs) related to the quality targets were identified.

The applicant have provided tables that summarise a large number of CQAs, including rationales, derived from systematic risk assessments for product-related attributes, process-related attributes and pharmaceutical attributes, respectively.

Process Characterisation Studies (PCS)

PCS have been performed in established small scale systems requiring suitable scale down models (SDMs) that appropriately represent the commercial scale of the manufacturing process. Based on development data, acceptance criteria were determined to evaluate the suitability of the developed SDM. Statistical analyses were performed.

The PCS then provided an in-depth understanding of each unit operation. Process parameters were systemically varied using the established SDMs and impact on product quality and/or process performance was monitored. The results of the PCS experiments were compared against predefined acceptance criteria that are acceptable for the examined CQAs and performance indicators.

For purification small-scale studies, the applicant has described the methodology and the conclusions, and has also provided detailed summaries, including data.

Analytical comparability

The manufacturing process underwent continuous improvements throughout development. The analytical comparability programme was described.

An overview of the types of batches used for the analytical comparability assessment was given.

Overall, the active substances derived from all processes are considered comparable, since the argumentation and conclusions by the applicant is found acceptable.

The analytical assessment confirms that a comparable product has been produced by each process. Therefore, material used in non-clinical, clinical studies, as well as for commercialisation can be considered equivalent, and support the product shelf life for the commercial finished product based on material from primary and supportive stability programs.

Characterisation

The spesolimab active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a human IgG1-type antibody directed against the human IL-36 receptor.

The antibody has been engineered to contain two mutations in the Fc region to reduce potential effector functions. A comprehensive physicochemical and biological characterisation of the active substance spesolimab is presented.

A panel of orthogonal state-of-the-art tests were applied. Studies of primary structure, higher order structure and heterogeneity, e.g., glycosylation, charge and oxidized variants as well as biological activity were included. Detailed results including peptide mapping profiles, intact mass spectrum, CD spectra, DSC profile, chromatograms and electropherograms, oligosaccharide mapping profile are provided in the dossier.

The analytical results are consistent with the proposed structure. Furthermore, heterogeneity of the active substance was adequately characterised. In summary, the characterisation is considered appropriate for this type of molecule.

The major process-related impurities have been controlled as IPCs during active substance manufacturing development. Continuously low levels of these impurities in in-process testing, active substance release testing and during PPQ adequately justifies the omission of routine testing of the impurities. HCP testing is included in the active substance specification.

The only product-related impurities discussed in this section of the dossier are molecular variants (high-molecular-weight (HMWs) and low-molecular-weight LMWs) and these are routinely controlled.

As concerns risk assessment for elemental impurities and nitrosamine contamination, information is presented in the finished product part of the dossier.

2.4.2.3. Specification

Specifications, with acceptance criteria are set in accordance with ICH Q6B and include control of appearance, identity, purity and impurities, concentration, potency, and general safety tests.

The active substance specification is set based on active substance batch data, which is found appropriate. The proposed acceptance criteria for the general tests; appearance, pH, osmolality, endotoxins and bioburden are found acceptable.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

Several of the non-compendial analytical procedures described are used for testing of both active substance and finished product. Validation summaries are provided for all non-compendial methods and these are demonstrating suitability for the intended use.

Batch analysis

Batch analysis data are presented for all batches used for non-clinical and clinical studies, as well as batches produced during validation of the active substance manufacturing process. All batches were tested according to the testing specifications and the analytical procedures that were in place at the time of release.

Batch results are generally consistent within process versions and confirm consistency of the manufacturing process versions.

Reference materials

The same reference standard is used for analysis of spesolimab active substance and finished product. The reference standards are tested and characterised using a panel of analytical methods and data is provided in the dossier.

An appropriate requalification programme for the primary reference standard and working reference standard is in place. This is acceptable.

The intended use of the reference standards is for the analytical testing of spesolimab active substance and the finished product.

2.4.2.4. Stability

The proposed commercial shelf life of the active substance is 36 months when stored at the intended storage condition.

For the accelerated stability study at 2 – 8°C results are available up to 12 months and no significant changes were observed for any test parameters.

Studies under stressed conditions show degradation trends, however the results still remained within the acceptance criteria.

The proposed shelf life of the active substance of 36 months when stored at the intended storage condition is acceptably supported by long-term stability data.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Description of the product and Pharmaceutical development

The finished medicinal product is a concentrate for solution for infusion 450 mg/vial (60 mg/mL) and is furthermore a buffered, isotonic, preservative-free solution, which is diluted with sodium chloride prior to administration to the target concentration.

The nominal fill volume is 7.5 mL in a 10 mL glass vial, and an overfill has been introduced and is sufficiently justified. There are no formula overages in the spesolimab finished product.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

The primary packaging is a colourless 10 mL glass vial (type I glass), with a coated rubber stopper and aluminium crimp cap with blue plastic button. The vial, stopper and seal components are compliant with appropriate Ph. Eur. monographs for primary containers and closures. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

During the development, different formulations have been developed and used for clinical studies of spesolimab.

From the commercial process, a single active substance is manufactured. The active substance is formulated as an isotonic aqueous solution in a buffer consisting of acetate buffer, sucrose, arginine HCl and polysorbate 20 (PS20). This formulation is the intended commercial formulation for spesolimab concentrate for solution for infusion 450 mg/vial (60 mg/mL).

A formulation robustness study has been performed. The study shows that the commercial formulation of spesolimab 450 mg/vial at 60 mg/mL is robust at the proposed storage condition.

The formulation development section in the dossier describes and justifies the chosen formulation and is sufficiently comprehensive.

Data has been provided in the dossier on the specific batches used in each specific clinical study for spesolimab including information on the formulation, strength, dosage form, fill volume, finished product batch and active substance batch numbers.

The manufacturing process development for the finished product has been sufficiently described and justifies the commercial manufacturing process.

The manufacturing process of finished product includes thawing, pooling/splitting and dilution of the active substance, sterile filtration of the final formulated bulk, filling and stoppering. The commercial manufacturing process has been characterised through process characterisation studies of each process step and details for these studies are provided in the dossier.

The process characterisation studies demonstrate at large that the finished product manufacturing process is robust and can deliver the required product quality and process consistency.

The number of multiple filtrations for final formulated bulk 60 mg/mL was evaluated. Furthermore, hold times studies have been performed. This is found acceptable.

The product-contact surface materials used during manufacturing of the finished product were evaluated with respect to potential leachables in relation to the safety concern threshold. Extractable data from the respective vendors of disposables or by extractable studies conducted by the applicant were utilised for the evaluation. A toxicological assessment was conducted for potential leachables and concluded to pose no risk to patients treated with spesolimab concentrate for solution for infusion 450 mg/vial (60 mg/mL). This is found acceptable.

During development, the manufacturing process of the finished product has been modified and several process changes implemented. Comparability has been performed in accordance with ICH Q5E.

An overview of the batches used in the comparability study as well as further details for the comparability assessment have been provided.

All quality attributes studied in the comparability study show a high degree of similarity with very few and minor differences noted and assessed as not expected to have any impact on safety or efficacy. Therefore, it can be agreed to the conclusion by the applicant that comparability has been sufficiently demonstrated for all the attributes tested and all the finished product presentations included and evaluated in this comparability study.

Compatibility of the finished product with the infusion medium (0.9% sodium chloride solution in a 100 mL infusion bag) has been studied and satisfactorily demonstrated during development and in-use stability studies. In-use stability has been studied to simulate in-use conditions and verify the chemical and physical stability of the finished product as well as to confirm the compatibility with the material of the infusion bags as specified in section 6.6 in the SmPC.

Based on the compatibility results and in-use stability results provided in the dossier, it is agreed that chemical and physical in-use stability of the diluted solution of finished product has been demonstrated for 24 hours at 2-30°C followed by 3 hours infusion time, in line with the wording in section 6.3 in the SmPC.

Provided results and described strategy for leachable monitoring of the PPQ batches are found acceptable.

Results for transport simulation studies have been provided in which the impact of the environmental risk factors shock and vibration on the finished product were studied with respect to worldwide distribution. The transport simulation study covered road, ocean and air during transport from the manufacturing site to the end customer and was performed under laboratory conditions. The transport simulation study show that the finished product is sufficiently protected against shock and vibration when stored in the secondary packaging box and case pack configuration.

2.4.3.2. Manufacture of the product and process controls

The finished medicinal product manufacturer is Boehringer Ingelheim Pharma GmbH & Co. KG located in Germany. Appropriate evidence of GMP certification has been provided for each site involved in finished product manufacturing and testing.

The manufacturing process for the finished product consist of thaw of active substance, splitting/pooling, dilution to 60 mg/mL, sterile filtration, aseptic filling, stoppering, crimping and visual inspection. The finished product is manufactured by aseptic technique.

The description of the sections for manufacturing process and process control and for control of critical steps and intermediates of the finished product manufacturing process is found acceptable.

Acceptable ranges are provided for the process parameters and brief process flow diagrams are provided for the manufacturing process of the finished product.

Hold times for the finished product manufacturing process have been defined in the dossier.

Commercial scale consecutive PPQ batches of spesolimab 450 mg/vial (60 mg/mL) finished product have been manufactured at commercial scale. Batch data are provided in the dossier for all commercial scale PPQ batches used for process validation. Stability studies have been initiated on these batches as well and are currently ongoing at long-term (2-8 °C) and accelerated and stressed conditions.

All validation batches complied with the established validation acceptance criteria for all process parameters as well as with the proposed finished product specifications and in-process controls.

Batch homogeneity after sterile filtration, filling and crimping has been successfully demonstrated.

Container closure integrity testing was successfully performed.

The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

2.4.3.3. Product specification

A comprehensive set of relevant tests is included in the specifications document for the finished product covering limits for both release and end-of-shelf life of the various attributes. The tests include controls for appearance, general tests, identity, purity and heterogeneity, potency, quantity and microbiological tests. Method numbers are detailed for all analytical procedures used in the finished product specifications document. The justification for each test and acceptance criteria have been provided in in the dossier

The proposed end-of-shelf-life limits for the purity tests, heterogeneity and potency have been justified and are based on levels in batches shown to be safe and efficacious in clinical trials and/or clinically qualified by other means.

The proposed acceptance criteria for appearance and description, general tests (identity, microbiological tests and container closure integrity) are all found acceptable.

The protein content is measured by UV absorbance.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

No new impurities have been identified in the finished product compared to the ones already identified for the active substance.

Analytical methods

Many tests used for release and stability testing of the finished product are also used for release and stability testing of the active substance.

The analytical procedures were validated in accordance with ICH Q2 and the compendial methods have been verified according to the appropriate compendia chapters and been determined to be suitable for use.

Batch analysis

Batch analyses data has been provided for finished product batches used in clinical trials and stability as well as PPQ-batches manufactured at full commercial scale. Information of these batches include manufacturing batch number, date, batch size, active substance batch(es) used, manufacturing process of the active substance(es) used, formulation and use of the batch. The batch analysis data complies with the limits in the proposed finished product release specification in place at the time of manufacture and confirm process and product consistency. In conclusion, the results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

Reference materials were discussed under the active substance section of this report.

2.4.3.4. Stability of the product

The proposed shelf life for the finished product is 36 months when stored at the recommended storage condition at 2°C to 8°C. In addition, unopened vial may be kept at room temperature (up to 30°C) for up to 24 hours.

The stability studies are performed in accordance with ICH Q5C.

Photostability testing has been performed according to ICH Q1B and showed that the spesolimab finished product should be kept in the outer carton in order to protect from light induced degradation, in line with the wording in section 6.4 in the SmPC.

Compatibility of the finished product with the infusion medium (0.9% sodium chloride solution in a 100 mL infusion bag) has been studied and satisfactorily demonstrated during development and in-use stability studies. In-use stability has been studied to simulate in-use conditions and verify the chemical and physical stability of the finished product as well as to confirm the compatibility with the material of the infusion bags as specified in section 6.6 in the SmPC.

From the compatibility results and in-use stability results, it is agreed that chemical and physical in-use stability of the diluted solution of the finished product has been demonstrated for 24 hours at 2-30°C followed by 3 hours infusion time, in-line with the wording in section 6.3 in the SmPC.

2.4.3.5. Adventitious agents

No material of biological origin (except for the CHO cells) is directly used in the manufacturing process. Precursor materials of bovine origin are used in the production process of one raw material used as a media component for cell line development and in MCB and WCB generation as well as early stages of cell culture process. For generation of the CHO Master Host Cell Bank (MHCB) and for cell line development, cell medium contained cholesterol component derived from wool. The insulin used in the cell bank generation and cell culture is of recombinant origin produced from yeast.

A risk evaluation regarding TSE is performed according to EU Guideline "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01, current revision)". Where applicable, TSE certificates from EDQM has been provided. The information provided is acceptable.

Viral testing of MCB, WCB and PPCB is in general performed in accordance with ICH Q5A. The exception is tests for bovine and porcine viruses. These tests were conducted on the host cell bank. This approach is found acceptable.

Data from viral testing of pre-harvest has been provided. No adventitious agents, only virus-like particles, could be detected. Furthermore, testing for MMV in unprocessed bulk is controlled by inclusion of the MMV-susceptible cell line 324K in the adventitious virus *in vitro* test. This is acceptable.

Viral clearance studies were performed on commercial scale material. Relevant model viruses have been used. The results demonstrate that several steps in the process are able to effectively reduce potential virus contamination of a broad spectrum of virus as requested in ICH Q5A.

A satisfactory safety margin for retrovirus has also been shown by calculation of residual risk. Sufficient information has been provided regarding the viral clearance studies.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process.

However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

The nonclinical pharmacology programme was designed to characterize the effects of spesolimab in blocking IL36R activation by cognate ligands cognate ligands (IL36 α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways in disease relevant cell types. The nonclinical

PK programme was designed to investigate both PK and immunogenicity of spesolimab following a single dose in monkeys and BI 674304 (rat-mouse chimeric IgG2a antibody, BI 674304) following a single dose in mice. In addition to the nonclinical PK studies, toxicokinetics (TK) and immunogenicity of BI 674304 following repeat doses over 4 weeks in mice was assessed. Exposure and immunogenicity (as applicable) of BI 674304 was evaluated as part of the 13-and 26-week repeat dose toxicity studies and reproductive toxicology studies in mice. Spesolimab exposure was also assessed as part of the repeat dose 2-week toxicology study in mice. Other studies with spesolimab included a human tissue cross-reactivity study, a subcutaneous local tolerance study in the rabbit and ex vivo evaluations of the potential of spesolimab to result in cytokine release and haemolytic potential using human blood. The potential for carcinogenicity was assessed through a weight of evidence approach and no genotoxicity or carcinogenicity studies have been conducted.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro

Spesolimab is a humanised antagonistic monoclonal IgG1 antibody binding to the human IL36R with a high affinity (K_D) of 223 pM (IgG). In functional assays, spesolimab inhibits all three IL36 ligands (α, β, γ)-stimulated NF-ĸB activation in primary human keratinocytes, primary human dermal fibroblasts and primary human intestinal myofibroblasts and in NCI/ADR-RES transformed epithelial cells. The IC_{90} values of spesolimab are in a range of 0.7 to 3.7 nM in all tested cell types. Spesolimab also inhibits IL8 release in primary human intestinal myofibroblasts stimulated with IL36 ligands. Primary human peripheral blood mononuclear cells (PBMCs) stimulated with IL36α, IL36ß, or IL36γ show a synergistic induction of IFNγ secretion when combined with IL12. These effects can be blocked by spesolimab. Of note spesolimab alone does not stimulate cytokine production in human PBMC, ruling out any agonistic activity of this antibody.

Spesolimab shows no cross-reactivity to IL36R from other common toxicology species (rhesus monkey, mouse, rat, mini pig, marmoset and hamster) and a very a weak binding to cynomolgus monkey IL36Rwas observed at 0.5 µM. The weak binding of spesolimab to cynomolgus monkey IL36R translated into poor potency in a cell-based assay. In primary cynomolgus dermal fibroblast stimulated with human or cynomolgus IL-36β, spesolimab inhibited IL-36 ligand-induced NFκB phosphorylation with an IC_{90} value above 3 µM.

Since spesolimab does not cross-react with mouse IL36R, a surrogate mouse-specific antibody was generated, BI674304, to evaluate effects of blocking IL36R in animal models of skin and gut inflammation. BI674304 binds to mouse IL36R with high affinity of 164 pM (Fab; average of 213 ± 32 pM and 114 ± 21 pM) and does not cross react to human, cynomolgus, minipig, rhesus, marmoset and rat IL36R. In functional assays, BI674304 inhibits IL36-stimulated (IL36α, β, γ) NF-κB activation in mouse NIH3T3 fibroblasts (IC_{90} 18 nM) and in primary dermal fibroblasts (IC_{90} 13 nM). BI674304 showed no agonistic activity in these assays. Similar to human PBMC experiments, BI674304 inhibits synergistic production of IFNγ in mouse splenocytes stimulated with murine IL36 plus IL12 suggesting that the pathways utilised by IL36 to drive inflammatory cytokine production are conserved between mouse and human systems.

To map the binding site of spesolimab to human IL36R, epitope mapping was performed by HXMS technology using clone 81B4E11 from which spesolimab was derived. The epitope mapping indicates that 81B4E11 and the BI674304 primarily bound within domain-2 of the human or mouse IL36R, respectively.

In vivo

The surrogate antibody was evaluated in two mouse models of skin inflammation. In one local inflammation model, injection of a mouse IL36 cytokine cocktail (IL36α, β, γ) alone, human TNFα alone or a combination of mouse IL36 cocktail and human TNFα into the skin of mice results in a marked increase in ear thickness (swelling) and an increased expression of pro-inflammatory mediators. Mice treated with a single IP dose of BI674304 prior to IL36 cytokine cocktail administration show a significant reduction in IL36-induced swelling response by about 77% and decreased tissue levels of Chi-3L1, LCN2 and IL33 by about 48-68%, 66-71% and 55-84%, respectively. The exacerbated inflammatory response following administration of IL36 cytokines and human TNFα was also attenuated by pre-treatment with BI674304. The ear swelling response was decreased by about 80% and the tissue levels of Chi-3L1, LCN2 and IL33 were decreased by about 73-75%, 69-76% and 66-99%, respectively.

The *in vivo* effect of BI674304 was also investigated in an imiquimod-induced ear swelling model. Skin inflammation was induced by topical application of 20 µL of imiquimod cream to the dorsal surface of each ear beginning on Day 0 and continuing daily for 7 consecutive days. On Days -1, 2 and 5, mice were treated by IP injection with vehicle or, BI674304 or control antibodies (isotype controls, anti-TNFα and anti-p40). Treatment with BI674304 at 500 µg attenuated the imiquimod-induced inflammatory response compared to isotype control (63% and 43% in two experiments). Treatment with an anti-mouse p40 antibody that blocks the function of IL12 and IL23 cytokines similarly reduces the skin inflammation (54%, only tested in 2nd experiment). Treatment with an anti-TNFα antibody was able to reduce imiquimod-induced skin inflammation inconsistently and to a lesser degree than BI674304 (24% in experiment 1, no significant inhibition experiment 2). These beneficial effects of IL36R antagonism are consistent with published results demonstrating protection of IL36R KO mice in the imiquimod-induced ear swelling model (Tortola et al, 2012).

The *in vivo* effect of IL36R blockade has also been investigated in three gut inflammation models, and the clinical development programme include studies in inflammatory bowel diseases, including Crohn`s disease and ulcerative colitis.

In an acute dextran sulfate sodium (DSS)-induced mouse colitis, male mice were given 3% DSS in drinking water from Day 0 through Day 5 resulting in a significant colitis at Day 7 which continued through Day 21 as measured by video endoscopic score and histopathology. Mice were treated with BI674304 IP twice weekly at 250 µg to evaluate the potential of IL36R blockade to impact colitis development in this model. Humira, anti-TNFα, anti-p40 and respective isotype controls were included as controls. Compared to isotype controls, BI674304 was able to diminish DSS-induced tissue inflammation at Day 21 when measured by endoscopic score and mean sum histopathologic score ((inflammation + oedema + necrosis).

In a chronic DSS-induced mouse colitis, male mice were given 3 repeated cycles of 2% DSS in drinking water for 1 week followed by regular drinking water for 2 weeks to resemble flares of disease activity typically seen in human IBD. This treatment results in a chronic inflammation and accompanying tissue fibrosis as measured by endoscopic score and Masson’s trichrome staining, respectively. IP administration of BI674304 twice weekly (250 µg) causes a slight reduction DSS-induced mucosal inflammation and tissue fibrosis.

Finally, the effect of BI674304 was evaluated in a 28-day murine adoptive T cell transfer-mediated colitis model, i.e. IP injection of CD4+CD62L+ effector T cells isolated from the spleen and mesenteric lymph nodes of BALB/c donor mice on study Day 0 into CB-17 scid mice. T cell-recipient mice developed a colitis characterized by the development of diarrhoea and colonic and intestinal histopathological changes. BI674304 or anti-TNFα were administered twice per week from Day -1, by IP injection at 250 µg/mouse. Treatment with either BI674304 or anti-TNFα resulted in a significant

reduction in mean cumulative diarrhoea score relative to their respective IgG controls. Histological evaluation showed that treatment with BI674304 ameliorated colitis with a more pronounced effect observed in the large bowel.

2.5.2.2. Secondary pharmacodynamic studies

IL36R is the newest member of the IL1R family that forms a heterodimeric complex with the IL1R accessory protein. In a SPR assay, no binding of spesolimab to the human IL1-R1 was observed.

To minimise Fc effector functions, two key residues in spesolimab, Leu234 and Leu235, of the heavy chain were mutated to alanine to abrogate FcR binding activity and function. The impact of the mutations in the IgG1 FcR binding sites was assessed in agreement with CHMP advice. The data show that spesolimab has weaker affinity and a decreased binding to the FcγRs tested (FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa and FcγRIIIb) in comparison to IgG1 wildtype control antibodies indicating that a risk of Fc effector functions is low.

2.5.2.3. Safety pharmacology programme

In line with ICHS6, no stand-alone safety pharmacology studies have been performed. No apparent effects on the central nervous or respiratory systems were observed in standard physical observations or pathology evaluations in the mouse toxicity studies.

2.5.2.4. Pharmacodynamic drug interactions

No dedicated pharmacodynamic drug interaction studies were conducted with spesolimab.

2.5.3. Pharmacokinetics

The non-clinical pharmacokinetics (PK) programme was designed to investigate both PK and immunogenicity of spesolimab following a single dose in cynomolgus monkeys and the mouse surrogate BI674304 following a single dose in mice. In addition, toxicokinetics (TK) and immunogenicity of BI674304 following repeat doses over 4 weeks in mice was assessed. Exposure and immunogenicity (as applicable) of BI674304 was evaluated as part of the 13- and 26-week repeat dose toxicity studies and reproductive toxicology studies in mice. Spesolimab exposure was also assessed as part of a repeat dose 2-week toxicology study in mice.

Methods of analysis

An ELISA assay was used for the determination of BI674304 in mouse serum. The provided validation reports show that the assay was sensitive, selective and suitable to assess BI674304 concentrations in mouse serum. The upper and lower limits of the assay were 2500 to 250 ng/mL in 100% serum, respectively.

For the detection of antibodies against BI674304 (i.e. ADAs), an ECL assay was developed for mouse serum. The sensitivity was determined to be 10 ng/mL and had a drug tolerance such that 500 ng/mL of positive control could be detected in the presence of 50 µg/mL of BI674304. ADA samples were analysed using a tiered approach where all samples were first analysed in the screening assay and those that screened positive were then assessed in the confirmatory assay.

Concentrations of spesolimab in mouse serum were measured using a validated sandwich ECL assay which used anti-idiotypic monoclonal antibodies specific to spesolimab for plate coating and detection. The upper and lower limits of the assay were 1000 to 10 ng/mL in 100% serum, respectively.

All methods were validated in compliance with GLP.

Absorption

The pharmacokinetics of spesolimab in cynomolgus monkeys were approximately dose linear following IV dosing of 0.3, 1.5 and 10 mg/kg. The mean CL, V_{ss}, and terminal $T_{1/2}$ for the three dose groups were similar and were in the range of 0.168 to 0.219 mL/h/kg, 65.2 to 83.0 mL/kg, and 284 to 349 h, respectively. The SC bioavailability was 62.6%.

The pharmacokinetics of BI674304 in mice were characterised by saturable clearance following IP dosing of 0.3, 1.5 and 10 mg/kg, suggestive of TMDD. Clearance for doses of 0.3, 1.5 and 10 mg/kg was 1.62, 0.47, and 0.13 mL/h/kg, respectively.

Distribution

In line with the guidance provided by ICH S6 (R1), no tissue distribution studies were conducted with spesolimab or BI674304.

Metabolism

No dedicated metabolism studies were performed with spesolimab or BI674304, and this is considered acceptable and in agreement with ICH S6(R1). The metabolic pathways of biotechnology-derived pharmaceuticals are generally understood and include degradation to small peptides and individual amino acids.

Excretion

As a monoclonal antibody, no urinary excretion is anticipated due to its molecular size. Therefore, no specific studies to measure excretion of spesolimab or BI 674304 were performed.

Pharmacokinetic interactions

No formal drug interaction studies with spesolimab have been performed. Also see section on Clinical pharmacology.

2.5.4. Toxicology

The applicant has performed a toxicology programme to support the MAA for Spevigo (spesolimab, BI 655130) for the treatment of flares in adult patients with generalised pustular psoriasis. The proposed clinical dose is 900mg as a single dose administered as an intravenous infusion. If flare symptoms persist, an additional dose may be given after 1 week after the initial dose. The programme has been performed in accordance with ICH S6, and the studies considered pivotal are in accordance with GLP regulations.

Spesolimab is a humanized monoclonal IgG1 antibody (mAb) against human IL-36R and blocks IL36α-, IL36β- and IL36γ-induced signalling by binding to the IL-36 receptor with an affinity of <1 pM.

However, spesolimab showed weak binding to cynomolgus IL-36R (affinity of 2nM) and no binding to rat, mouse, minipig, rhesus or marmoset monkey IL-36R, why a surrogate mouse antibody was generated to support toxicology studies. This molecule, BI 674304, which binds mouse IL-36 with an affinity of 164 pM, inhibits IL36 stimulated NF-κB activation *in vitro* in mouse primary dermal cells and has also been shown to produce relevant pharmacological effects in mouse *in vivo*. BI 674304 has therefore been used in this toxicology programme to identify hazards related to IL36R antagonism in mouse that should be similar to responses to spesolimab in humans.

The toxicology programme with the surrogate Ab BI 674304 includes repeat-dose toxicity studies of up to 26-weeks duration and DART studies. Intravenous administration has overall been used in the *in vivo* studies with dosing q2w at doses up to 50mg/kg/dose. The highest dose used in the pivotal general toxicity studies was 50mg/kg/dose, and no higher doses were used in the non-GLP studies. As no margins to clinical exposure has been calculated for the surrogate antibody, Cmax at NOAEL in the 4-week study was compared to the IC_{90} of NF-kB inhibition in primary mouse dermal fibroblasts. For IL-36α (with the highest IC_{90} of 2.2nM according to study n00246306-02) the difference to NOAEL is around 500x. Further, the NOAEL of 50mg/kg/dose was 5x higher than the 10mg/kg dose which was protective in an experimental mouse colonic inflammation model. The vehicle used in the pivotal studies was BI 674304 Dilution Buffer (also known as BI 674304 Formulation Buffer) which was composed of 20 mM sodium citrate, 230 mM Trehalose, 0.05% w/v polysorbate 80, pH 6.0.

Spesolimab was evaluated in a 2-week repeated-dose toxicity study in mouse ("off-target" study to evaluate the formulation), a human cross-reactivity study, a local tolerance study in rabbit (s.c. administration), a cytokine release study and a study which evaluated the haemolytic potential.

2.5.4.1. Single dose toxicity

No dedicated single-dose studies have been performed with spesolimab.

2.5.4.2. Repeat dose toxicity

Repeated-dose toxicity studies of up to 26-weeks duration have been performed with the surrogate antibody BI 674304. It is noted that not all animals have been evaluated macro and microscopically, and that in the 4- and 26-week GLP studies the 10mg/kg/dose group was not evaluated microscopically. No clear target organs of toxicity were identified, and the studies did not find any adverse toxicities.

A few findings in the repeated-dose toxicity studies have been further elaborated on below.

Mortalities
In the non-GLP 4 -week study 2 TK animals were found dead on study day 5. The deaths were considered related to the jugular bleeding experimental procedure, as clots were found in the skeletal muscles of the right ventral cervical region. In the 26-week study, 10 mortalities were evident. Of the eight animals found dead, one female at 10mg/kg/dose had a malignant lymphoma of the haemolymphoreticular tissue. While lymphomas have been noted previously in development programs for drugs targeting the immune system, the single occurrence in this study is not likely treatment related. The causes of death were unclear for the remaining animals. Given the lack of essential toxicities in the study and that three of the deaths occurred in the vehicle group, a relation to treatment with BI 674304 is considered unlikely.

In the FEED study, two animals (not yet dosed) were found dead, and one female at 50mg/kg/day was found dead on SD16. No cause of death was identified based on gross pathology. In the EFD-study, one dam at 10 mg/kg/dose was found dead post dosing on Day 15 pc, but the cause of death

remained undetermined. While the cause of death was not identified for most animals in the non-clinical programme, the lack of essential toxicities in any of the studies supports that a treatment-relation is unlikely.

Other findings

In the 4-week GLP study with BI 674304 administration, increased serum activities of liver enzymes (AST, ALT) were noted in few animals at 10mg/kg/dose which were increased up to 3x control levels in animals receiving the 50mg/kg dose. Creatine kinase was also increased 2.6x control values in these animals, which perhaps in combination with AST and ALT effects suggest myotoxicity rather than liver toxicity. However, in the absence of any macro- or microscopic correlates, the enzyme findings are not considered adverse. Further, no effects were noted on transaminases in the other studies (including the 13- and 26-week studies).

In the 4-week GLP study with BI 674304 administration, the mean values of red blood cell parameters (RBC, HGB and HCT) were slightly increased (1.1x control values) on SD30 but without correlating findings. While likely treatment-related, the finding in isolation is not considered adverse.

In the 26-week GLP study, a slight reduction in the absolute levels of white blood cells (WBC) and subsets of WBC (lymphocytes and neutrophils) were noted in males from 10mg/kg/dose. In the immunophenotyping study, a mild decrease (0.6-0.8x control) was also here seen in total lymphocytes in males which correlated with similar decreases in T lymphocytes, T helper lymphocytes, cytotoxic T lymphocytes and B lymphocytes. Recovery females previously dosed at 50mg/kg/dose had reduced absolute total levels of T lymphocytes, T helper lymphocytes and Cytotoxic T Lymphocytes (0.6-0.7x control) suggestive of delayed effects on immune parameters. Creatine kinase levels were increased in males at 50mg/dose at SD 183. This effect on CK was also seen in males of the 4-week study in mice but is considered an observation with unclear significance. No effects were identified on gross- or histopathology.

2.5.4.3. Genotoxicity

No genotoxicity studies have been performed with spesolimab.

2.5.4.4. Carcinogenicity

Spesolimab is not pharmacologically active in rodents (or any other relevant species) why no meaningful data would be generated in long-term carcinogenicity studies. Therefore, an evaluation of the potential carcinogenicity risk of spesolimab has been performed using a weight-of-evidence (WoE) approach. This is in line with the Scientific advice EMA/CHMP/SAWP/181383/2019.

In the risk assessment, the applicant has referenced the toxicology programme performed for Spevigo where repeat-dose studies up to 26-week did not identify clear hazards related to the IL-36 inhibition as such, including increased infection or proliferative changes suggestive of a carcinogenic potential. Further, referenced 6-month data from a knock-out study (illrl2 gene ablation in mouse) did not indicate an increased cancer risk.

2.5.4.5. Reproductive and developmental toxicity

An embryo-foetal development (EFD) study was performed in Crl:CD1 mice administered iv injections of BI 674304 on days 6, 9, 12 and 15 pc. Exposures were overall dose proportional on SD18, but the exposures are considered low and only around 30% of the exposures in the FEED study on SD15. This difference is not explained by ADA, as only one confirmed ADA positive sample was identified. The

treatment was overall well tolerated in the dams and no maternal toxicity was noted. One dam at 10mg/kg/dose was found dead on day 15 pc. No cause of death was identified. An increase in post-implantation losses was evident at 50mg/kg/day compared to study controls, but the incidence was within the historical control range of the test facility (3.3 to 9.8% post implantation loss per litter and 0.3 to 1.3 total resorptions per litter).

4 malformations were identified. In the control and 10mg/kg/dose group, hyperflexion of hindlimbs was noted in one foetus each in the control and 10mg/kg/dose groups. Further, one foetus was identified with omphalocele and one foetus with cleft palate at 10 and 50mg/kg/dose respectively. The incidences are within historical control data, they are not considered treatment related at this point.

There was an increase in skeletal variations in the BI 674304 treated groups. In foetuses to mothers exposed to 50mg/kg/dose, there was a significant increase in the incidence of foetuses with a reduced number of caudal vertebrae and a slight increase in the incidence of foetuses with reduced number of (ossified) phalanges in forepaws. The variation in the number of phalanges were within the historical control range of the Test Facility.

A FEED study was performed in Crl:CD1(ICR) mice administered Q2w with 0, 10 or 50 mg/kg/dose. In the previous embryo-foetal development study the number of resorptions after the administration of BI 674304 was increased compared to the control group (but was within the historical control range of the test facility). Therefore, a fourth group was included in this study with females dosed on days 6, 9 and 12 pc to further investigate this finding.

4 animals were found dead during the study (2 in control and 1 each at 10 and 50mg/kg/dose). Gross examination did not identify a cause of death in any of the animals. No parental toxicity or effects on fertility parameters including oestrous cycle numbers and length were evident. No increased resorptions were found in group 4 dams, which diminishes the plausibility of treatment-relation for the increased resorptions seen in the EFD study. Based on the lack of effects on fertility and early embryonic development parameters in this study, the NOAEL is considered to be 50mg/kg/dose.

A PPND study was performed in Crl:CD1 (ICR) where female mice were exposed to BI 674304 (0, 10 or 50mg/kg/dose) during gestation, parturition and lactation (treated twice weekly on Days 6, 9, 12, 15, and 17 of gestation and on Lactation Days 3, 6, 9, 12,15, and 18). Exposure was generally well tolerated in the dams and no mortalities or clinical signs related to the exposure were identified. There were overall no BI 674304-related effects on body weight or food consumption noted. The pregnancy rate was slightly reduced at 50mg/kg/day (100%, 100% and 86% at control, 10 and 50mg/kg/dose respectively) but no BI 674304-related effects were noted in parturition or litter data.

One F1 pup at 10mg/kg/day found dead on SD0 is considered unrelated to treatment. Pup weights were comparable during the pup period. The mean day of development for vaginal opening was statistically significantly delayed in both BI 674304-treated groups, and at 10mg/kg/dose it correlated with increased body weight at the day of vaginal opening. Vaginal patency is positively correlated with body weight, and substantial changes in growth can alter the day of acquisition. There were indeed fluctuations in body weight gain for the F1 generation females in the 10 and 50 mg/kg/dose groups which resulted in slightly (6-7%) lower mean body weights. Thus, while the mean weights were increased compared to controls at attainment of vaginal patency, it is considered likely that the weight fluctuations resulted in the delay in patency attainment. There were no effects on reproduction performance of the F1-generation, and while ovarian and uterine examination parameters fluctuated, no clear adversities were identified. Collectively, as the delayed vaginal patency was not considered adverse, a developmental (and maternal) NOAEL is set at 50mg/kg/dose.

Given that the MAA concerns treatment of generalised pustular psoriasis in adult patients, no juvenile toxicity study has been performed to support this application.

2.5.4.6. Toxicokinetic data

Very limited toxicokinetic evaluations have been performed. In the 4-week GLP study there were dose-proportional exposures across study groups on SD1 and SD29 with dose-normalized Cmax and AUC_{0-96} values within 1.3x. No apparent differences between sexes were noted (1.2x). No half-life has been determined. In the remaining toxicity studies only exposures (µg/mL) were determined. The NOAEL of 50mg/kg/dose was 5x higher than the 10mg/kg dose which was protective in an experimental mouse colonic inflammation model. Further, based on IC90-values of BI674304 to inhibit mouse IL36α, β or γ-induced IL-2 and IFNγ cytokine production or NFκB phosphorylation in primary mouse cells (3.8-18 nM corresponding to 0.57-2.68 µg/mL), the exposures in the toxicology studies were higher.

ADAs are frequent problems in non-clinical antibody programmes, and they have been identified in all pivotal repeated-dose- and DART studies with spesolimab. However, according to the applicant the ADA data should be interpreted with caution, as drug concentrations in many ADA samples exceeded the drug tolerance level. This limits the usefulness of the ADA data in the studies. Based on the clinical AR, a relatively high proportion of patients were positive for antidrug-antibodies (ADAs) and/or neutralising antibodies (NAbs) against spesolimab in the spesolimab clinical studies (see Clinical aspects section of the report).

2.5.4.7. Local Tolerance

The local tolerance of spesolimab was evaluated as part of the 2-week toxicity in mice by the intravenous route (study No n00255497) and no adverse effects were observed, including at the injection sites. The intravenous formulation of spesolimab was provided as ready-to-use with no further information on the excipients.

The local tolerance of spesolimab was also assessed in rabbits following a single subcutaneous injection. There were no treatment-related effects with regard to mortality, clinical signs or body weight and no macroscopic or microscopic changes were observed at findings at the injection site (study No n00248748).

2.5.4.8. Other toxicity studies

A tissue cross-reactivity study was performed to evaluate the cross-reactivity of spesolimab with cryosections of normal human tissues (3 donors per tissue) at two concentrations (10 and 2 µg/mL). Spesolimab stained lymphocytes in tonsil epithelial cells in a variety of tissues, which was considered expected based on previous data and literature on IL-36R expression.

The haemolytic potential of spesolimab was evaluated in human whole blood. Human blood was incubated at 37°C in the presence of spesolimab, negative control (saline) or positive control (10% Saponin). After incubation the samples were analysed for haemolysis by flow cytometry in a haematology analyser. No haemolysis was identified for spesolimab. Based on the negative study results, no haemolytic potential of spesolimab is expected.

An *in vitro cytokine release study* was performed in human whole blood using both soluble and wet-bound antibody presentation. Whole blood from 10 donors (6 male, 4 female) was used and the cytokines IL-2, IL-6, IL-8, TNF-α, and IFN-γ were analysed. No specific IL-2, IL-6, TNF-α, or IFN-γ release was observed. Regarding IL-8, increased release was noted after spesolimab treatment in blood from three donors, but also after treatment with the negative controls (Avastin and culture medium) why the release was considered spontaneous. Accordingly, spesolimab has low potential to cause cytokine release.

2.5.5. Ecotoxicity/environmental risk assessment

No ERA data have been submitted. The product is a humanized protein which is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

Pharmacology

The submitted pharmacology programme for spesolimab is considered appropriate and sufficient.

Spesolimab binds with high affinity primarily to domain 2 of the human IL36R and it is effective in neutralising the biological activity of IL36R in cell types of relevance for the GPP indication.

Spesolimab showed a weak binding to cynomolgus monkey IL36R that translated into poor potency of spesolimab in cynomolgus monkey cells. The position of the applicant that cynomolgus monkey is not a suitable species to evaluate potential effects of IL36 antagonism is agreed. Even high doses of spesolimab are considered unlikely to produce the same pharmacological effects in cynomolgus monkeys as would been expected in humans.

Since spesolimab does not cross react with mouse IL36R, a surrogate mouse-specific antibody was generated, BI674304, to evaluate effects of blocking IL36R in animal models of skin and gut inflammation and for safety assessment. BI674304 binds to domain 2 of the mouse IL36R with high affinity and neutralises the biological activity of IL36R in murine cells. Given that spesolimab and its surrogate BI674304 show comparable binding and functional activity, the use of BI674304 as a suitable surrogate to evaluate potential effects of IL36 antagonism in toxicology studies mice is agreed. This strategy was also endorsed by CHMP.

In murine skin inflammation models, beneficial effects of blocking IL36R by BI674304 was shown. It should also be mentioned that human genetic studies have established a strong link between IL36R signalling and skin inflammation, as demonstrated by occurrence of familial generalised pustular psoriasis in patients with a loss of function mutation in the natural IL36R antagonist (encoded by *IL36RN*) which results in uncontrolled IL36R signalling (Marrakchi et al, 2011). Mutations in other genes linked to the IL36 pathway such as CARD14 also lead to GPP (Berki et al, 2015).

The effect of IL36R antagonism was also studies in murine gut inflammation models. However, the beneficial effects in these models were rather modest. In literature, beneficial effects of blocking IL-36 signalling in two different models of chronic DSS colitis were recently reported (Scheibe et al, 2019). Overall, these results may support a role of IL36R in mediating gut inflammation.

No evaluation of BI674304 exposure was included in the *in vivo* studies. However, the exposure following an IP administration of 250 µg BI674304 (as used in the IL36 ligand-induced inflammation model) is extrapolated to a C_{max} of about 247 µg/mL corresponding to approximately 166 nM. This concentration is about 10-fold the IC_{90} values in the functional assays in murine cells.

In the updated SmPC section 5.1, the mechanism of action of spesolimab is described as follows;

Spesolimab is a humanised antagonistic monoclonal immunoglobulin G1 (IgG1) antibody blocking human IL36R signalling. Binding of spesolimab to IL36R prevents the subsequent activation of IL36R by cognate ligands (IL36 α, β and γ) and downstream activation of pro-inflammatory pathways.

The mechanism of action is supported by available data.

To minimise Fc effector functions, two key residues in spesolimab, Leu234 and Leu235, of the heavy chain were mutated to alanine to abrogate FcR binding activity and function. The impact of the mutations in the IgG1 FcR binding sites of spesolimab was evaluated by SPR indicating a low risk of Fc effector functions. No binding data of the surrogate antibody BI674304 to FcγR proteins has been presented which was suggested by CHMP. This deficiency is considered acceptable given the lack of adverse effects, including FcγR-mediated effects, in the mouse toxicology studies.

Given the expression of the IL36R in epithelium of various tissues including skin and lung, and as the IL36 pathway has been implicated in host-defence, spesolimab treatment may be expected to increase the risk for serious, severe or opportunistic infections. This potential risk is further discussed in the Clinical and RMP sections.

Overall, *in vitro* and *in vivo* proof of concept and mode of action of spesolimab in relation to the treatment of flares in adult patients with generalised pustular psoriasis was established and is supported.

In line with ICHS6, no stand-alone safety pharmacology studies have been performed. It is agreed that no effects are anticipated in the CV system given the nature of the test item and the expression pattern.

Pharmacokinetics

The binding affinity of spesolimab to cynomolgus monkey IL36R is significantly reduced compared to the affinity to human IL36R. Therefore, target-mediated drug disposition (TMDD), expected to be seen in humans, was not expected to be seen in cynomolgus monkeys. Therefore, the PK characteristics of spesolimab in the monkey describe only the overall catabolic stability and FcRn recycling properties of the molecule, rather than full PK evaluation including possible specific TMDD.

The pharmacokinetic profile of spesolimab and the mouse surrogate BI674304 are considered adequately characterised for the proposed indication. No dedicated distribution, metabolism or excretion studies were performed, and this is considered acceptable and in agreement with the ICH S6(R1) guideline.

The metabolic pathways of biotechnology-derived pharmaceuticals are generally understood and include degradation to small peptides and individual amino acids.

Given that spesolimab and BI674304 are IgG1 and IgG2a antibodies, respectively, transport across the placenta is expected. In addition, like other therapeutic IgG antibodies, spesolimab is expected to be excreted in colostrum during the first few days after birth, decreasing to low concentrations in breast milk soon afterwards (see SmPC section 4.6).

Toxicology

The applicant has performed a toxicology programme to support the MAA for Spevigo (spesolimab, BI 655130) for the treatment of flares in adult patients with generalised pustular psoriasis. The proposed clinical dose is 900mg as a single dose administered as an intravenous infusion. If flare symptoms persist, an additional dose may be given after 1 week after the initial dose. The programme has been performed in accordance with ICH S6, and the studies considered pivotal are in accordance with GLP regulations.

Spesolimab is a humanized monoclonal IgG1 antibody (mAb) against human IL-36R and blocks IL36α-, IL36β- and IL36γ-induced signalling by binding to the IL-36 receptor with an affinity of <1 pM. However, spesolimab showed weak binding to cynomolgus IL-36R (affinity of 2nM) and no binding to rat, mouse, minipig, rhesus or marmoset monkey IL-36R, why a surrogate mouse antibody was generated to support toxicology studies. This molecule, BI 674304, which binds mouse IL-36 with an

affinity of 164 pM, inhibits IL36 stimulated NF-κB activation *in vitro* in mouse primary dermal cells and has also been shown to produce relevant pharmacological effects in mouse *in vivo*. BI 674304 has therefore been used in this toxicology programme to identify hazards related to IL36R antagonism in mouse that should be similar to responses to spesolimab in humans. While potential hazards associated with target pathway inhibition can be identified using surrogate molecules, there are also inherent limitations with their use in toxicity programmes why it is noted in ICH S6 that studies conducted with homologous monoclonal antibodies are useful for hazard identification but are not useful for quantitative risk assessment.

The toxicology programme with the surrogate Ab BI 674304 includes repeat-dose toxicity studies of up to 26-weeks duration and DART studies. Intravenous administration has overall been used in the *in vivo* studies with dosing q2w at doses up to 50mg/kg/dose. The highest dose used in the pivotal general toxicity studies was 50mg/kg/dose, and no higher doses were used in the non-GLP studies. As no margins to clinical exposure has been calculated for the surrogate antibody, the applicant has compared Cmax at NOAEL in the 4-week study was compared to the IC_{90} of NF-kB inhibition in primary mouse dermal fibroblasts. For IL-36α (with the highest IC_{90} of 2.2nM according to study n00246306-02) the difference to NOAEL is around 500x. Further, the applicant notes that the NOAEL of 50mg/kg/dose was 5x higher than the 10mg/kg dose which was protective in an experimental mouse colonic inflammation model. The vehicle used in the pivotal studies was BI 674304 Dilution Buffer (also known as BI 674304 Formulation Buffer) which was composed of 20 mM sodium citrate, 230 mM Trehalose, 0.05% w/v polysorbate 80, pH 6.0. Further, based on IC90-values of BI674304 to inhibit mouse IL36α, β or γ-induced IL-2 and IFNγ cytokine production or NFκB phosphorylation in primary mouse cells (3.8-18 nM corresponding to 0.57-2.68 µg/mL), the exposures in the toxicology studies were higher. Thus, sufficient exposures have been reached in the studies.

Spesolimab was evaluated in a 2-week repeated-dose toxicity study in mouse ("off-target" study to evaluate the formulation), a human cross-reactivity study, a local tolerance study in rabbit (s.c. administration), a cytokine release study and a study which evaluated the haemolytic potential.

Repeated-dose toxicity studies of up to 26-weeks duration have been performed with the surrogate antibody BI 674304. It is noted that not all animals have been evaluated macro and microscopically, and that in the 4- and 26-week GLP studies the 10mg/kg/dose group was not evaluated microscopically. Given the lack of effect in the 50mg/kg/dose group this may be appropriate. However, for antibody products reliance on dose-response effects and relations is not recommended as bell-shaped dose-response responses are commonly encountered. The results section was missing from the report of the 13-week repeated dose toxicity study. The company provided the full report which supported the earlier conclusions.

No treatment-related mortalities occurred in the general toxicology study programme, and few toxicities were identified. The slight effects on blood parameters and the effects on immune parameters in the 26-week study are considered expected based on the pharmacology of BI 674304. The effects on liver enzymes in the 4-week study are considered of limited clinical relevance.

No genotoxicity studies have been performed with spesolimab. This is considered acceptable as monoclonal antibodies are unlikely to interact directly with DNA or other chromosomal material (see SmPC section 5.3).

Spesolimab is not pharmacologically active in rodents (or any other relevant species) thus no meaningful data would be generated in long-term carcinogenicity studies. Therefore, an evaluation of the potential carcinogenicity risk of spesolimab has been performed using a WoE approach. This is in line with the Scientific advice EMA/CHMP/SAWP/181383/2019.

There is limited clinical data on the potential carcinogenicity risk of IL-36 inhibition, as there are no approved products on the market. Limited data from humans with mutations (loss of function mutations) have not shown increased risk of malignancies. Further, while the clinical programme in a total of 597 spesolimab exposed subjects identified 4 malignancies (3 in spesolimab treated groups) none of the malignancies were considered related to spesolimab administration. The types of malignancies were heterogenous and were identified between 8-10 weeks after treatment start which reduces the association between drug administration and malignancy.

Cancer immunosurveillance is likely an important mechanism to prevent the development of cancer, where the immune system identifies pre-cancerous and cancerous cells leading to their elimination. This requires a complex interaction of different immune cells, immune cell differentiation and cytokine release. As activation of the IL-36 pathway in the tumour microenvironment can induce multiple cytokines and other molecules leading to a pro-inflammatory response supporting the innate and adaptive immune systems (as exemplified by several relevant publications by the applicant), blocking this receptor may prevent this response.

Taking into account the MoA of spesolimab and data in the publication domain supporting potential negative effects of IL-36 inhibition on immunosurveillance, carcinogenicity is considered a potential risk in the RMP. It will be followed post-authorisation in the PASS 1368-0128.

A full Developmental and reproductive toxicology (DART) programme was performed with BI 674304.

Some findings which after assessment deemed as not related to the treatment or not adverse were reported including increased late resorptions seen in the EFD study, vaginal patency seen in PPND study. Only 3 administrations were performed in Foetal and early embryonic development (FEED) study (D6, 9, 12) compared to 4 in the EFD study (6, 9, 12, 15). It is unclear if this difference in dosing has impacted the outcome of late resorptions, but as most post-implantation losses were early, this is considered unlikely. In the PPND study the weight fluctuations may have resulted in the delay in vaginal patency attainment. According to the applicant, the means in all groups were below the historical control data (24.8 to 28.5 days) why the finding is of unclear relation to treatment and should not be considered adverse. The CHMP agreed that although findings can be considered a developmental delay, but in isolation and in the absence of effects on e.g. fertility parameters or other potentially related effects, it is not considered adverse.

There were no treatment-related findings in the studies which are considered important for the pregnancy and breast-feeding labelling. Based on exposure data from the PPND study, pup exposure on PND4 and PND22 was similar to the dam exposure. As IgG in the rat foetuses remains low until birth, the exposure noted in the rat pups is mainly transmitted postnatally via lactation (Halliday, 1955). This is in contrast with the human situation, where exposure is low during organogenesis but increases to considerable foetal exposure during the latter half of gestation (Pentsuk et al, 2009). These differences in maternofoetal transfer between rodents and human limit the relevance of the rodent models for human risk during pregnancy, thus the lack of significant effects in the FEED and EFD studies is no assurance of a safe use during human early pregnancy. Further, given the extended half-life of spesolimab (28.8 days in healthy subjects, shorter in GPP patients) it is anticipated that exposure early during pregnancy may produce sufficient exposure to produce foetal harm not discovered in the rat studies. As a precautionary measure, it is preferable to avoid the use of spesolimab during pregnancy (see SmPC section 4.6).

As already noted above, lactational transfer is substantial in the rat. However, in human the lactational transfer of IgG is considered low with the exception of the first postnatal day (Palmeira et. Al, 2009) Consequently, limited exposure of the child is anticipated during the period of breast feeding. The SmPC has been updated accordingly.

Regarding breast-feeding, it is recommended that the following "standard" wording is used in SmPC section 4.6 for IgG mAbs which has been proposed by the SWP:

"No data are present on excretion of spesolimab in human milk. In humans, excretion of IgG antibodies in milk occurs during the first few days after birth, which is decreasing to low concentrations soon afterwards. Consequently, transfer of IgG antibodies to the newborns through milk, may happen during the first few days. In this short period, a risk to the breastfed child cannot be excluded. Afterwards, spesolimab can be used during breast-feeding if clinically needed. When treatment has occurred up to the last few months of pregnancy, breastfeeding can be started immediately after birth."

Regarding pregnancy, the following wording is proposed:

"There are no or limited data from the use of spesolimab in pregnant women. Pre-clinical studies using a surrogate, mouse specific anti-IL36R monoclonal antibody do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Human immunoglobulin (IgG) is known to cross the placental barrier. As a precautionary measure, it is preferable to avoid the use of spesolimab in during pregnancy."

Collectively, the DART programme did not evidence findings of concern for use during pregnancy and lactation. While an increase (within historical control data) in post-implantation loss was noted in the EFD study, an additional study group in the FEED study where this was further evaluated could not replicate this increase.

Very limited toxicokinetic evaluations have been performed. In the 4-week GLP study there were dose-proportional exposures across study groups on SD1 and SD29 with dose-normalized Cmax and AUC_{0-96} values within 1.3x. No apparent differences between sexes were noted (1.2x).

ADAs have been identified in all pivotal repeated-dose- and DART studies with spesolimab. However, according to the applicant the ADA data should be interpreted with caution, as drug concentrations in many ADA samples exceeded the drug tolerance level. This limits the usefulness of the ADA data in the studies. That said, ADA development in animal studies is usually of limited relevance for the clinical ADA situation. However, based on the clinical AR, a relatively high proportion of patients were positive for antidrug-antibodies (ADAs) and/or neutralising antibodies (NAbs) against spesolimab in the spesolimab clinical studies (see discussion on clinical pharmacology).

The local tolerance of spesolimab was evaluated as part of the 2-week toxicity in mice by the intravenous route (study No n00255497) and no adverse effects were observed, including at the injection sites. The intravenous formulation of spesolimab was provided as ready-to-use with no further information on the excipients.

The spesolimab induced staining in a tissue cross-reactivity study was considered expected based on previous data and literature on IL-36R expression.

A study to evaluate the haemolytic potential of spesolimab concluded that no haemolytic potential of spesolimab is expected and based on an *in vitro* cytokine release study, the overall impression is that spesolimab has low potential to cause cytokine release.

To conclude, a surrogate mouse antibody was generated to support toxicology studies to identify hazards related to IL36R antagonism. While limited toxicities were identified, findings noted include effects on transaminases, haematology parameters and immune parameters. These are all toxicities considered monitorable in the clinic, and which may receive further clinical attention.

The local tolerance of spesolimab was evaluated as part of the 2-week toxicity in mice by the intravenous route (study No n00255497) and no adverse effects were observed, including at the

injection sites. According to the ICH guidelines M3(R2) and S6(R1) it is preferable to evaluate local tolerance by the intended therapeutic route as part of the general toxicity studies; stand-alone studies are generally not recommended.

No ERA data have been submitted. The product is a humanized protein which is not expected to pose a risk to the environment.

2.5.7. Conclusion on non-clinical aspects

The review of non-clinical data available for spesolimab indicates no major issues for concern. All raised other concerns and SmPC comments have been resolved.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 3. Tabular overview of clinical studies

Study No./ Status	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	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	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	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
1368-0009				Placebo (i.v., s.c.) (pmbl)	8

Phase I Completed	PK in Japanese volunteers Double-blind, randomized, placebo-controlled	i.v. infusion s.c. injection	Single dose	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	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.)	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	Proof of concept (POC) in GPP patients Open-label, single-arm design	i.v. infusion	Single dose	10 mg/kg i.v.	7
1368-0013 Phase II Completed	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]	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	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 And interim TFLs[1]	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
1368-0032 Phase IIa Completed	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	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	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	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

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The clinical pharmacology of spesolimab has been investigated in six Phase I studies in healthy volunteers (HV) and three studies in patients with GPP. Further clinical studies with sparse PK sampling have also been conducted for spesolimab for GPP flare prevention, Palmoplantar Pustulosis (PPP), Atopic Dermatitis (AD), and Ulcerative Colitis (UC). Data from trials in patients with indications other than GPP that are complete or have a relevant amount of data available (e.g. completed primary analysis period) are included in the popPK analysis.

Methods

- *Analysis of spesolimab PK*

Concentrations of free (active) spesolimab in human plasma were determined using a blocking anti-spesolimab monoclonal antibody capture and detection GyroLabTM method. Anti-spesolimab clone 8H11 (anti-spesolimab murine monoclonal antibody that blocks the binding of spesolimab to IL-36R) antibody was biotinylated and the 5C8 antibody (anti-spesolimab murine monoclonal antibody that blocks the binding of spesolimab to IL-36R) was conjugated to Alexa Fluor 647. Spesolimab was captured on the CD by the biotinylated antibody and detected by the Alexa-labelled antibody.

- *Analysis of spesolimab immunogenicity*

A standard multi-tiered approach was developed including screening, confirmatory and titre to evaluate anti-drug antibodies. An Electrochemiluminescent (ECL) bridging assay with labelled spesolimab and acid dissociation sample pre-treatment step was used for the screening, confirmatory and titre assays.

Confirmed positive ADA samples from trials in GPP (1368-0013 and 1368-0025) and in AD (1368-0032) were further characterized in a validated cell based NAb assay.

Pharmacokinetic data analysis

Standard non-compartmental analysis was performed in all studies where rich sampling was applied.

Evaluation and Qualification of Models

PopPK analysis

Objectives:

- Characterize the pharmacokinetics of spesolimab in patients with GPP, healthy volunteers and other indications
- Evaluate the effect of pre-specified covariates on the PK parameters of spesolimab
- Derive individual exposure measures for patients in study 1368-0013 from the final popPK model for a subsequent exposure response assessment.

PopPK dataset:

The population PK model was developed with all available data from healthy volunteers, patients with GPP and patients in other indications who received spesolimab via intravenous infusions or subcutaneous injections. The BI 655130 dataset was comprised of 557 subjects, including 36 subjects who were first enrolled in Study 1368.13 and then were rolled over into Study 1368.25. The subjects contributed a total of 6631 observations. Of these, 6369 samples had quantifiable BI 655130 concentrations, 262 samples were BLQ (4.1%) and three were missing. Note that samples collected prior to the first BI 655130 dose were excluded.

Data summary (subject type, rout of administration) are shown in Table 4. Data summary (subject type, rout of administration).

Table 4. Data summary (subject type, rout of administration)

	Number				Percent	
Subject type	SUBJ	MISS	OBS	BQL	OBS	BQL
Route: IV						
HV	106	3	2157	139	60.5	3.9
GPP	57	0	382	36	10.7	1.0
UC	96	0	431	13	12.1	0.4
PPP	37	0	356	14	10.0	0.4
AD	36	0	237	9	6.7	0.3
Group Total	332	3	3563	211	100.0	5.9
Route: SC						
HV	78	0	1767	32	63.0	1.1
GPP	36	0	67	18	2.4	0.6
PPP	146	0	972	1	34.6	0.0
Group Total	260	0	2806	51	100.0	1.8

SUBJ: subjects; BQL: below quantitation limit; MISS: missing observations (not BQL); OBS: observations; IV: intravenous; SC: subcutaneous; HV: healthy volunteers; GPP: generalized pustular psoriasis; UC: ulcerative colitis; PPP: palmoplantar pustulosis; AD: atopic dermatitis
Subjects in Study 1368.25 were all originally enrolled in Study 1368.13 although one subject only contributed data to the PK analysis dataset during Study 1368.25.
Source code: eda-tables.R
Source file: pk-data-inv-route-sub.tex

PopPK analysis - Methods:

The population pharmacokinetic analyses were conducted using non-linear mixed effects modelling techniques after a thorough exploratory data analysis. Inclusion of covariates was not driven by hypothesis testing but was rather informed by mechanistic plausibility, clinical interest and exploratory graphical assessments. A final model was developed based on a combination of factors, including parameter identifiability, model stability, model diagnostics, and the objective function value.

To describe the effect of body size on clearances and volumes, the physiologically known allometric relationship was incorporated into the covariate-parameter model, with fixed coefficients of 0.85 for clearances and 1 for volumes, respectively.

Assessing the impact of ADA formation on plasma pharmacokinetics was of high clinical interest given that incidence and impact appeared to be different between disease states.

Final popPK model

Spesolimab disposition was best described by a two-compartment model with linear elimination in the absence of ADA. Absorption following subcutaneous injection was best described by a sequential zero-order, first order absorption model. Covariates included in the final model were body weight on clearances and volumes (with fixed allometric coefficients of 0.85 and 1 respectively), UC/AD indication on linear clearance, and injection site on bioavailability. Patients with UC/AD typically had a 41% higher estimated linear clearance compared to healthy volunteers, patients with GPP and patients with PPP. A reduced bioavailability was estimated for subcutaneous injection into the periumbilical area (87 %) compared to thigh/other sites (98 %). Sites were classified as 'other' in case an injection was given into the arm, or if a dosing event contained a mix of

multiple sites (e.g. injected into both thigh and periumbilical region). To describe the impact of ADA on plasma pharmacokinetics of spesolimab in ADA positive patients (making up 33 % of the dataset), an additional, saturable elimination pathway was included as function of ADA titres (time varying). This was parameterized with Michaelis-Menten parameters VmaxADA (representing the typical maximum ADA related clearance) and KmADA (representing the typical ADA titre value resulting in half maximal ADA clearance). Due to the differences observed in the GPP population compared to other disease states, a GPP specific effect was estimated for maximum ADA clearance. It should be stressed that ADA parameters (VmaxADA and KmADA), interindividual variability in ADA parameters, and the GPP covariate effect on VmaxADA were all estimated with high uncertainty (as indicated by the wide confidence intervals from the non-parametric bootstrap). The variability for ADA parameters should be interpreted with caution.

Model parameter estimates are shown in the Table 5 and visual predictive checks are shown in Figure 1.

Table 5. parameter estimates - final model

		Final Model		*Non-parametric bootstrap*	
Parameter	**Description**	**Estimate**	**Shrinkage**	**Median**	**95% CI**
CL (L/day)	Linear clearance	0.184	-	0.184	0.175, 0.194
V2 (L)	Volume of central compartment	3.77	-	3.73	3.46, 4.08
Q (L/day)	Intercompartmental clearance	0.617	-	0.625	0.545, 0.747
V3 (L)	Volume of peripheral compartment	2.69	-	2.68	2.53, 2.82
KA (1/day)	Absorption rate constant	0.229	-	0.243	0.192, 0.311
D1 (day)	Duration of zero order absorption	0.130	-	0.134	0.107, 0.166
F1 $SC_{,not\ Peri}$	Bioavailability after SC dosing into thigh or other sites	0.980	-	0.978	0.934, 0.996
F1 $SC_{,Peri}$	Bioavailability after SC dosing into periumbilicum	0.880	-	0.874	0.803, 0.940
VmaxADA (L/day)	Maximum ADA related clearance	0.140	-	0.0489	0.00576, 0.339
KmADA (titer)	ADA titer resulting in half maximal ADA related clearance	31400	-	41100	960, 506000
$VmaxADA_{GPP}$	Fold increase on VmaxADA for a GPP patient	9.49	-	15.7	4.94, 71.9
$CL_{UC\&AD}$	Fold increase in linear clearance for UC and AD patients	1.39	-	1.41	1.30, 1.50
IIV-CL	Interindividual variability in CL	0.110 [CV% = 34.2]	8.43	0.109	0.0780, 0.153
IIV-V2	Interindividual variability in V2	0.201 [CV% = 47.2]	22.9	0.198	0.111, 0.302
IIV-KA	Interindividual variability in KA	0.748 [CV% = 105]	53.1	1.21	0.540, 1.95

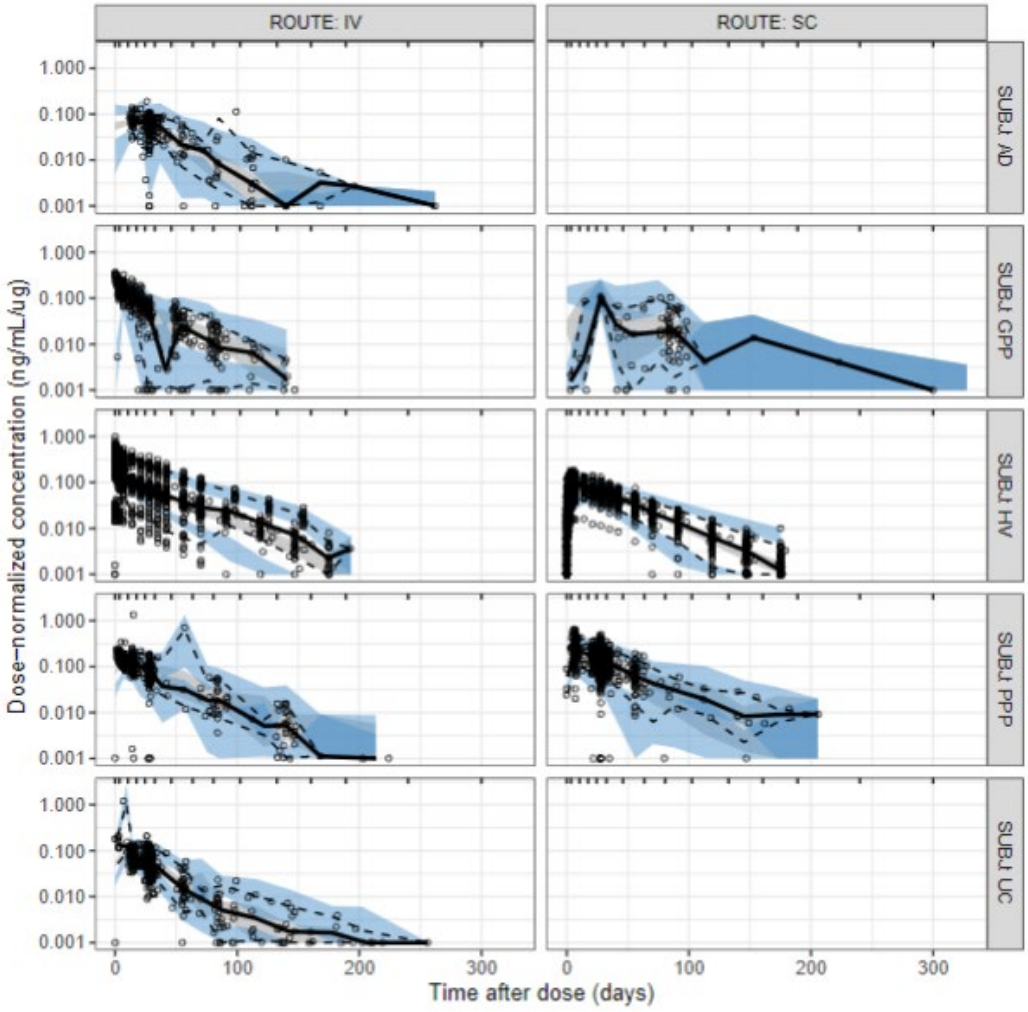
		Final Model		*Non-parametric bootstrap*	
Parameter	**Description**	**Estimate**	**Shrinkage**	**Median**	**95% CI**
IIV-F1	Interindividual variability in F1	1.13 [SD=0.0387]	68.5	1.07	0.0610, 2.67
IIV-VmaxADA	Interindividual variability in VmaxADA	7.85 [CV% = 5.06e+03]	67.3	13.9	5.84, 34.4
IIV-KmADA	Interindividual variability in KmADA	10.9 [CV% = 2.30e+04]	76.9	16.4	0.506, 80.2
VmaxADA-KmADA	Covariance between IIV-VmaxADA and IIV-KmADA	4.51 [Corr=0.488]	-	9.85	-1.48, 44.8
CL-V2	Covariance between IIV-CL and IIV-V2	0.0871 [Corr=0.584]	-	0.0793	0.0446, 0.140
RUV	Proportional residual error	0.0552 [CV%=23.5]	6.06	0.0567	0.0441, 0.0743

Abbreviations: CI = confidence interval, Corr = correlation coefficient, CV = coefficient of variation, SD = standard deviation, AD = atopic dermatitis, UC= ulcerative colitis ; Source data: [c35520225, Table 4, Table 5]

Parameter	Description	Median (95%CI)
$t_{1/2\alpha}$	Alpha half-life (days)	1.63, (1.41,1.85)
$t_{1/2\beta}$	Beta half-life (days)	25.5, (24.4,26.3)
Vd_{ss}	Apparent volume of distribution at steady-state (L)	6.39, (6.17,6.70)
$Cmax_{iv}$	Cmax single 900 mg iv dose (mg/L)	238, (218,256)
$Cmax_{sc}$	Cmax single 300 mg sc dose (mg/L)	36.2, (33.4,39.4)
$AUC_{iv,0-\infty}$	AUC iv 900 mg dose (mg/L*day)	4.75e+03, (4.51e+03,4.97e+03)
$AUC_{sc,0-\infty}$	AUC sc 300 mg dose (mg/L*day)	1.54e+03, (1.46e+03,1.61e+03)

Source data:[c35520225, Table 29]

Black lines represent the median (solid), 5th and 95th percentiles (dashed) of the observed data. Blue and grey shaded regions represent the 95% prediction interval of the corresponding (i.e. 5th, 50th and 95th) percentiles. Black circles represent the observed concentrations. SC: Subcutaneous; SUBJ: subject; IV: intravenous; HV: healthy volunteers; AD: atopic dermatitis; GPP: generalized pustular psoriasis; PPP: palmoplantar pustulosis.



Source code: BI15701F−vpcs.R
Source graphic: pk−vpc−11436−dose−norm.pdf page: 2

Figure 1. VPCs, final model

Absorption

In the treatment of flares in GPP patients, spesolimab is administered iv, bioavailability is 100% by definition. Food effect was not studied.

Three investigational intravenous spesolimab drug products /drug substances have been used

- DP1: trial formulation 1 (TF1) DP with drug substance (DS) derived from the initial manufacturing process
- DP2: iFF DP with DS derived from the optimized manufacturing process
- DP3 = intended commercial drug product: iFF DP with DS derived from commercial scale

In the pivotal GPP flare treatment 1368-0013 trial, out of 51 spesolimab treated patients, 48 patients received DP2 and 3 patients received the intended commercial product DP3. The majority of earlier studies in healthy subjects and non-GPP patients were conducted with DP1.

Comprehensive analytical comparability studies have been carried out, see Quality section. No dedicated clinical PK comparability study was conducted. The *in vivo* performance of different DPs/DSs was assessed by pooling dose-normalized AUC and Cmax values after single i.v. dose administration (in the linear range, >= 0.3 mg/kg). Comparison was made separately within healthy subjects and within GPP patients.

In studies in healthy subjects, the dose-normalized AUC0-inf and C max ratio (DP3/DP1) (90% CI) was 1.11 (1.03, 1.19) and 1.16 (1.09, 1.23), respectively. For those studies analysed with the final ADA method, the incidence of ADAs was 17-46% for DP1 and 40-44% for the intended commercial product DP3.

PK data is available only for 3 GPP patients who received the to be marketed DP3 in study 1368-0013. Additional 9 patients in the ongoing open label extension trial 1368-0025 required treatment for a GPP flare and were administered spesolimab DP3. However, PK parameters could not be estimated using NCA for these 9 patients due to limited sampling.

The plasma profiles of spesolimab from the three processes overlap with each other.

Distribution

In healthy subjects, gMean Vss was 5.94 L (CV 23.4%) and 6.7 L (CV 37.1%) in GPP patients based on NCA, while it was 6.4L in the popPK.

Due to the size of spesolimab (~150 kDa), spesolimab will be mainly distributed in blood and interstitial fluids, with a smaller portion distributing to tissues through diffusion and convection. The target expression profile of IL-36R can influence the distribution of spesolimab.

Elimination

In healthy subjects, gMean CL was 0.146 L/day (CV 23.3%) and 0.246 L/day (CV 46.8%) in GPP patients based on NCA.

In healthy subjects, gMean t1/2 was 28.8 days (CV 25.1%) and 16.4 days (CV 84.4%) in GPP patients based on NCA.

In the linear dose range (0.3-20 mg/kg), based on the population PK model, spesolimab clearance (95% CI) in a typical GPP patient without ADA, weighing 70 kg was 0.184. In a typical ADA negative GPP patient after single IV and SC dose the half-life (t1/2β) was 25.5 days.

The expected consequence of metabolism of biological products is degradation to small peptides and amino acids.

Dose proportionality, time dependencies & immunogenicity

Spesolimab exhibited target-mediated drug disposition (TMDD) kinetics after single i.v. dose administration. Spesolimab AUC increased approximately linearly with dose from 0.3 to 20 mg/kg, and CL and terminal half-life were independent of dose.

In studies in non-GPP patients, the formation of ADA did not appear to have impact on the plasma concentration of spesolimab in study 1368-004 (UC), 1368-0010 (UC). ADA titres in these studies were

<720. Formation of ADA appeared to decrease the plasma concentration of spesolimab in patients with titre values ≥ 11400 in study 1368-0005 (UC), 1368-0015 (PPP, with a potential link to lack of efficacy), 1368-0016 (PPP) and 1368-0032 (AD).

Following administration of i.v. spesolimab 900 mg to GPP patients (study 1368-0013), 46% patients (23/50) developed ADA by Week 12-17 with median onset time of 2.3 weeks and maximum titre at a median time of 11.7 weeks. A total of 24% of patients (12/50) had a maximum ADA titre greater than 4000. NAb was detected at a median onset time of 6.7 weeks. Females appeared to have higher immunogenicity response. The ADA incidence rate and percentage of patients with titre greater than 4000 were 58% (19/33) and 30% (10/33) in females, and 24% (4/17) and 12% (2/17) in males, respectively. At the end of the study (12-17 week after the first active dose), the ADA was resolved in 4 out of 23 ADA-positive patients. Nineteen (38% of total treated) patients remained ADA positive, 18 (36%) patients remained NAb positive.

Following administration of i.v. and s.c. administration of spesolimab (study 1368-0025), 64% patients (23/36) developed ADA while 28% patients (10/36) had a maximum titre greater than 4000 in patients who rolled over from 1368-0013 to 1368-0025. Females continued to have higher immunogenicity response. The ADA incidence rate and percentage of patients with titre greater than 4000 were 75% (18/24) and 38% (9/24) in females, and 42% (5/12) and 8% (1/12) in males, respectively. Out of 23 ADA-positive patients, 17 (74%) patients were also NAb-positive, which constituted 47% of total treated patients. The higher ADA and NAb incidences may be related to the longer observation duration since first i.v. dose or the background treatment of s.c. spesolimab, or both. At the last sample, 44% and 28% of treated patients remained ADA-positive and NAb-positive, respectively. Seven (19%) patients still had a titre value greater than 4000.

In patients with GPP, the NAb status appeared to be associated with the titre value. All ADA samples with titre value greater than 4000 were also NAb positive.

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

Terminal t 1/2 was most sensitive to formation of ADA (Table 6). It was shorter and more variable in ADA-positive patients compared with ADA-negative patients. In addition, CL was higher and AUC was lower with higher inter-patient variability in ADA-positive patients.

PK in target population

PK parameters from studies in GPP patients are presented in Table 6 for the first dose, whether given on D1 or D8 if the patient was originally in the placebo group. Regarding immunogenicity, please see the section above.

Table 6. Pharmacokinetic parameters of spesolimab after single i.v. dose administration in patients with GPP

Study	Dose	ADA status	N	$AUC_{0-\infty}$ [µg·day/mL]	C_{max} [µg/mL]	CL [L/day]	$t_{1/2}$ [day]	Vss [L]
1368-0011	10 mg/kg	Total	6	2350 (41.1)	203 (11.1)	0.268 (45.7)	14.2 (75.8)	5.08 (31)
		ADA-	3	3030 (26.3)	192 (13.8)	0.191 (30.5)	23.9 (9.18)	5.85 (25.6)
		ADA+	3	1820 (36.9)	214 (5.3)	0.377 (18.8)	8.38 (59.2)	4.42 (33.7)
1368-0013 [3]	900 mg	Total	32	3680 (47.2)[2]	--[1]	0.242 (47.6)[2]	16.8 (87.0)	7.06 (27.1)

		ADA-	18	4380 (29.6)[2]	--[1]	0.203 (31.2)[2]	23.7 (17.7)	7.11 (23.0)
		ADA+	14	2950 (56.4)[2]	--[1]	0.303 (55.5)[2]	10.8 (123)	7.00 (32.7)
All		Total	38	--	--	0.246 (46.8)	16.4 (84.4)	6.7 (30.1)
		ADA-	21	--	--	0.201 (30.4)	23.8 (16.6)	6.91 (23.8)
		ADA+	17	--	--	0.315 (50.9)	10.3 (111)	6.45 (37.1)

[1] plasma samples not collected at the end of infusion for PK; C_{max} could not be determined. [2] AUC slightly under-estimated and CL slightly over-estimated as plasma samples not collected at the end of infusion. The earliest sample was 3 days or one week after the dosing. [3] Includes patients who received 1 spesolimab dose only, i.e. patients randomized to spesolimab who received 1 spesolimab dose at Day 1 only and patients randomized to placebo who received 1 dose of open-label spesolimab at Day 8

In Study 1368-0011, all patients received a single i.v. infusion of 10 mg/kg spesolimab over 60 min. Individual plasma concentration time (c/t) profiles for spesolimab stratified by ADA titre are displayed in Figure 2. ADA appears to have an impact on the plasma time concentration profiles of spesolimab in patients with active GPP, particularly at titres > 4000, as apparent both in the c/t profiles and in the PK parameters upon stratification per ADA serology (Table 6).

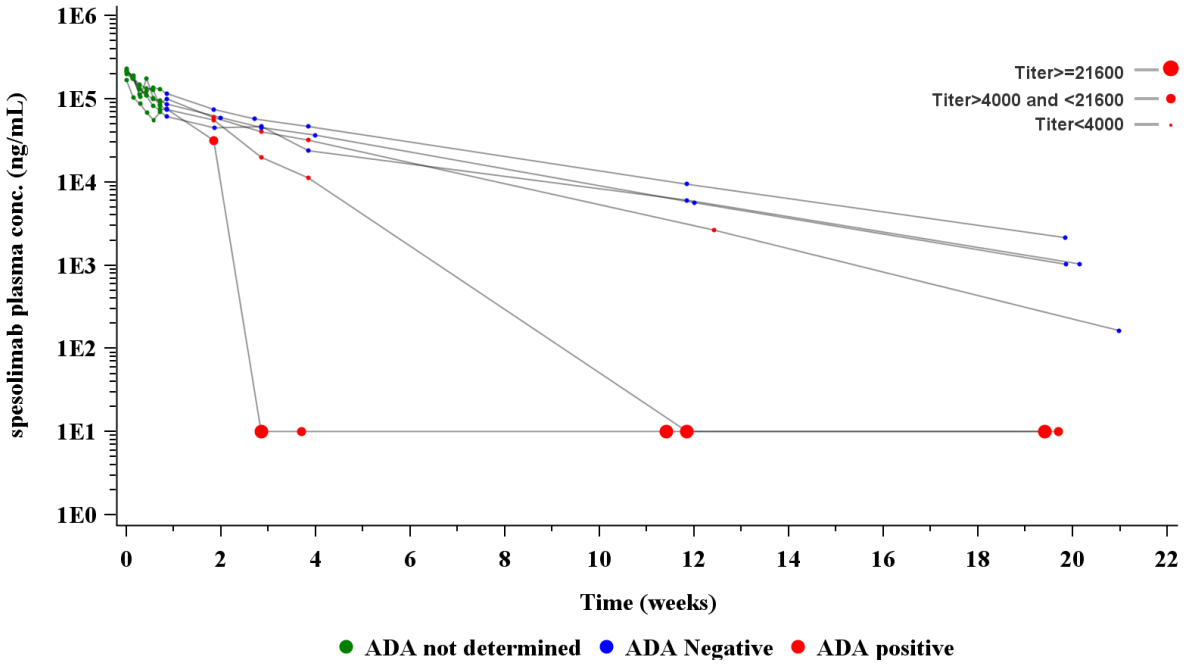


Figure 2. Individual spesolimab concentration-time profiles after a single intravenous infusion of 10 mg/kg in patients with GPP in 1368-0011. Spesolimab concentrations below LLOQ have been assigned the value of 10 ng/mL (1/2 of LLOQ).

In the pivotal Study 1368-0013, patients were administered a single-dose of either 900 mg i.v. spesolimab or placebo on Day 1. Patients could qualify to receive an open-label treatment with 900 mg i.v. spesolimab on Day 8 depending on clinical response (GPPGA score). As noted previously, ADA appeared to reduce plasma concentrations of spesolimab, particularly at titres greater than 4000. The PK parameters after one dose of i.v. spesolimab are shown in Table 6, and the gMean PK parameters after two doses of i.v. spesolimab on Day 1 and Day 8 are shown in Table 7.

Table 7. PK parameters of spesolimab after i.v. administration of two doses of spesolimab 900 mg (Day 1 and Day 8)

Patient Group	N	$AUC_{0\text{-}tz}$ [µg·day/mL]	$t_{1/2}$ [day]
All Patients[2]	9[2]	5840 [50.0]	20.2 [37.2]
All ADA-neg Patients	5	7280 [19.9]	25.3 [11.7]
All ADA-pos Patients	4[2]	4430 [65.8]	15.2 [38.0]

[1] Includes patients randomized to spesolimab who received 2 spesolimab doses, i.e. on Day 1 and open-label spesolimab on Day 8 [2] Patient #184001002 excluded from descriptive statistics due to insufficient number of data points to determine PK parameters

39 patients (73.6%) who achieved clinical improvement with spesolimab rolled over into the open-label extension (OLE) trial 1368-0025.These patients received s.c. spesolimab 300 mg q12w if they had not received any rescue treatment with open-label spesolimab i.v. in the previous trial, or more intensified treatment 300 mg q6w if they had. If a patient experienced a recurrence of a GPP flare during study 1368-0025, a rescue treatment with one i.v. dose of 900 mg spesolimab was to be administered. Twelve weeks after receiving the rescue treatment and upon resolution of the GPP flare, the patients would be on an intensified maintenance treatment of 300 mg q6w s.c. The c/t profiles of spesolimab are shown stratified by ADA titre and number of flares in Figure 3.

Of the 9 patients with flare, 6 patients had 1 disease flare, 3 patients had 2 flares. Seven of the 9 patients with recurrent flare were ADA-positive with maximum titre greater than 21600. Upon re-exposure to i.v. spesolimab, the $AUC_{0\text{-}7day}$ was reduced by ~75% with large inter-patient variability in the 7 ADA-positive patients compared with their initial $AUC_{0\text{-}7day}$ after first i.v. dose in 1368-0013, as estimated in the pop PK analysis. In contrast, only a slight decrease in gMean C_{max} (~ 10%) was observed.

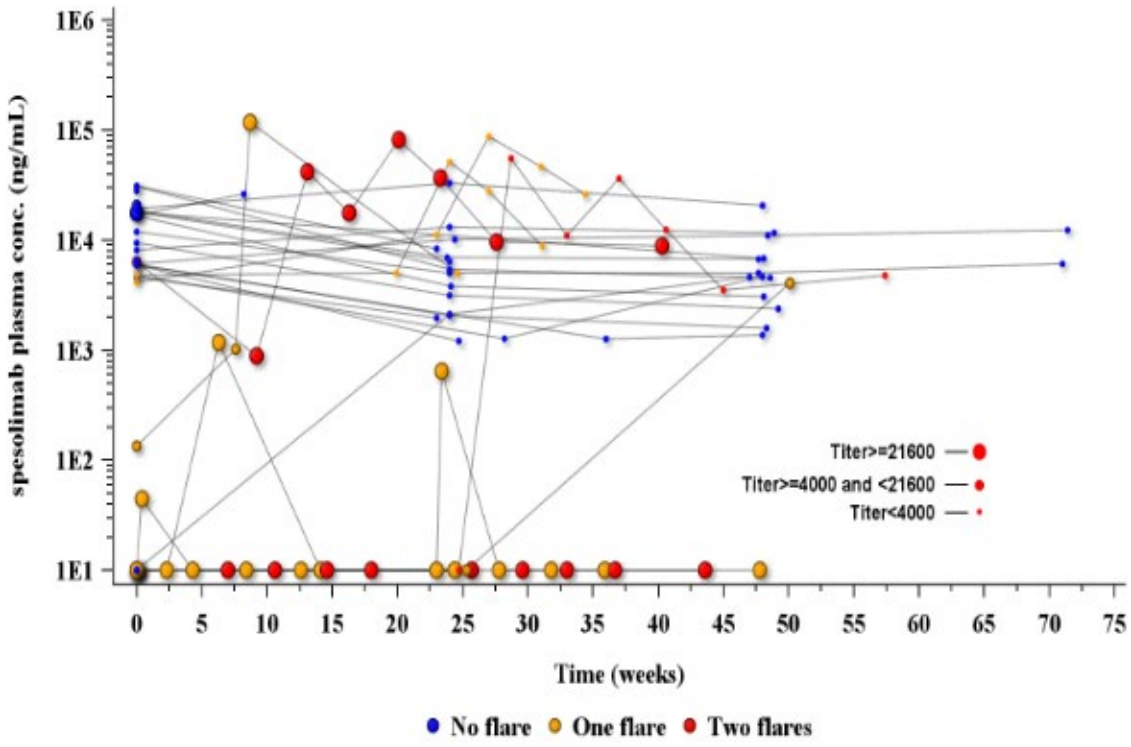


Figure 3: Individual trough concentrations of spesolimab after s.c. administration of spesolimab in all patients of study 1368-0025, stratified by number of flares and ADA titre

Exposure in typical GPP, ADA negative patient

Parameter estimates for a typical ADA negative GPP patient after single IV and SC dose are depicted in the Table 9.

Table 8. Parameter estimates for a typical ADA negative GPP patient after single IV and SC dose

Parameter	Description	Median (95%CI)
$t_{1/2\alpha}$	Alpha half-life (days)	1.63, (1.41,1.85)
$t_{1/2\beta}$	Beta half-life (days)	25.5, (24.4,26.3)
Vd_{ss}	Apparent volume of distribution at steady-state (L)	6.39, (6.17,6.70)
$Cmax_{iv}$	Cmax single 900 mg iv dose (mg/L)	238, (218,256)
$Cmax_{sc}$	Cmax single 300 mg sc dose (mg/L)	36.2, (33.4,39.4)
$AUC_{iv,0-\infty}$	AUC iv 900 mg dose (mg/L*day)	4.75e+03, (4.51e+03,4.97e+03)
$AUC_{sc,0-\infty}$	AUC sc 300 mg dose (mg/L*day)	1.54e+03, (1.46e+03,1.61e+03)

Source code: BII5701F-calc-endpoints.Rmd
Source file: PK_nca-like-parameters_V2.tex

Special populations

No dedicated studies have been conducted to investigate the pharmacokinetics of spesolimab in special populations. The effects of renal or hepatic impairment on the clearance of spesolimab were not studied. Spesolimab is not expected to undergo renal elimination or to be metabolised by hepatic enzymes. Spesolimab concentrations were lower in subjects with higher body weight. A GPP patient

with body weight of 40 kg may have an AUC ~60% higher and Cmax ~ 75% higher than a typical patient. A GPP patient with body weight of 160 kg may have an AUC ~ 50% lower and Cmax ~ 55% lower than a typical patient. No effects of age, race or gender were identified. The distribution of elderly in clinical trials is summarised in Table 9.

Table 9. Age distribution of spesolimab treated subjects

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Healthy volunteers			
1368-0001	0 / 58	0 / 58	0 / 58
1368-0002	0 / 30	0 / 30	0 / 30
1368-0003	0 / 36	0 / 36	0 / 36
1368-0009	0 / 24	0 / 24	0 / 24
1368-0029	0 / 48	0 / 48	0 / 48
1368-0043 (i.v. portion)	0 / 30	0 / 30	0 / 30
GPP patients			
1368-0011	0 / 7	0 / 7	0 / 7
1368-0013	2 / 51	0 / 51	0 / 51
1368-0025[1]	0 / 39	0 / 39	0 / 39
Patients with other Dermatologic Indications (PPP or AD)			
1368-0015[2]	0 / 39	0 / 39	0 / 39
1368-0016	24 / 147	1 / 147	0 / 147
1368-0032	3 / 39	0 / 39	0 / 39
Trials in Ulcerative Colitis (UC)			
1368-0004	0 / 8	1 / 8	0 / 8
1368-0005	5 / 74	0 / 74	0 / 74
1368-0010[3]	0 / 15	0 / 15	0 / 15

[1] all patients rolled over from trial 1368-0013

[2] including one patient assigned to placebo but accidentally received 100 mg spesolimab at week 4.

[3] including one patient assigned to placebo but accidentally received spesolimab at week 8. No spesolimab plasma concentration results were available for this patient.

Pharmacokinetic interaction studies

No formal drug interaction trials with spesolimab have been performed. For the treatment of GPP flares, the potential of spesolimab to cause clinically significant DDI as a perpetrator is low.

The acute and transient increase in pro-inflammatory cytokines in patients with GPP flare, combined with the rapid anti-inflammatory effect of spesolimab makes the potential indirect DDI risk associated with normalisation of pro-inflammatory cytokine minimal.

The effect of concomitant use of immunosuppressants or oral corticosteroids on the PK of spesolimab was investigated in the popPK.

Exposure relevant for safety evaluation

After a single intravenous i.v. dose of 900 mg, the population PK model-estimated AUC0-∞ (95% CI) and Cmax (95% CI) in a typical ADA-negative patient with GPP were 4750 (4510, 4970) µg·day/mL and 238 (218, 256) µg/mL, respectively. Exposure is expected to be lower in ADA positive patients.

2.6.2.2. Pharmacodynamics

Mechanism of action

The classic presentation of GPP flares as described by von Zumbusch is strongly correlated with polymorphisms in the IL36-R signalling pathway (Marrakchi, 2011; Onoufriadis, 2011). Individuals with loss-of-function mutations of the IL36RN gene which encodes an endogenous IL36R antagonist (IL-36RN) have dramatically higher incidence of GPP, indicating that uncontrolled upregulation of IL36 signalling due to defective IL36RN antagonism leads to the inflammatory episodes observed in GPP.

Spesolimab is a humanized, antagonistic, monoclonal IgG1 antibody that binds to IL-36R and blocks human IL-36α-, IL-36β-, and IL-36γ-induced IL-36R activation, leading to suppressed pro-inflammatory and pro-fibrotic pathways in inflammatory skin diseases. In patients with GPP, blockade of IL-36R signalling is a novel, targeted therapeutic approach. IL-36R inhibition with spesolimab led to normalisation of inflammatory blood biomarkers (CRP, neutrophils, leukocytes) and of the gene expression profile of lesional skin in patients with GPP, and the downregulation of biomarkers correlated with decreases in clinical disease severity (see further details below).

Thus, based on published data, there is a plausible mechanism of action for spesolimab in GPP, as a blocker of human IL-36R activation.

Primary and secondary pharmacology

The primary PD effect of spesolimab has been assessed by indirect target engagement of IL36R using an *ex vivo* whole blood stimulation assay, since a direct measurement did not seem possible. Whole blood was taken before and after treatment of subjects with spesolimab or placebo and stimulated with IL36γ ligand. After preparation of plasma, the resulting production of macrophage inflammatory protein (MIP-1β) or TNFα was quantified via immunoassay as exploratory biomarker. MIP-1β or TNFα levels were expected to be inversely correlated with the level of IL36R engagement by the anti-IL36R antibody. This approach was used in the Phase 1 single (1368-0001) and multiple dose studies (1368-0002) in healthy volunteers.

Engagement of peripheral interleukin (IL)-36R (as measured by inhibition of MIP-1β or TNF) was saturated after single dose administration of spesolimab 3 mg/kg or above (Study 1368-0001). After single spesolimab doses, the percent inhibition for both MIP-1β and TNFα was at least 94% compared to baseline during the entire time course up to 10 weeks.

Results from the Phase 1 multiple dose study 1368-0002 are shown in Figure 4 and Figure 5. For all multiple dose groups (as well as the single dose group of 20 mg/kg), a median %-inhibition of MIP-1β of at least 90% was observed as compared to baseline (pre-dose) during the entire time course until the end of study (week 25), with placebo groups showing negligible inhibition. These results were also confirmed using TNFα as assay readout.

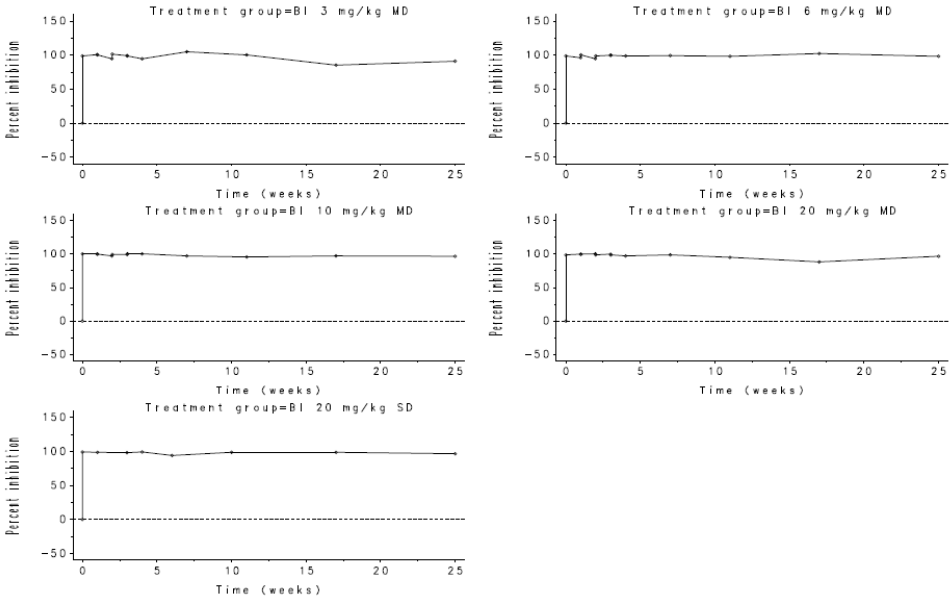


Figure 4. Time profile of MIP-1β % inhibition after multiple dosing, Study 1368-0002

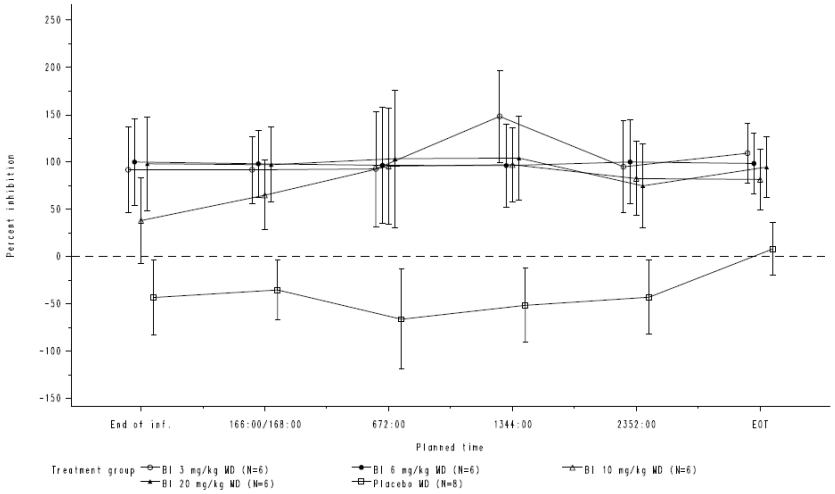


Figure 5. Time profile of TNFα % inhibition (adjusted means and 90% CI per dose group) after multiple dosing, Study 1368-0002

Studies have also shown reductions in CRP, IL-6 as well as other cytokines/biomarkers after a single dose of spesolimab. In the proof-of-concept study 1368-0011 in GPP patients, biomarkers associated with the IL-36 pathway, T helper cells (Th1/Th17), innate inflammation signalling, neutrophilic mediators and keratinocyte-driven inflammation pathways were downregulated by spesolimab treatment at Week 1 in lesional GPP skin. Spesolimab decreased serum biomarker levels such as CRP and IL-6 as early as week 1. The overall biomarker changes were consistent across 12 weeks.

For CRP, reductions were apparent from Day 2 and were maintained until Week 20 (last follow-up). Median percentage change (reduction) in CRP from baseline reached -90.7% at Week 4. Not all

patients had baseline values for these biomarkers that were above the upper limit of normal (for example, for CRP).

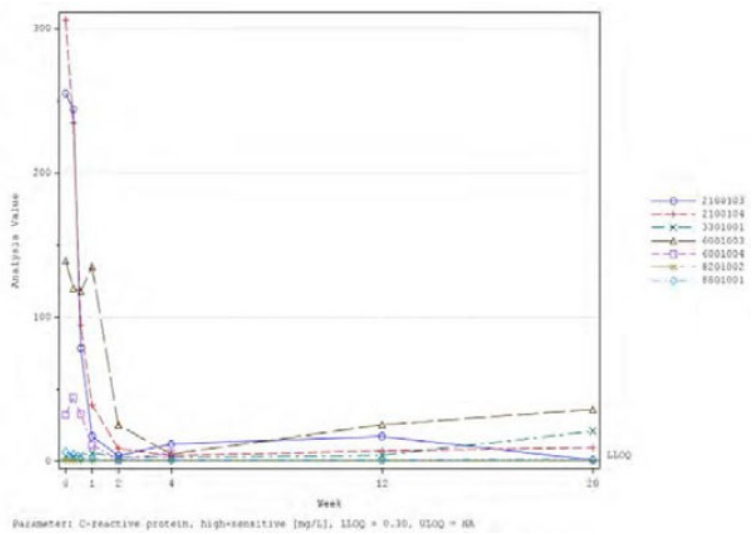


Figure 6. Absolute CRP values over time by patient – FAS (OC), Study 1368-0011

Reductions in IL-6 were apparent from Day 2 (except for 1 patient) and were maintained until Week 20. Median percentage decreases in IL-6 from baseline reached a maximum of -87.9% at week 12. Reductions in CRP and IL-6 coincided with reductions in GPPASI score up to Week 12.

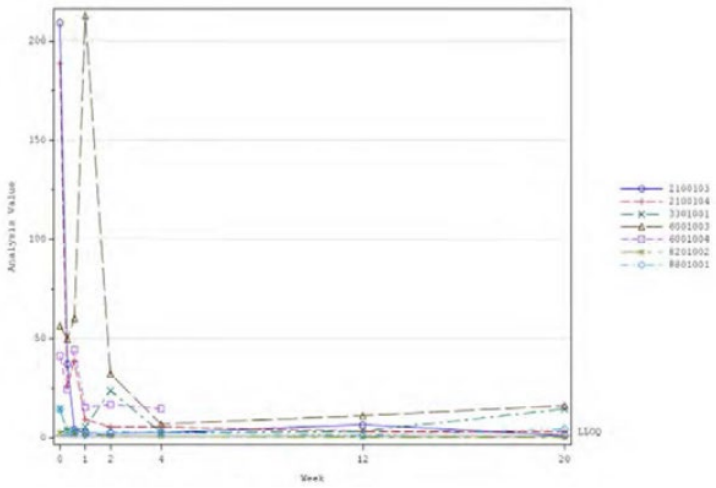


Figure 7. Absolute IL-6 values over time by patient – FAS (OC), Study 1368-0011

Decreases in biomarkers of keratinocyte activation were observed across all patients to different extents over time, e.g. in Chemokine (C-C motif) ligand 20 (CCL20) and IL-22 levels. In patients with elevated levels of beta-defensin 4A at baseline, decreases in levels were observed on Day 2 in 2 of 7 patients and at Week 12 in 5 of 7 patients. IL-17A and IL-19 levels decreased at Weeks 4 and 12 in those patients with elevated levels at baseline.

Median decreases in biomarkers of neutrophil activation were observed across all patients to different extents over time. Decreases in median levels of IL-8 from baseline were observed at Week 4 in 5 of 7

patients and at Week 12 in 6 patients. Median decreases from baseline in IL-1RN levels were observed at Week 2 in 6 of 7 patients, and 6 of 7 patients at Week 12. Marked down-regulation of selected serum biomarkers at Week 12 compared with baseline was accompanied by decreases in clinical severity of disease based on changes in GPPASI pustules severity, GPPASI score, and GPpustASI score.

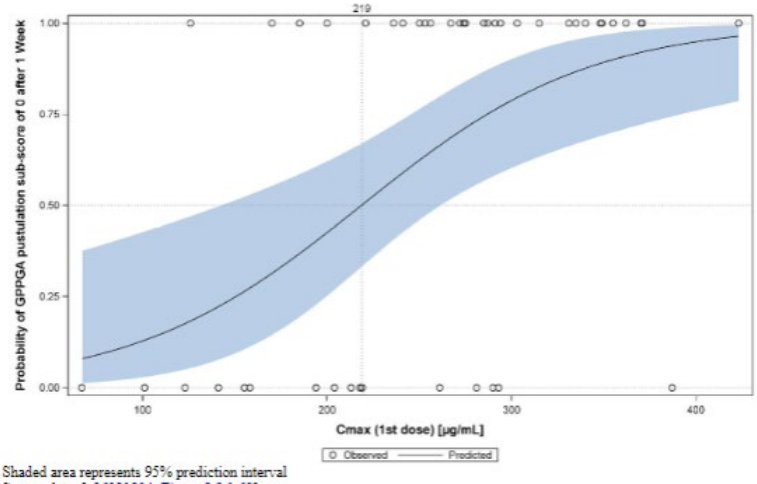
No dedicated secondary pharmacology studies have been performed with spesolimab. No obvious need for specific studies on secondary pharmacological effects of spesolimab can be foreseen. Various biomarkers (e.g. CRP, IL-6) have been followed in the clinical studies. No thorough QT study has been conducted. However, this has been addressed by ECG monitoring and concentration-QT modelling. No dedicated vaccine efficacy study has been conducted, to evaluate the effect of spesolimab on vaccination response to common vaccines. This is further discussed in the safety section.

Exposure-response analyses

Spesolimab exposure-response relationship in patients with GPP flares were assessed based on results from the pivotal trial 1368-0013 in which 53 patients were randomised to receive 900 mg i.v. spesolimab or placebo (2:1) on Day 1 with option of a second dose if symptoms persisted on Day 8. As the optional second dose given on Day 8 was based on the response status, it complicated the PK/PD relationship investigation beyond Day 8 since patients with higher PK exposure (due to the second dose) may not have better clinical response than patients with lower exposure (from 1 dose). The exposure – efficacy evaluation was therefore limited to efficacy endpoints at Week 1 after first dose only.

Exposure-efficacy

The exposure-response relationship was investigated using a logistic regression model linking spesolimab PK exposure to the probability of achieving efficacy outcome. The modelling results for Cmax,1st dose vs. the primary endpoint GPPGA pustulation subscore of 0 are shown in Figure 9. Based on the analysis, a patient with typical high exposure (i.e. at 75th percentile = 303 µg/mL) is expected to have about 35% higher probability of response than that of a patient with typical low exposure (i.e. at 25th percentile = 204 µg/mL).



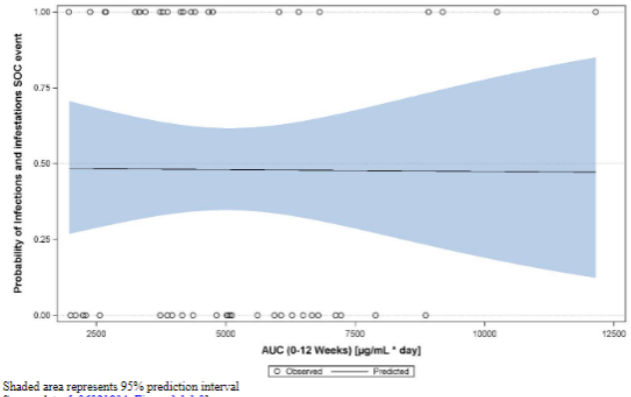
Shaded area represents 95% prediction interval
Source data: [c36321904, Figure 2.2.1.63]

Figure 8. Logistic Regression of probability of achieving GPPGA pustulation score of 0 vs spesolimab Cmax after 1st active dose

Exposure Response Analysis for Safety

Infection-related AE

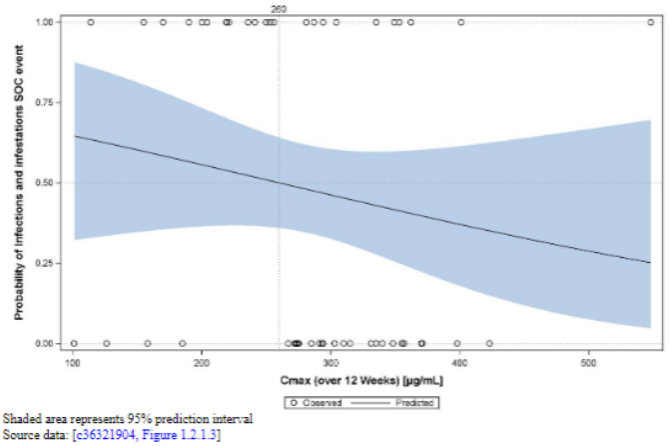
Spesolimab exposure measures were population PK model-projected AUC0-12wk and Cmax during the trial 1368-0013. The individual patient PK exposure metrics were simulated based on empirical Bayes estimates derived from the population pharmacokinetic model. Exposure-response relationship was investigated using a logistic regression model linking spesolimab PK exposure to the probability of occurrence of an infection related AE. There was no significant correlation between AUC0-12wk and infection-related events. There was a negative trend between Cmax and infection-related events. Taken all together, E-R modelling results do not indicate elevated risk for infection with increasing spesolimab exposures.



Shaded area represents 95% prediction interval
Source data: [c36321904, Figure 1.1.1.3]

Figure 17 Logistic regression of probability of occurrence of an infection related AE vs spesolimab $AUC_{0\text{-}12wk}$

Figure 9. Logistic regression of probability of occurrence of an infection relates to AE vs spesolimab AUC0-12wk.



Shaded area represents 95% prediction interval
Source data: [c36321904, Figure 1.2.1.3]

Figure 18 Logistic regression of probability of occurrence of an infection related AE vs spesolimab C_{max}

Figure 10. Logistic regression of probability of occurrence of an infection relates to AE vs spesolimab Cmax.

Liver enzymes

Potential correlation between drug exposure (population PK model projected Cmax and AUC0-12wk) and liver enzyme values during trial 1368-0013 was investigated using linear regression models. For both ALT and AST, there was a numerical negative trend. That is, the higher Cmax appeared to be associated with lower maximum ALT or AST. For total bilirubin, there was a numerical positive trend. The slope was not statistically different from zero.

Taken all together, there was no meaningful correlation between spesolimab exposure and liver enzyme values.

2.6.3. Discussion on clinical pharmacology

Methods

Analysis of spesolimab PK

The PK assay and thus spesolimab quantification was directly influenced by presence of ADA's. Thus, development of ADA/NAbs have major impact on spesolimab exposure. The applicant presented results of a non-validated total spesolimab PK assay for comparison with the validated free (active) PK assay of 76 samples in subjects with a positive ADA titre. The two assays gave roughly comparable results. As noted above, an effect on PK for ADA titres from 4000 has been noted.

Overall, the bioanalytical method is considered to have been validated in accordance with the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1) and adequate for its purpose.

Analysis of spesolimab immunogenicity

A standard multi-tiered approach was developed including screening, confirmatory and titre to evaluate anti-drug antibodies. An ECL bridging assay with labelled spesolimab and acid dissociation sample pre-treatment step was used for the screening, confirmatory and titre assays.

Confirmed positive ADA samples from trials in GPP (1368-0013 and 1368-0025) and in AD (1368-0032) were further characterised in a validated cell based NAb assay. To evaluate the drug tolerance of the assay, positive control antibody was prepared in negative control pooled human serum at the concentrations used for HPC (2.0µg/mL), MPC (0.9 µg/mL), and the calculated LPC normal (LPC-N, 0.5065 µg/mL) and disease state (LPC-DS, 0.7827 µg/mL) concentrations. At the Normal low SPC, the drug tolerance was 100 µg/mL. Drug tolerance at a level of 100 ng/mL positive control is desirable, as apparent from the studies in GPP patients. The applicant considered that it was unlikely to succeed in obtaining better drug tolerance for the LPC in the NAb assay. This is acknowledged.

popPK analysis

Dataset and methods

93 GPP subjects (IV 57, SC 36) were included in the dataset out of 557 total subjects. BQL was low and omitting BQL samples here is considered acceptable. Using the fixed allometric coefficients of 0,85 and 1 is considered adequate for mAbs. The Methods used are considered acceptable.

Final popPK model

The pcVPC support that the model has satisfactory predictive performance. The parameter estimates generally appear satisfactory estimated with acceptable CI from the bootstrap. RSE could have been useful in the table but this issue is not further pursued. CI for ADA parameters are high and ADA parameters should be interpreted with some caution.

Shrinkage on clearance was low, however for other parameters such as ka, it was higher. Absorption parameters often have higher shrinkage. The low shrinkage on clearance indicates the model is satisfactory to derive individual exposures to use in the exposure-response.

Visual predictive checks stratified by ADA status and route of administration (IV vs SC) did not indicate any difference between subjects with ADA positive or negative status.

About 17% of subjects included were GPP patients, where the majority was administered iv. The VPCs indicated an appropriate fit for GPP iv, however, very few GPP observations came from s.c. administered patients. It is not clear from the VPC if this patient group is adequately described by the Pop PK model. Since the indication sought is for iv infusion, the issues regarding Sc administration in GPP patients is not pursued.

Overall, the popPK model is considered acceptable to support section 5.2 in the SmPC. The model is also considered adequate to derive individual exposures to use in the exploratory exposure-response analyses here.

Absorption

No human bioequivalence studies were performed to demonstrate comparability between the formulations/processes used during the clinical development programme of spesolimab. All analytical methods were cross-validated between the substance batches. Since all studies except for 1368-0001 were analysed with the same bioanalytical assay, across-study comparisons are acceptable. Similarly, ADA were analysed with the same method except for studies 1368-0001 and -2, which were excluded

from the comparison. Even though only limited PK data is available for the to be marketed product DP3, there were no apparent differences in PK and immunogenicity for all three process materials.

Distribution

The distribution of spesolimab is consistent with reported PK parameters for other IgG1s in human. Based on the population pharmacokinetic analysis, the typical volume of distribution at steady state was 6.4 L (SmPC 5.2).

Elimination

The metabolic pathways of spesolimab have not been investigated. This is acceptable for an IgG antibody. Commonly the t½ reported for human IgG is around 20 days, though there is a wide range in the reported values. This is reflected in the SmPC (section 4.8 and 5.2): *In some patients with ADA titre values > 4 000, plasma spesolimab concentrations were reduced, with no apparent impact on pharmacokinetics at ADA titres below 4 000*.

Dose proportionality, time dependencies & immunogenicity

TMDD was apparent at lower doses, and PK was linear in the range 0.3 -20 mg/kg. This is adequately reflected in the SmPC section 5.2.

The incidence of ADAs appears to be in the same range in the different patient populations and healthy subjects, with the exception of UC patients who have a lower incidence of immunogenicity. A hypothesis would be that these patients receive other immunosuppressive medicines that also affect the formation of ADAs.

ADAs did not have a significant impact on the PK of spesolimab at low titres. At higher titres (>4000), decrease exposure, shorter t1/2 and higher CL are denoted in certain patients, however the variability is large.

The observation that the NAb status appeared to be associated with high titre of ADA is likely confounded by the (lack of) drug tolerance at the NAb method, so that those samples with lower levels of NAb were likely false negative.

The ADA titres were adjusted with the MRD for healthy subjects and non-GPP patients in the Integrated summary of immunogenicity (ISI) for the early clinical trials. The applicant clarified that MRD was already reflected in the reported values for later clinicals, thus no further adjustment is needed.

The applicant notes a higher immunogenicity in females compared to males, and lower titres in those patients who received two doses in study 1368-0013. As the number of patients is small, the immunogenicity of the second dose should be interpreted with caution. While more female patients have ADA titres >4000, not all patients with ADA >4000 have reduced spesolimab concentration, thus the impact of the higher immunogenicity in females on PK and efficacy is unknown.

ADAs had an onset time of 2.3 weeks, so that the incidence of ADAs has no impact on the decision to administer a second dose at day 8. It may however have an impact in case of recurrent flares treated by spesolimab as lower exposure was noted at high ADA titres.

The currently available data is adequately reflected in the SmPC.

PK in target population

Exposure in study 1368-0013 may appear lower than predicted by popPK, however this is misleading as no end of infusion PK samples were taken in this study, thus a potentially non negligible part of the AUC is missing in the NCA based parameters of this study.

In study 1368-0013, a large number of the NAb samples had spesolimab concentrations above 100 µg/mL. It is likely that the earlier results were false negative due to the presence of high concentrations of spesolimab in the samples. All subjects tested for NAbs eventually became positive, except for one subject. In study 1368-0025, all samples with high spesolimab level were positive despite the drug levels. This is not expected to change the overall results of NAb incidence, however in general, the time to onset of NAb may be shorter than reported.

ADAs had an onset time of 2.3 weeks, so that the incidence of ADAs has no impact on the decision to administer a second dose at day 8. It may however have an impact in case of recurrent flares treated by spesolimab as lower exposure was noted at high ADA titres. The impact of re-treatment of flares with spesolimab on the formation of ADAs will be assessed in the planned SOB study 1368-0120.

With regards to safety, the exposure in a typical ADA negative GPP patients is considered acceptable to present in SmPC section 5.2 since this exposure will be higher than in a typical ADA positive patient. The model estimated PK parameters for ADA positive patients are to be interpreted with caution due to the high variability of the data and consequently the model. The effect of ADAs on the PK is now described in SmPC sections 5.2 and 4.8.

Special populations

No dedicated studies have been conducted to investigate the pharmacokinetics of spesolimab in special populations. Since spesolimab is not expected to undergo renal elimination or to be metabolised by hepatic enzymes, this is acceptable. No effects of age, race or gender were identified. Spesolimab concentrations were lower in subjects with higher body weight. These conclusions are agreed with. The currently available data is adequately reflected in the SmPC.

The PopPK model indicates that weight impacts exposure. Efficacy studies have been undertaken with the flat dose, meaning less exposure for the higher body weight individuals. This is acceptable as there is the possibility for a 2nd dose in case of lacking efficacy.

Evaluation of body weight impact on exposure at body weight extremes did not indicate any required changes to the proposed dosing regimen except for patients with body weights >130 kg. Thus SmPC Section 5.2 was reworded with the following text on body weight:

"*Spesolimab concentrations were lower in subjects with higher body weight. The impact of body weight on spesolimab exposure is not expected to be clinically meaningful up to approximately 130 kg. The clinical relevance of higher body weight greater than 130 kg is unknown*".

Pharmacokinetic interaction studies

No formal drug interaction trials with spesolimab have been performed. For the treatment of GPP flares, the potential of spesolimab to cause clinically significant DDI as a perpetrator is low, and the applicant considers a clinical DDI evaluation for the target indication to be unnecessary. The applicant's justification for the low risk of cytokine mediated CYP interactions is agreed. This is now reflected in the SmPC.

As pointed out by the applicant, a study will be performed for other indications. This is however not considered relevant for the treatment of GPP flares and the justification is sufficient.

The effect of concomitant use of immunosuppressants or oral corticosteroids on the PK of spesolimab was investigated in the popPK. Since PK sampling is limited in the studies with co-medication, this analysis is not considered sufficiently robust to support the claim in SmPC section 5.2 that 'oral corticosteroids did not have a direct impact on the pharmacokinetics of spesolimab. The SmPC has been updated accordingly and the 'reference to corticosteroids has been removed. The section 4.5 of the SmPc mentions 'There is limited experience from the use of spesolimab in combination with immunosuppressants in GPP patients.'

Exposure-response

Efficacy

The applicant has provided information regarding exposure-efficacy and exposure-safety analyses in the clinical pharmacology summary. No full analysis reports were found. The exposure-efficacy analysis indicate that a higher exposure was correlated to a higher probability of response. Since the exposure-response (E-R) model for efficacy was developed based on limited data (50 spesolimab treated patients in total) from a single dose level of spesolimab, the E-R relationship observed for spesolimab should be interpreted with some caution.

Safety

The exposure-safety analysis does not indicate an elevated risk for infection with increasing spesolimab exposures and there was no meaningful correlation between spesolimab exposure and liver enzyme values.

The exposure-safety analyses are considered exploratory. The pivotal trial has already been conducted and the B/R of the proposed posology is based on the clinical data.

Pharmacodynamics

The presence of GPP has been strongly associated to polymorphisms in the IL36-R signalling pathway. Individuals with loss-of-function mutations of the IL36RN gene which encodes an endogenous IL36R antagonist (IL-36RN) have dramatically higher incidence of GPP, indicating that uncontrolled upregulation of IL36 signalling due to defective IL36RN antagonism leads to the inflammatory episodes observed in GPP. Based on this, there is a plausible mechanism of action for spesolimab in GPP, as a blocker of human IL-36R activation.

The primary PD effect of spesolimab has been assessed by indirect target engagement of IL36R using an *ex vivo* whole blood stimulation assay, since a direct measurement did not seem possible. Levels of macrophage inflammatory protein (MIP-1β) and TNFα were expected to be inversely correlated with the level of IL36R engagement by the anti-IL36R antibody. This approach was used in the Phase 1 single (1368-0001) and multiple dose studies (1368-0002) in healthy volunteers. Engagement of peripheral interleukin (IL)-36R (as measured by inhibition of MIP-1β or TNF) was saturated after single dose administration of spesolimab 3 mg/kg or above. After single spesolimab doses, the percent inhibition for both MIP-1β and TNFα was at least 94% compared to baseline during the entire time course up to 10 weeks. After multiple dosing up to 20 mg/kg, a median %-inhibition of MIP-1β of at least 90% was observed compared to baseline (pre-dose) during the entire time course until the end of study (week 25). Based on this, it seems as if a pronounced inhibition of IL-36 signalling is obtained at single doses of spesolimab already from 3 mg/kg and that this inhibition is maintained for several months. However, this is based on data in healthy volunteers and corresponding data on indirect target

engagement was not found in studies in GPP patients. Hence, whether the target is equally saturated at the chosen dose in GPP patients is not fully clear and the applicant was asked to provide any available data or discuss/justify the dose in relation to target levels in GPP flare patients. No data on indirect target engagement data in GPP patients are available, however, some data from skin biopsies showed about a 5-fold downregulation in expression of IL36A and a 2.3-fold downregulation of IL-36G ligand levels at week 8 in lesional skin biopsies compared to baseline levels. Relating these data to the choice of dose is difficult. The applicant has compared the characteristics of patients achieving improvement with a single dose of spesolimab vs. those in need of a second dose. It is agreed that there seems to be no obvious factor observed that could guide the prescribers in identifying patients who would be in need of a second dose. No updates of the posology are therefore deemed possible or necessary.

Studies have also shown reductions in CRP, IL-6 as well as other cytokines/biomarkers after a single dose of spesolimab. This has been reflected in SmPC section 5.1.

No dedicated secondary pharmacology studies have been performed with spesolimab and no obvious need for specific studies on secondary pharmacological effects of spesolimab can be foreseen. No thorough QT study has been conducted. However, this has been addressed by ECG monitoring and concentration-QT modelling (see above). No dedicated vaccine efficacy study has been conducted, to evaluate the effect of spesolimab on vaccination response to common vaccines. This is further discussed in the safety section.

No dedicated PD interaction studies have been performed and in the clinical studies, spesolimab was not to be combined with products commonly used to treat GPP, and there were restrictions in concomitant medications. Hence, there is no vast experience from the use of spesolimab concomitantly with other immunomodulating drugs. This is reflected in the SmPC (section 4.4).

Spesolimab is directed towards IL36 cytokines and it is known that mutations in the IL36RN gene is associated with GPP (Marrakchi, 2011; Onoufriadis, 2011; Johnston, 2017). The IL-36RN mutation status has been evaluated in the clinical studies, although this was not among the inclusion criteria, and sub-group analyses for efficacy have been performed based on the mutation status. Aspects related to this are further discussed in other sections of this report.

2.6.4. Conclusions on clinical pharmacology

The PK of spesolimab after 900 mg iv administration is well described.

There were no studies in special populations. Based on population pharmacokinetic analyses, age, gender and race do not have an effect on the pharmacokinetics of spesolimab. This is in line with the nature of the drug being an IgG antibody. Spesolimab concentrations were lower in subjects with higher body weight. The clinical relevance of higher body weight greater than 130 kg is unknown. This is adequately reflected in the SmPC.

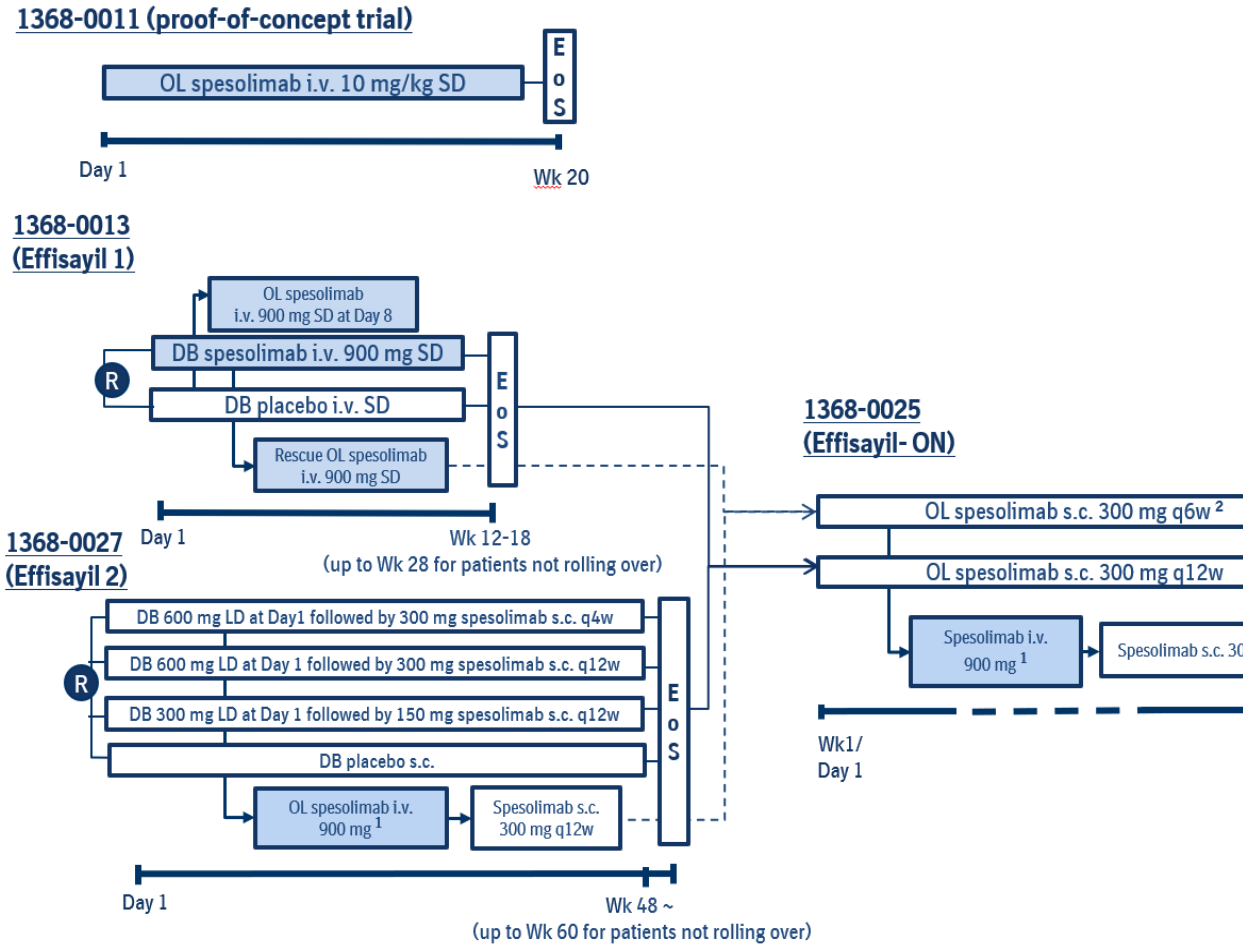
There is a plausible mechanism of action for spesolimab in GPP, as a blocker of human IL-36R activation. In healthy volunteers, pronounced inhibition of IL-36 signalling is obtained at single doses of spesolimab already from 3 mg/kg and this inhibition is maintained for several months. Corresponding data on indirect target engagement are not available in GPP patients. However, GPP patient skin biopsy data show downregulation in expression of IL36A and IL-36G ligand levels at week 8 in lesional skin biopsies compared to baseline levels.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

The impact of re-treatment of flares with spesolimab on the formation of ADAs together with the effect of immunogenicity on efficacy, safety, and pharmacokinetics of spesolimab i.v. in treatment of recurrent flares in patients with generalised pustular psoriasis will be assessed in the planned interventional study 1368-0120.

2.6.5. Clinical efficacy

The current application for spesolimab concerns an indication for the acute treatment of GPP flares, i.e. not a prevention, maintenance indication in GPP. The overall clinical development programme for spesolimab contains both a study evaluating efficacy in flare treatment (1368-0013; the pivotal study for the current submission) and a study evaluating efficacy in prevention of GPP flares (1368-0027; ongoing study). A long-term, open-label study is also ongoing (1368-0025). Some support for the flare indication also comes from the small, uncontrolled PoC study (1368-0011). The studies are depicted in Figure 11 and Table 10 below.



DB = double-blind, LD = loading dose, OL = open-label, SD = single dose

[1] 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.

[2] The dosing frequency of q4w (implemented via CTP amendment) had not been in place at the cut-off date for the interim analysis of 08 Jan 2021.

Figure 11. Overview of clinical trials with spesolimab in patients with GPP

Table 10. Clinical trials with spesolimab in patients with GPP

Trial	Duration (follow-up period)	Trial design / Trial objectives	N[1] Treated *(planned)*	Doses studied	Trial data support: Current MAA; flare treatment	Trial data support: Later MAA; Maintenance treatment	Trial status / [Report no.][2]
Phase I							
1368-0011 Proof of Concept	Single dose (20 weeks)	Multi-center, open-label, single-arm trial / efficacy and safety in GPP flare treatment	**7**	Spesolimab 10 mg/kg bw i.v.	✓		Completed / Final CTR
Phase II							
1368-0013 Effisayil™ 1	Single dose (up to 16 weeks)	Multi-center, randomized, double-blind, parallel-group, placebo-controlled trial / efficacy and safety in GPP flare treatment	**35** **18**	Spesolimab 900 mg i.v. Placebo	✓		Completed / Final CTR
1368-0027 Effisayil™ 2	48 weeks (up to 16 weeks)	Multi-center, randomized, double-blind, parallel-group, placebo-controlled trial / efficacy and safety in GPP flare prevention	*(90)* *(30)* *(30)* *(30)* **6** *(30)*	Spesolimab 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 Spesolimab 900 mg i.v. (open-label) as flare treatment (see 0) Placebo	✓ (i.v. flare treatment data)[3]	✓ (s.c. data)	Ongoing,
1368-0025 Effisayil™-ON	252 weeks (16 weeks)	Open-label extension of trials 1368-0013 and 1368-0027 / long-term safety and efficacy of spesolimab in patients with GPP	*(171)* **7** **32** **9**	Spesolimab 300 mg s.c. q6w[5] or q12w Spesolimab 900 mg i.v. as flare treatment (see 0)	✓ (i.v. flare treatment data)[3]	✓ (s.c. data)	Ongoing[6], Planned DBL Q1 2028/interim TFL before DBL

Bw = body weight, i.v. = intravenous, LD = loading dose, MAA = Marketing Authorization Application, q4w = once every 4 weeks, q6w = once every 6 weeks, q12w = once every 12 weeks, s.c. = subcutaneous, TFL = tables, listings, and figures

[1] For completed trials, number of actually treated patients *(for ongoing trials, number of patients planned to be treated)*

[2] For the completed trials, final clinical trial reports (CTR) are included in the MAA dossier. For the ongoing trials, results of the interim analyses conducted for the submission are included as tables, listings, or figures (TFL) and referenced in the clinical summary documents (SCE, SCS) in Module 2.7.

[3] To support safety in patients with GPP, open-label s.c. data were also analyzed.

2.6.5.1. Dose response study

No formal dose response studies for spesolimab in GPP are included in the MAA. One Phase 1 Proof of concept study (1368-0011) has been performed and this study is described below.

Study 1368-0011

Multi-centre, open-label, single arm, phase I study to investigate safety, tolerability, pharmacokinetics, pharmacogenomics and efficacy of a single intravenous dose of BI 655130 in patients with active generalized pustular psoriasis

Methods

This multi-national, multi-centre exploratory Phase I trial had an open-label design and all patients received a single intravenous administration of BI 655130 and were to be followed up for 140 days (20 weeks) after dosing.

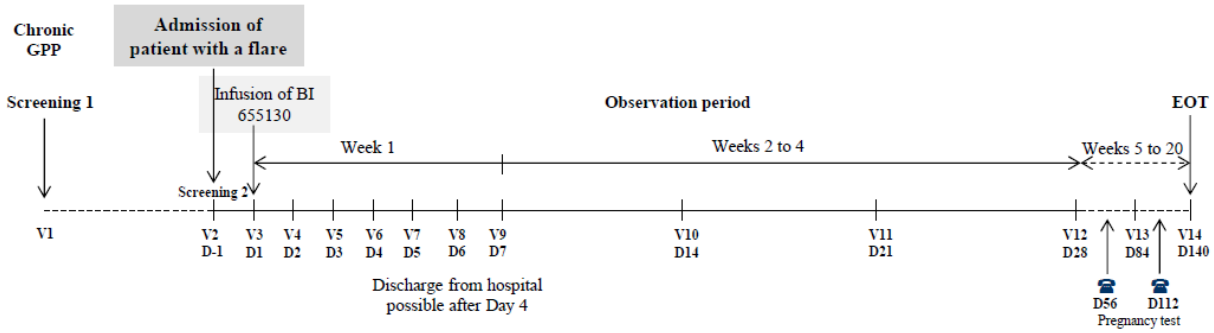


Figure 12. Trial design of study 1368-0011

The main criteria for inclusion were: Male and female patients aged ≥18 (Japan 20) and ≤75 years were included in this trial provided they (i) had a known and documented history of GPP (regardless of IL36RN status) with previous evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leukocytosis with peripheral blood neutrophilia, (ii) presented with a flare of GPP with at least 10% body surface area with erythema and pustules, (iii) and had a GPPGA score (GPP Physician Global Assessment) of at least moderate severity. The inclusion and exclusion criteria were partly similar to those applied in the pivotal flare study 1368-0013 assessed below. In this PoC study, a known and documented history of GPP regardless of the IL36RN mutation status was required, similar to study 0013. For inclusion, patients should be presenting with an acute GPP flare with a GPPGA total score of moderate (also similar to study 0013). In this study, there was a requirement for a higher body surface area (BSA) affected by erythema and pustules (10%) compared with the 1368-0013 study (5%). The 1368-0013 study included more specific requirements for the presence of fresh pustules (new appearance or worsening of pustules), and a GPPGA pustulation subscore of ≥2 (mild).

At the screening visit, patients had to be on stable maintenance treatment (for at least 4 weeks) with retinoids and/or methotrexate or not to receive any maintenance therapy at all. All patients were to use an effective birth control method throughout the trial.

The participants received BI 655130 (spesolimab) at a dose of 10 mg/kg body weight administered as a single intravenous infusion over 60 min, which could be prolonged by the investigator up to 240 min.

Patients on a stable background treatment with methotrexate or retinoids at Visit 2 (i.e. administration for at least 4 weeks preceding V2 without any escalation in dose) could be included in the trial, provided background therapy was continued at the same dose throughout the trial. Any change in dose was not permitted. Patients not receiving methotrexate or retinoids at V2 were not allowed to start these during the trial (except in situations requiring rescue therapy). Rescue medication could be used based on the severity and progression of the disease. In case of a worsening of the flare, this decision as well as the choice of a rescue medication was left at the discretion of the investigator; sites were not supplied with any rescue medication. Background therapy with ciclosporin or with other biologics was not permitted throughout the trial. Patients could be included in the trial provided the last intake of those compounds had been ≥30 days prior to V2.

The study objective was to investigate safety, tolerability, PK, pharmacogenomics and efficacy of a single intravenous dose of BI 655130 in patients with active generalised pustular psoriasis.

The primary endpoint was defined as the number (N, %) of patients with adverse reactions (i.e. drug-related AEs).

Secondary endpoints included efficacy and PK endpoints, e.g.:

- Percent change from baseline in GPPASI (GPP Area and Severity Index) total score at Week 2
- Proportion of patients with GPPGA (GPP Physician Global Assessment) total score of 0 (clear) or 1 (almost clear) at Week 2
- Change from baseline in FACIT (Functional Assessment of Chronic Illness Therapy) - Fatigue scale score at Week 2
- Change from baseline in Pain VAS (Visual Analogue Scale) score at Week 2
- C_{max}, $AUC_{0-\infty}$

The evaluation of safety and tolerability was based on adverse events (AEs) and serious AEs, clinically relevant findings from physical examinations, safety laboratory parameters, 12-lead electrocardiograms (ECG), vital signs (blood pressure, pulse rate, body temperature, body weight), injection site reactions, immunogenicity (anti-drug-antibodies; ADA).

Descriptive statistics were used to analyse safety, PK, and efficacy endpoints. Formal hypothesis testing was not planned and not performed. An interim analysis of the Week 4 efficacy and safety data was planned and performed.

Results

The trial was initiated in 7 countries including a total of 8 trial sites. Out of 16 enrolled GPP patients, 7 patients entered the trial. All 7 patients were included in the entered set, the treated set, and the full analysis set (FAS). Six patients were included in the per-protocol set (PPS); 1 patient was excluded due to a major protocol violation. No patient discontinued the trial prematurely.

Four patients were Asian, 2 patients were White; 4 patients were female and 3 patients were male. Patients' mean (SD) age was 38.6 (13.8) years and their mean (SD) BMI was 23.33 (4.35) kg/m^2.

With respect to IL36RN mutation status, based on historical data, an IL36RN mutation had been documented in 2 patients (28.6%), while it was stated as negative in 3 patients (42.9%) and unknown in 2 patients (28.6%). Following genotyping (DSS), in 3 patients (50%) a potential pathogenic homozygous mutation associated with GPP was observed in IL36RN. One of those patients (16.7%) in addition carries a heterozygous CARD14 mutation. No AP1S3 mutation was detected.

All 7 patients (100%) reported at least 1 medication for GPP in their medical history (including corticoids, antihistamines, nonsteroidal anti-inflammatory drugs, or topical antipsoriatics [71.4%], retinoids [57.1%], ciclosporin [42.9%], and methotrexate [28.6%]). No patient received an ongoing background medication for GPP (methotrexate and/or retinoids, ciclosporin) and no patient started with a concomitant medication on Day 1/V3.

Safety results (primary endpoint) and PK results are discussed in other sections of this report.

The secondary efficacy endpoints showed the following results:

Table 11. Overview on the outcome of the secondary efficacy endpoints following single i.v. administration of BI 655130 10 mg/kg (FAS N = 7; PPS N = 6)

Outcome by analysis population	GPPASI total score[a]				
	Baseline	Week 2	Week 2 change vs baseline	**% Reduction vs baseline at Week 2** [%]	95% CI for secondary endpoint
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	95% CI for mean
FAS (LOCF)	27.47 (12.25)	7.19 (4.54)	-20.29 (11.24)	**73.2 (16.2)**	(58.1, 88.2)
PPS (LOCF)	-	-	-	**73.9 (17.7)**	(55.3, 92.4)
	Patients with GPPGA total score of 0 or 1[b]				
	Number, % at baseline	Number, % at Week 2	Total number of patients	**Proportion**	95% CI for secondary endpoint
	n, %	n, %	N	**n/N**	95% CI for n/N
FAS (NRI)	0, 0%	5, 71.4%	7	**0.714**	(0.359, 0.918)
PPS (NRI)	0, 0%	4, 66.7%	6	**0.667**	(0.300, 0.903)
	FACIT-Fatigue scale score [c]				
	Baseline	Week 2	**Week 2 change vs baseline**	-	95% CI for secondary endpoint
	Mean (SD)	Mean (SD)	Mean (SD)	-	95% CI for mean
FAS (LOCF)	31.7 (13.3)	44.0 (5.6)	**12.3 (10.1)**	-	(2.9, 21.6)
PPS (LOCF)	31.7 (14.6)	44.2 (6.1)	**12.5 (11.0)**	-	(0.9, 24.1)
	Pain VAS score [d]				
	Baseline	Week 2	**Week 2 change vs baseline**	-	95% CI for secondary endpoint
	Mean (SD)	Mean (SD)	Mean (SD)	-	95% CI for mean
FAS (LOCF)	72.1 (22.0)	26.3 (25.8)	**-45.9 (32.3)**	-	(-75.7, -16.0)
PPS (LOCF)	72.5 (24.0)	22.3 (25.8)	**-50.2 (33.1)**	-	(-84.9, -15.4)

[a] GPPASI = GPP Area and Severity Index, higher score indicates worse symptoms, higher reduction indicates larger improvement of disease; [b] GPPGA = GPP Physician Global Assessment, higher score indicates worse symptoms; [c] FACIT = Functional Assessment of Chronic Illness Therapy, lower score represents greater fatigue; [d] VAS = Visual Analogue Scale, higher score indicates more pain; FAS = full analysis set, PPS = per protocol set, LOCF = last observation carried forward, NIR = no response imputed

The mean percentage reductions from baseline in GPPASI total score following the administration of BI 655130 indicated an improvement of GPP disease symptoms in patients with an IL36RN mutation and in patients without this mutation. Variability was greater in patients without the potentially GPP causing gene mutation than in patients with the mutation, however, results should be interpreted with caution given the limited sample size.

Overall, 3 patients developed ADA following treatment with BI 655130 and 3 patients did not. Efficacy results did not indicate any systematic differences between ADA-positive and ADA-negative patients.

Two patients were reported with a GPP recurrence as an AE ('pustular psoriasis' of moderate intensity in one patient and of mild intensity in a second patient). The event in the first patient was reported in the residual effect period (i.e. later than 28 days but within 140 days after dosing), while the event in the other patient was reported in the follow-up period (i.e. later than 140 days after dosing).

2.6.5.2. Main study(ies)

Study 1368-0013 (Effisayil): Multi-center, double-blind, randomized, placebo-controlled, Phase II study to evaluate efficacy, safety and tolerability of a single

intravenous dose of BI 655130 in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity.

Methods

Study Participants

Inclusion criteria

Patients aged 18 to 75 years were eligible for enrolment into this trial if they had a diagnosis of GPP based on the consensus diagnostic criteria by the European Rare and Severe Psoriasis Expert Network (ERASPEN), defined as follows:

- 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
- Either relapsing (>1 episode) or persistent (>3 months)

In addition, patients were required to have either:

- GPPGA total score of 0 or 1; history of GPP (per ERASPEN criteria); previous evidence of fever, asthenia, myalgia, elevated C-reactive protein (CRP), or leukocytosis with peripheral blood neutrophilia (above the upper limit of normal [ULN]) or
- Acute flare of moderate to severe intensity; history of GPP (per ERASPEN criteria); previous evidence of fever, asthenia, myalgia, elevated CRP, or leukocytosis with peripheral blood neutrophilia (above ULN), or
- First episode of an acute GPP flare of moderate to severe intensity with evidence of fever, asthenia, myalgia, elevated CRP, or leukocytosis with peripheral blood neutrophilia (above ULN). For these patients, the diagnosis was to be confirmed retrospectively by a central external expert/committee.

Patients may or may not have been receiving background treatment with retinoids and/or methotrexate and/or cyclosporine. Patients had to discontinue retinoids/methotrexate/cyclosporine prior to receiving the first dose of BI 655130 or placebo.

Signed and dated written informed consent prior to admission to the study in accordance with ICH-GCP and local legislation prior to start of any screening procedures.

Women of childbearing potential had to be ready and able to use highly effective methods of birth control per ICH M3 (R2) that resulted in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria was provided in the protocol as well as in the patient information. A woman was considered of childbearing potential, i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods included hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Tubal ligation was not a method of permanent sterilisation. A postmenopausal state was defined as no menses for 12 months without an alternative medical cause.

Treatment (Visit 2) was initiated immediately in patients:

- Who met the inclusion criteria and did not meet any of the exclusion criteria
- Who were presenting with an acute GPP flare of moderate to severe intensity, defined by emergence of:

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

Exclusion criteria

Patients were not to be screened or treated if any of the following criteria applied:

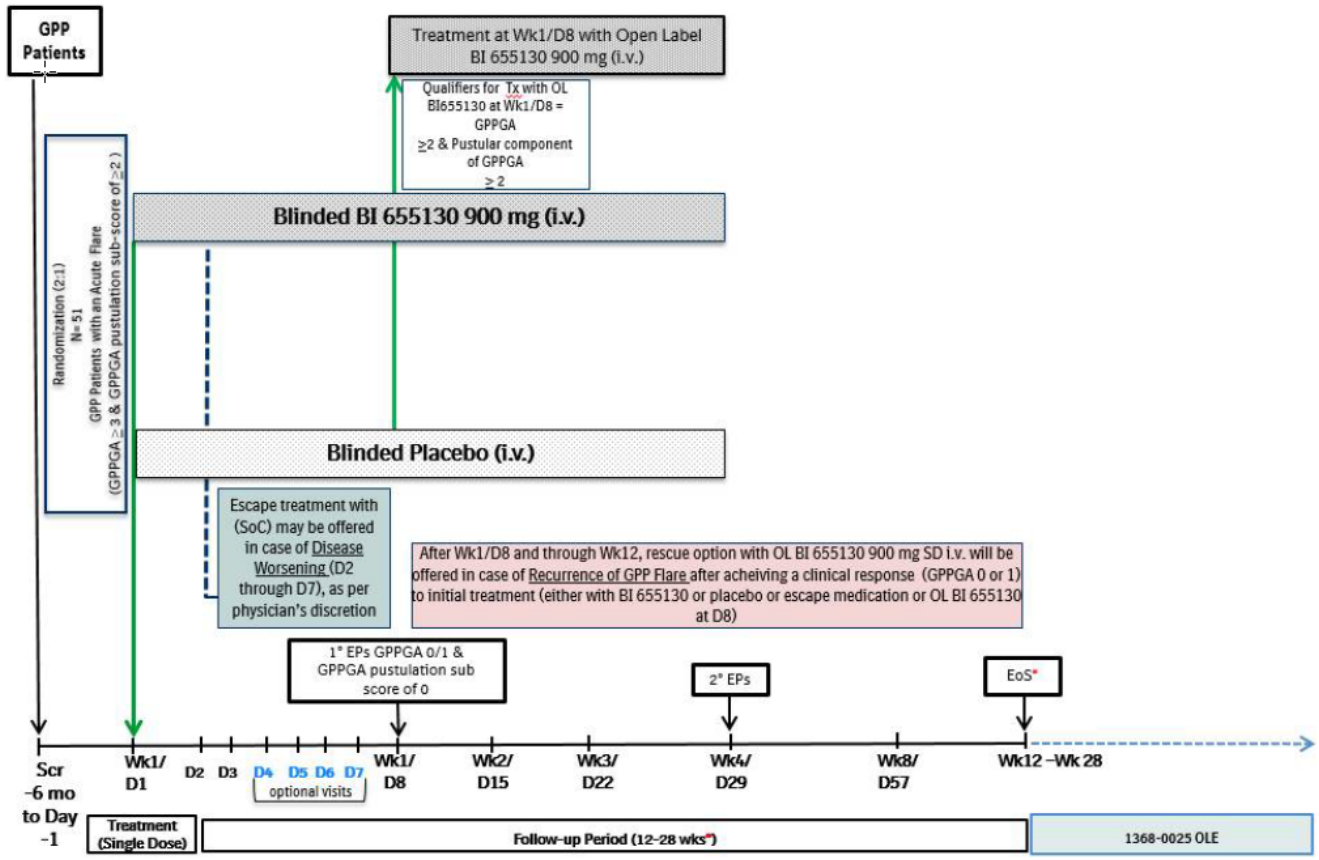
- Patients with SAPHO (Synovitis-acne-pustulosis-hyperostosis-osteitis) syndrome, or primary erythrodermic psoriasis vulgaris, or patients with primary plaque psoriasis vulgaris without presence of pustules or with pustules that were restricted to psoriatic plaques.
- Drug-triggered Acute Generalised Exanthematous Pustulosis (AGEP).
- Immediate life-threatening flare of GPP or requiring intensive care treatment, according to the investigator's judgement. Life-threatening complications mainly included, but were not limited to, cardiovascular/cytokine driven shock, pulmonary distress syndrome, or renal failure.
- Severe, progressive, or uncontrolled hepatic disease, defined as >3-fold Upper Limit of Normal (ULN) elevation in AST or ALT or alkaline phosphatase, or >2-fold ULN elevation in total bilirubin.
- Treatment with:
  a. Any restricted medication as specified in the protocol: 1 or any drug considered likely to interfere with the safe conduct of the study, as assessed by the investigator.
  b. any prior exposure to BI 655130 or another IL-36R inhibitor
- Patients with dose escalation of their maintenance therapy with cyclosporine and/or methotrexate and/or retinoids within the 2 weeks prior to receiving the first dose of BI 655130/placebo.
- The initiation of systemic agents such as cyclosporine and/or retinoids and/or methotrexate 2 weeks prior to receiving the first dose of BI 655130/placebo.
- Patients with congestive heart disease, as assessed by the investigator.
- Active systemic infections (fungal and bacterial disease) during the last 2 weeks prior to receiving first drug administration, as assessed by the investigator.
- Increased risk of infectious complications (e.g. recent pyogenic infection, any congenital or acquired immunodeficiency [e.g. HIV], past organ or stem cell transplantation)
- Relevant chronic or acute infections including HIV or viral hepatitis.
- Active or latent TB
- History of allergy/hypersensitivity to a systemically administered trial medication or its excipients.
- Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal or squamous cell carcinoma of the skin or in-situ carcinoma of uterine cervix.
- Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device/drug study(s) or receiving other investigational treatment(s).
- Women who were pregnant, nursing, or who planned to become pregnant while in the trial.

- Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to receiving first dose of study drug or planned during the study
- Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse or any condition) other than GPP, surgical procedure, psychiatric or social problems, medical examination finding (including vital signs and electrocardiogram [ECG]), or laboratory value at the screening outside the reference range that in the opinion of the investigator was clinically significant and would have affected the safety of the patient or compromise the quality of the data.

The enrolment into this study was made in a step-wise manner for most patients; i.e. first identifying patients with a diagnosis and history of GPP and then, upon experiencing a new acute flare, they were randomised and treatment was initiated. Patients could also be enrolled and randomised upon their first experience of an acute GPP flare event (with formal diagnosis performed later).

Treatments

An overview of the study design is provided below.



D = day, EoS = End of Study, EPs = Endpoints, Fup = Follow-up, GPP(GA) = generalized pustular psoriasis (physician global assessment), OL(E) = open-label (extension), R = randomization, Scr = screening, SD = single dose, Wk = week

* Patients who did not require rescue treatment with OL spesolimab were to be followed until Wk12 (V14/EoS) prior to entering OLE trial 1368-0025
* Patients who received rescue treatment with OL spesolimab between Wk2 and Wk6 were to be followed until Wk12 (V14/EoS) prior to entering the OLE trial. If at V14 they qualified to enter OLE trial, then V14 was considered as EoS for these patients. If not, then patients were to have an additional 10 weeks follow-up and to have an EoS at V16 (Wk16-28).
* Patients who received rescue treatment with OL spesolimab between Wk7 and Wk12 were to be followed for additional 6 weeks and were to have a response evaluation at V15 (Wk13-18). These patients did not have a V14. If at V15, they qualified to enter the OLE trial, then V15 was to be considered as EoS for these patients. If not, then the patients were to have an additional 10-week follow-up and had an EoS at V16 (Wk16-28).
* Patients who did not qualify to enter into the OLE trial were to be followed for 16 weeks (EoS/V16/Wk16-28) after the last dose of trial medication, which was the latest time point of trial medication given during the study (i.e. the latest of D1, D8 if OL spesolimab/rescue with OL spesolimab was given).

Figure 13. Study design

Spesolimab (investigational drug)

Substance:	Spesolimab (BI 655130)
Pharmaceutical formulation:	Solution for infusion
Source:	BI Pharma GmbH & Co. KG, Biberach, Germany
Unit strengths:	Spesolimab 450 mg/vial (concentration 60 mg/mL, fill volume 7.5 mL)

Posology:	Single dose of 900 mg on Day 1
Route of administration:	Intravenous infusion

Placebo (comparator product)

Substance:	Placebo to spesolimab (BI 655130)
Pharmaceutical formulation:	Solution for infusion
Source:	BI Pharma GmbH & Co. KG, Biberach, Germany
Unit strengths:	Vials with a fill volume of 7.5 mL
Posology:	Single dose on Day 1
Route of administration:	Intravenous infusion

In addition to the doses administered on Day 1, an additional dose of spesolimab could be administered on Day 8 and later in the study as rescue treatment (see further details below and in Table 12).

The infusion solution was to be administered intravenously over a period of 90 minutes. In the case of safety concerns (e.g. infusion reactions), it was at the discretion of the investigator or his/her designee to adapt the infusion scheme. The total duration of infusion should not exceed 180 minutes (3 hours).

Table 12. Treatments used in Study 1368-0013

Initial treatment (blinded)	**Week 1/Day 1**
900 mg SD i.v. spesolimab	2 × spesolimab 450 mg/vial (60 mg/mL, 7.5 mL)
0 mg SD i.v. placebo to spesolimab	2 × placebo to spesolimab 450 mg/vial (60 mg/mL, 7.5 mL)
Open-label treatment with spesolimab	**Week 1/Day 8**
900 mg SD i.v. spesolimab	2 × spesolimab 450 mg/vial (60 mg/mL, 7.5 mL)
Rescue treatment with spesolimab (open label)	**After Week 1/Day 8 through Week 12**
900 mg SD i.v. spesolimab	2 × spesolimab 450 mg/vial (60 mg/mL, 7.5 mL)

SD = single dose

Study procedures

Patients were considered as enrolled (screened) in the trial once they had signed the informed consent. Patients eligible to receive treatment after screening were randomized; 51 patients (increased from 27 patients with global CTP amendment 1) were to be randomized in a 2:1 ratio to receive spesolimab or placebo. All randomized patients received the first dose of study medication (900 mg i.v. spesolimab or placebo) on Day 1 of Week 1 (Randomisation). Based on the subsequent treatment response, patients were then to be followed up for 12 to 28 weeks.

During Week 1, there were mandatory visits on Days 1, 2, 3, and 8 and optional visits on Days 4 to 7, which patients did not need to attend if they had achieved complete pustular clearance (GPPGA

pustulation subscore = 0) at the previous visit. At the discretion of the investigator, patients may have been hospitalised prior to, during, or following first study drug administration. Thereafter, the decision to discharge a patient from the hospital was also at the discretion of the investigator, based on the evolution of the GPP flare and the patient's health status.

If the severity and progression of the disease worsened within the first week (Week1/D2-D7) (defined as worsening of clinical status or GPP skin and/or systemic symptoms), the investigator could treat the patient with a Standard of Care (SoC) treatment of his/her choice (escape medication). If the disease condition was stable, it was recommended to wait until the primary endpoint visit (Week1/D8) before prescribing an escape medication (SoC) since there was an option to administer OL spesolimab instead at this time. If escape medication was administered within the first week, the patient was not eligible to receive treatment with a single OL i.v. dose of 900 mg spesolimab on Day 8.

At the Week 1/Day 8 Visit, the primary endpoint and key secondary endpoint were assessed. Patients who had not received escape treatment and who had a GPPGA ≥2 at Week 1 and a GPPGA pustulation subscore of ≥2 were eligible to receive treatment with a single OL i.v. dose of 900 mg spesolimab. All randomised patients were to continue through the subsequent visits until the End of Study (EoS). If patients receiving escape medication during Week 1 (D2-D7) were not willing to attend all subsequent visits, then assessments at V9 (Wk1), V12 (Wk4), and EoS (V14 or V15 or V16 as applicable) should have been encouraged or at the very minimum an early EoS Visit.

If a patient with a previous clinical response (GPPGA 0 or 1) with spesolimab or placebo on Day 1 or escape medication or OL spesolimab on Day 8 experienced a recurrence of a GPP flare after Week1/D8 and through the follow-up period, rescue treatment with a single i.v. dose of 900 mg spesolimab was to be administered. This could occur at a scheduled or unscheduled visit anytime between after Day 8 and Week 12. After Day 8, only 1 rescue dose with spesolimab for treatment of a GPP flare recurrence was permitted; subsequent flares were to be treated with escape treatment (SoC) per physician's discretion.

Patients who achieved a clinical improvement to spesolimab and showed no flare symptoms of moderate/severe intensity at Visit 14 or Visit 15 were offered to enter into the open-label extension trial 1368-0025, if they had completed this study (EoS/V14 or V15) and met the eligibility criteria for the OLE trial.

Patients who did not roll over into the OLE trial 1368-0025 were to be followed up for 16 weeks (EoS/V16/Wk16-Wk28) after the last dose of trial medication, which was the latest time point of trial medication given during the study (i.e. the latest of V2, V9 if OL spesolimab or rescue with OL spesolimab was given).

Concomitant therapy, restrictions, and rescue treatment

Stable doses of concomitant therapies for chronic conditions, for which neither the condition nor the treatment were judged to exclude the patient from participation, were permissible.

During the trial, if the severity and progression of the disease worsened, the investigator could treat the patient with Standard of Care (SoC, escape treatment) of his/her choice. Overall, the choice of the escape treatment (i.e. SoC) was left at the discretion of the investigator. The sponsor did not provide/supply SoC treatment(s) to the sites.

In case of AEs in need of treatment, the investigator could authorise symptomatic therapy, these were to be recorded on the appropriate pages of the eCRF.

A number of medications (or classes of medications) listed in Table 13 were not allowed to have been taken before inclusion for the time periods specified, and were not permitted throughout the study participation, except in special circumstances. These drugs were permitted only when used as escape

treatment in the event of disease worsening and/or recurrence of GPP flare. Escape treatment with any of the drugs listed excluded the patient from qualification to receive treatment with open-label spesolimab on Day 8. After Day 8, these patients qualified to receive treatment with open-label spesolimab if they experienced a recurrence of GPP flare.

Table 13. Restricted medications

Medication or class of medications	Restriction duration (through EoS Visit[1])
Secukinumab (Cosentyx®)	2 months (reduced from 5.5 months with global CTP amendment 1) prior to Visit 2
Risankizumab (introduced with global CTP amendment 1)	2 months prior to Visit 2
Tildrakizumab	2 months (reduced from 5 months with global CTP amendment 1) prior to Visit 2
Rituximab, ustekinumab (Stelara®)	2 months (reduced from 4 months with global CTP amendment 1) prior to Visit 2
Natalizumab, alemtuzumab, guselkumab, ixekizumab, adalimumab (Humira®), investigational products for psoriasis (non-biologics)	2 months (reduced from 3 months with global CTP amendment 1) prior to Visit 2
Brodalumab, efalizumab, visilizumab, briakinumab. infliximab (Remicade®)	2 months prior to Visit 2
IL-36R inhibitors	Not allowed before or during trial participation
Etanercept (Enbrel®), live virus vaccinations	6 weeks prior to Visit 2
Any investigational device or product (excluded psoriasis products), other systemic immunomodulating treatments (e.g. corticosteroids[2], cyclophosphamide), tofacitinib (Xeljanz®), apremilast (Otezla®), other systemic psoriasis treatments (e.g. fumarates, any other drug known to possibly benefit psoriasis), photochemotherapy (e.g. PUVA), GMA (Granulocytes and monocytes adsorptive apheresis)	30 days prior to Visit 2
Phototherapy (e.g. UVA, UVB) topical treatment for psoriasis or any other skin condition (e.g. topical corticosteroids, topical vitamin D analogues, tar, anthralin, topical retinoids)	No treatment initiation of topical treatment 1 week prior to Visit 2 and use of these medications was not allowed Post Visit 2.
Anakinra	7 days prior to Visit 2
Methotrexate, cyclosporine, retinoids	No treatment initiation 2 weeks prior to Visit 2 No dose escalation within 2 weeks prior to Visit 2 Had to be discontinued prior to receiving the first dose of spesolimab/placebo and not allowed post Visit 2

[1] In the case of worsening of the flare (disease worsening), please refer to Section 9.4.2.1 for the details on the use of escape treatment.

[2] No restriction on inhaled corticosteroids to treat asthma or corticosteroid drops administered in the eye or ear

Objectives

The primary objective of this trial was to evaluate efficacy, safety, and tolerability of a single i.v. dose of spesolimab (BI 655130) compared with placebo in patients with Generalised Pustular Psoriasis (GPP) presenting with a flare of moderate to severe intensity.

Further objectives of this trial were to investigate the pharmacokinetics (PK) and anti-drug antibodies (ADA) of spesolimab as well as pharmacogenomics and specific biomarkers in patients with GPP presenting with a flare of moderate to severe intensity. In addition, a further objective was to explore the efficacy and safety of an open label spesolimab i.v. dose when administered on Day 8 of the trial, subsequent to the randomised treatment on Day 1.

Outcomes/endpoints

Primary efficacy endpoint

The primary efficacy endpoint was a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0, indicating no visible pustules, at Week 1.

For the estimand concept (EN) on the above-defined primary binary endpoint definition, death or any use of escape medication prior to Week 1 was considered to represent a non-response at the Week 1 time point.

Secondary Endpoints

The *key* secondary efficacy endpoint was a GPPGA total score of 0 or 1 at Week 1. The same estimand concept (EN) as for the primary endpoint was used.

Secondary efficacy endpoints in this trial at Week 4 that were *included in the hierarchical testing strategy*, subsequent to performance of the tests on the primary endpoint and key secondary endpoint, were:

A Psoriasis Area and Severity Index for Generalized Pustular Psoriasis (GPPASI) 75 at Week 4

Change from baseline in Pain Visual Analog Scale (VAS) score at Week 4

Change from baseline in Psoriasis Symptom Scale (PSS) score at Week 4

Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue score at Week 4

Other secondary efficacy endpoints in this trial were:

A GPPGA pustulation subscore of 0 at Week 4

A GPPGA total score of 0 or 1 at Week 4

Percent change from baseline in GPPASI total score at Week 1 and at Week 4

A GPPASI 50 at Week 1 and at Week 4

For the estimand concept (EN) on each of the above-defined secondary and each of the below-defined further endpoint definitions, the following was considered to represent a non-response if it occurred prior to observing the endpoint: Death, any use of escape medication, OL spesolimab use on Day 8, any use of rescue medication with spesolimab.

A large number of other and further efficacy endpoints were also assessed, however, not included in the hierarchical, statistical testing procedure.

Sample size

Based on an application of the defined testing strategy, a simulation-based power calculation was performed for sample size assessment on both the primary and key secondary endpoints. For this purpose, the correlation of the 2 endpoints was set to be 0.65, which was derived from efficacy data of the PoC study 1368.11. A 1-sided type I error of 0.025 was used. For N=51 (2:1 ratio) effects investigated ranged from 0.5 in the spesolimab group and 0.05 in the placebo group: with estimated

power for the primary and secondary endpoint of 95.7 % and 92.9 %, to 0.65 in the spesolimab group and 0.1 in the placebo group: with estimated power for the primary and secondary endpoint of 98.5 % and 97.3 %. The sample size was changed from 27 to 51 (calculation described above) in amendment 1. At the time of the change only 9 patients had been randomised and 8 patients had completed the week 1 Visit.

Randomisation and blinding (masking)

An Interactive Response Technology (IRT) was used to screen eligible patients, to perform drug assignment, to manage initial/re-supply ordering of drug supplies, and to handle emergency unblinding.

During Visit 2 and after the patient's eligibility had been confirmed (verification of all inclusion and exclusion criteria, and verification of criteria for initiation of treatment), the treatment was to be assigned via IRT. Patients were randomised to receive spesolimab 900 mg or placebo in a ratio of 2:1.

Stratification for Japan versus non-Japan was done to ensure that sufficient patients per treatment group were recruited specifically to support submission in Japan; these strata were treated as operational strata and were not included in the analyses of efficacy endpoints. Within each stratum (Japan vs. non-Japan), patients were randomised in a 2:1 ratio (spesolimab vs. placebo). The randomisation was done in blocks to achieve balanced allocation (block size of 3).

With respect to blinding, patients and investigators involved in the trial conduct were to remain blinded with regard to the randomised treatment assignments until after the database lock for the final analysis of the trial.

The first interim database lock (iDBL) on 18 Jan 2021 was performed when the trial had been clinically completed (LPO: 05 Jan 2021). Afterwards, treatment was unblinded to trial and project team members while sponsor personnel directly involved in the trial conduct with sites, investigators (except for the coordinating investigator and investigators involved in the primary manuscript preparation or who were members of the consultancy board), and patients remained blinded with regard to individual patient level data until the final database lock (dated 01 Apr 2021).

A fully external DMC performed an unblinded safety and efficacy assessment at specified intervals in order to ensure that patients were protected from potential harm. Rules for breaking the randomisation code were in place, in case of a need for emergency unblinding. For none of the patients, the medication code was broken by the investigator.

Statistical methods

Analysis methods

The treatment effect was tested on the randomised set (RS) at a 1-sided α-level of 0.025. For the binary endpoints, the Suissa-Shuster Z-pooled test was used, and 95% confidence intervals (CIs) of the risk difference were produced using the Chan and Zhang method. For the continuous endpoints, the effect was evaluated by a Wilcoxon rank test, where modified Hodges-Lehmann estimates of the median difference and 95% CIs were calculated.

In addition, for further endpoints to assess the effect of a single randomised dose of spesolimab, the time to first achievement of a response was analysed using Kaplan-Meier methods.

Analysis sets

The following analysis sets were to be defined for this trial:

Enrolled Set (ES)

This patient set includes all patients who signed informed consent. It was to be used for analyses of patient disposition.

Randomised Set (RS):

This patient set includes all randomised patients. Treatment assignment was to be as randomised. It was to be used for analyses of patient baseline demographics and disease characteristics, and is the main set for the analyses of efficacy endpoints.

Safety Analysis Set (SAF):

This patient set includes all patients who were randomised and received at least one dose of study drug on Day 1. This is the main analysis set for safety. Patients were to be analysed according to the actual treatment received.

Per-Protocol Set (PPS):

This patient set includes all patients in the randomised set who adhered to the CTP without any iPDs which are flagged for exclusion from the PPS in the table above. The PPS was to be used for sensitivity analysis on the primary and key secondary endpoints.

Multiplicity

The treatment effect on the following endpoints were to be tested in a hierarchical manner as a part of the pre-specified testing strategy:

Primary endpoint GPPGA pustulation subscore of 0 at Week 1
Key secondary endpoint on patients achieving a GPPGA score 0 or 1 at Week 1
Secondary endpoint on the proportion of patients achieving a GPPASI 75 at Week 4,
Secondary endpoint on the change from baseline in pain VAS score at week 4,
Secondary endpoint on the change from baseline in PSS score at week 4, and,
Secondary endpoint on the change from baseline in the total FACIT-Fatigue score at Week 4.

The analyses of endpoints that were not included in the hierarchical testing strategy were considered exploratory in nature.

No interim analysis was planned or conducted in this trial. However, the sample size and the multiple testing procedure were changed in amendment 1.

Intercurrent events and Missing data

For the primary estimands for binary and continuous endpoints, any observation post intercurrent events of interests (i.e., death, escape medication, rescue medication with Spesolimab or OL Spesolimab at day 8) were set to be "non-response". Further, within the extended time window of a visit, if the day of the intercurrent event is prior to the date of planned visit, then a "non-response" observation was to be assigned to that day. If the day of the intercurrent event is on or after the date of planned visit, then a "nonresponse" observation was to be assigned to that day only if there is no other observation on the same day, otherwise, no additional observation will be assigned. For continuous outcomes the primary estimand imputed these as the worst possible score. For week 1 endpoints the number of intercurrent events was low and balanced between treatment groups. For week 4 endpoints the number of open label use Spesolimab at day 8 was high, especially in the placebo group. Based on the different reasons for patients data being missing for different endpoints, various approaches were used to assess the impact of missing data on the efficacy endpoints of this trial, depending on the type of the endpoint. For binary endpoints, the primary imputation strategy of missing values was Non-Response Imputation (NRI). For continuous endpoints, missing data were primarily imputed using the last observation carried forward (LOCF) method.

Missing data imputations were performed using all available on-treatment data observed up to the respective analysis cut-off date, if applicable.

For continuous endpoints, the alternative estimand EC and the MMRM method were also implemented where any values after use of escape medication, open-label spesolimab at Day 8, or rescue medication were excluded. The MMRM method handled the missing values under a missing at random

(MAR) assumption. These results are available for Week 1, after that the proportion imputed was too large.

Censoring rules

For Kaplan-Meier methods all patients without a response before death, any use of escape medication, open-label spesolimab use on Day 8, or rescue medication with spesolimab were censored at the right limit of the extended time window of Week 12 (Day 99).

Stratification and subgroup analyses

Stratification of randomisation was performed for Japan versus non-Japan. Stratification for Japan versus non-Japan was done to ensure that sufficient patients per treatment group were recruited specifically to support individual country submission in Japan; This factor does not appear to be a stratification factor in the analyses. Race (Asian/White) was however included in the subgroup analyses and does not appear to affect efficacy.

Subgroup analyses were performed for sex, age, race, body mass index (BMI), GPPGA pustulation subscore at baseline, JDA GPP Severity score at baseline, pain VAS score at baseline, plaque psoriasis at baseline, mutation status in IL-36RN, renal impairment, hepatic impairment, and background treatment prior to randomisation.

Results

Participant flow

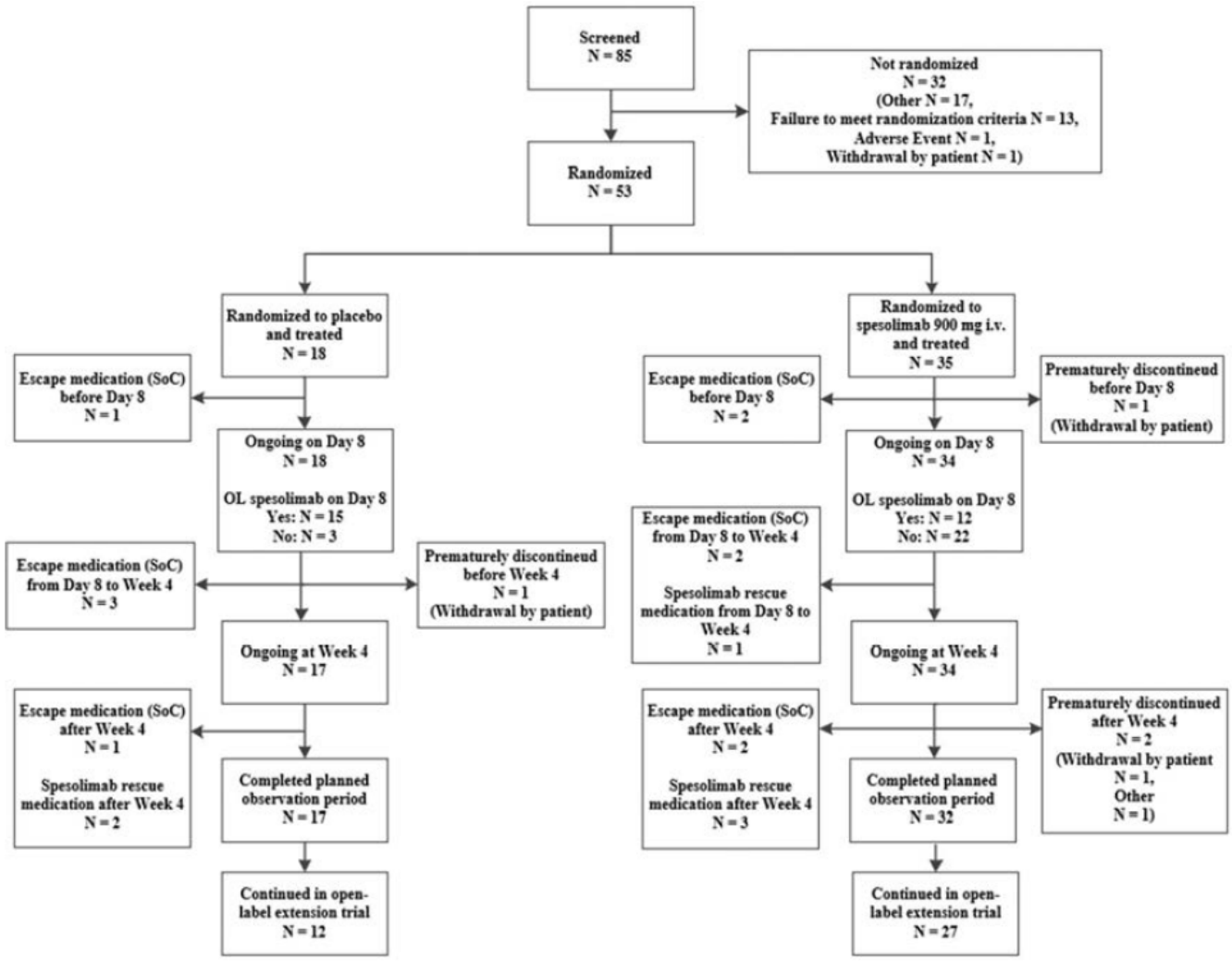


Figure. 14

For the assignment to a time period (i.e. before Day 8, from Day 8 to Week 4, after Week 4), the earliest use of escape medication of a patient was considered.

Table 14. Disposition of patients – ES, Study 1368-0013

	Placebo N (%)	Spesolimab N (%)	Overall total N (%)
Enrolled			85
Not entered/randomized			32
Entered/randomized	18	35	53
Treated	18 (100.0)	35 (100.0)	53 (100.0)
Prematurely stopped study medication[1]	0	0	0
Received OL treatment with spesolimab on Day 8	15 (83.3)	12 (34.3)	27 (50.9)
Received rescue treatment with spesolimab	2 (11.1)	4 (11.4)	6 (11.3)
Completed planned observation period	17 (94.4)	32 (91.4)	49 (92.5)
Prematurely discontinued from trial	1 (5.6)	3 (8.6)	4 (7.5)
Withdrawal by patient	1 (5.6)	2 (5.7)	3 (5.7)
Other	0	1 (2.9)	1 (1.9)
Lost to follow-up	0	0	0
Death	0	0	0
Continued in the extension study	12 (66.7)	27 (77.1)	39 (73.6)

[1] Infusion of study drug was permanently discontinued before the whole amount of prepared solution had been administered on Day 1

Recruitment

The study was conducted between 20 February 2019 and 05 January 2021. Study 1368-0013 was a global study and a total of 85 patients were enrolled (screened) across 37 centres in 12 countries (China, France, Germany, Japan, Malaysia, Singapore, South Korea, Switzerland, Taiwan, Thailand, Tunisia, USA). In all aforementioned countries, except South Korea, patients were randomised across 26 centres, with the number of patients randomised ranging from 1 to 12 in each country. Countries that contributed most randomised patients were Malaysia (12 patients), France (10 patients), and Tunisia (7 patients). A total of 16 European patients were enrolled (calculated by assessor), of which one from Switzerland who discontinued the trial.

Conduct of the study

Protocol amendments

The original CTP was dated 27 June 2018. A total of 2 global amendments and 1 local amendment to the CTP were issued. All amendments were implemented only after approval of the IRB/IEC or competent authority. The first patient was enrolled on 20 Feb 2019, and the first patient was randomised on 04 Mar 2019. The last patient completed the trial on 05 Jan 2021.

Global amendment 1 (dated 19 Jul 2019)

The following are examples of main changes introduced by the amendment:

Based on Health Authority recommendation, the sample size was increased from 27 to 51 patients (placebo: 17, spesolimab: 34) to enhance the safety database and to allow a more robust assessment of efficacy and of the benefit-risk ratio.

Based on Health Authority recommendation, the former 2 co-primary endpoints were changed into a primary and a key secondary endpoint. The statistical design - model, the null and alternative hypotheses, the statistical methods, and the analyses were updated.

The methods for the handling of missing data were updated.

For the estimand concept for the primary and secondary endpoints at Weeks 1 and 4, death was removed from the items considered as non-response.

For the AESI "hepatic injury", ALT and/or AST ≥10×ULN was added to the definition.

The AESI "Infusion reactions including anaphylactic reaction" was renamed to "systemic hypersensitivity including infusion reactions".

The definition of disease worsening and scenarios for escape treatment were clarified.

Not flaring within the 6-month screening period was added as screening failure. The requirement to assign a new patient number in the case of re-screening was added.

Global amendment 2 (dated 26 Jun 2020)

The following are examples of main changes introduced by the amendment:

To explore the efficacy and safety of open-label spesolimab i.v. treatment on Day 8 was added as additional objective.

A set of further endpoints to explore the efficacy of OL spesolimab on Day 8 were added.

2 further endpoints were added (change from baseline in GPPGA total score by visit, change from baseline in GPPGA pustulation subscore by visit).

Time points for a primary analysis at Week 12 (i.e. including data up to Week 12) and a final analysis, if applicable, were added and the blinding plans for these analyses were updated.

A sensitivity analysis for the primary endpoint using logistic regression and an estimand for the analysis of secondary continuous endpoints were added.

The methods for the handling of missing data were updated.

Local amendment 1 in Japan (dated 14 Dec 2018)

With this amendment, changes to meet Japanese regulation, Japanese medical practice, and PMDA requests were implemented.

Impact of the COVID-19 pandemic

The trial was initiated in Feb 2019 and completed in Jan 2021, which included the period during which the COVID-19 pandemic was occurring globally. For this trial, 01 Mar 2020 is considered as start of the COVID-19 pandemic. At that time, the trial was recruiting patients into the trial. Due to the COVID-19 pandemic, screening and site initiation were paused globally on 17 March 2020 and restarted at different time points, depending on when the COVID-19 situation had improved locally (China: March 2020; Taiwan, Thailand, and France (site FRA1): April 2020; remaining countries and sites: May/June 2020). All sites were re-opened for recruitment in June 2020. The trial was completed as planned despite the disruption that had occurred, and the trial objectives were not affected.

To maintain participant safety, feasibility, and data integrity the following measures were taken:

- Allocation of additional CRA resources in Malaysia to overcome monitoring constraints

- Employment of remote source data verification if allowed by local regulations and if needed

- Conduct of remote site initiation and virtual monitoring visits if allowed by local regulations and if needed

- Conduct of remote site visits by phone for 1 patient each in Germany and Tunisia. Delayed visits due to COVID-19 were noticed for 2 patients

- Information of investigators to report

--a positive corona test without clinical symptoms as non-serious AE

--a COVID-19 infection of RCTC grade ≥3 as an AESI.

For 3 patients, individual site visits had to be conducted by phone or were slightly delayed because of the COVID-19 situation at the sites. For some visits, the PRO questionnaires were completed at home

or based on the patient's information. For the visits conducted by phone, other assessments (e.g. ECG, vital signs) or blood sampling could not be performed.

To assess the potential impact of the COVID-19 pandemic on this trial, analyses of COVID-19 related study disruption, (i)PDs, and adverse events were added to the TSAP. No change in the conduct of the trial (i.e. no amendment to the CTP) was required. There was neither an impact of COVID-19 on the IMP administration nor on the distribution of laboratory kits from the central laboratories. There is no indication of a potential change in the AE reporting during the disruption.

The other changes in the amendments are not considered to have had a major influence on the conduct or analyses of the study.

Protocol deviations

Important protocol deviations (iPDs) were defined as deviations that could potentially affect the efficacy assessments or the patients' rights or safety.

Overall, 13 patients (24.5%) had iPDs. For 1 patient in the spesolimab group, manual review identified the iPD "GPP per CTP was not confirmed" that led to exclusion of this patient from the PPS.

A total of 12 patients (22.6%) used prohibited (restricted) medications, which does not include the use of escape medication. For 1 of these 12 patients, this iPD was detected after the first iDBL only. All prohibited (restricted) medications were administered after Week 1, i.e. after the assessment of the primary and key secondary endpoints, and thus did not lead to exclusion of the patients from the PPS. Overall, the iPDs did not have a significant impact on the outcome of the trial, in the applicant's view.

None of the patients missed or received incorrect randomised medication due to COVID-19, i.e. there was no impact of the COVID-19 pandemic on the IMP administration. For 3 patients, individual site visits had to be conducted by phone or were slightly delayed because of the COVID-19 situation at the sites.

Table 15. Patients with important protocol deviations and subcategories of iPDs – RS

	Placebo N (%)	Spesolimab N (%)	Overall total N (%)
Number of patients	18 (100.0)	35 (100.0)	53 (100.0)
Number of patients with at least 1 important protocol deviation	4 (22.2)	9 (25.7)	13 (24.5)
A: Entrance criteria violated	0	1 (2.9)	1 (1.9)
A1: Inclusion criteria not met	0	1 (2.9)[1]	1 (1.9)[1]
A2: Exclusion criteria violated	0	0	0
B: Informed consent	0	0	0
C: Trial medication and randomization	0	0	0
C1: Incorrect trial medication	0	0	0
C2: Non-compliance	0	0	0
C3: Randomization not followed	0	0	0
C4: Medication code broken	0	0	0
D: Concomitant medication	4 (22.2)	8 (22.9)	12 (22.6)
D1: Previous medication	0	0	0
D2: Prohibited medication use[2]	4 (22.2)	8 (22.9)	12 (22.6)
D3: Change in background medication	0	0	0
F: Study specific analysis	0	0	0
G: Other safety-related deviations	0	0	0

[1] GPP per CTP not confirmed; iPD that led to exclusion from the PPS

[2] With potential influence on efficacy data when not provided as an escape medication to stabilize a worsening disease condition - after Week 1

Compliance

Trial medication was to be administered in the study centre under the supervision of the investigator or a designee. Treatment compliance to the randomised study treatment on Day 1 was characterised by dose intensity (%), defined as the total volume of spesolimab or placebo [mL] that the patient received, divided by the total volume of spesolimab or placebo [mL] the patient should have received [100 mL] × 100. For all patients, 80 to 100% of the planned volume was infused. The mean (SD) volume infused was 99.6 (1.8) % of the planned volume.

Baseline data

In the following tables, baseline demographic data, GPP severity, the disease characteristics for the current flare and baseline conditions/medical history are shown.

Table 16. Demographic data in trial 1368-0013 – RS

		Placebo	Spesolimab	Overall total
Number of patients (N, %)		18 (100.0)	35 (100.0)	53 (100.0)
Sex (N, %)	Male	3 (16.7)	14 (40.0)	17 (32.1)
	Female	15 (83.3)	21 (60.0)	36 (67.9)
Race (N, %)	Asian	13 (72.2)	16 (45.7)	29 (54.7)
	White	5 (27.8)	19 (54.3)	24 (45.3)
Ethnicity (N, %)	Not Hispanic or Latino	18 (100.0)	35 (100.0)	53 (100.0)
Age [years]	Mean (SD)	42.6 (8.4)	43.2 (12.1)	43.0 (10.9)
	Median (min, max)	41.5 (30, 57)	41.0 (21, 69)	41.0 (21, 69)
Age categories (N, %)	<50 years	14 (77.8)	24 (68.6)	38 (71.7)
	50 to <65 years	4 (22.2)	9 (25.7)	13 (24.5)
	≥65 years	0	2 (5.7)	2 (3.8)
Weight [kg]	Mean (SD)	68.75 (26.55)	73.71 (23.95)	72.03 (24.72)
	Median (min, max)	62.90 (36.2, 152.5)	69.30 (47.1, 163.8)	67.00 (36.2, 163.8)
Body mass index [kg/m^2]	Mean (SD)	26.29 (9.62)	27.36 (7.64)	26.99 (8.29)
	Median (min, max)	24.87 (15.7, 53.4)	26.17 (17.4, 54.7)	25.34 (15.7, 54.7)
BMI categories (N, %)	<25 kg/m^2	9 (50.0)	15 (42.9)	24 (45.3)
	25 to <30 kg/m^2	6 (33.3)	10 (28.6)	16 (30.2)
	≥30 kg/m^2	3 (16.7)	10 (28.6)	13 (24.5)
Smoking status (N, %)	Never	14 (77.8)	24 (68.6)	38 (71.7)
	Former	2 (11.1)	2 (5.7)	4 (7.5)
	Current	2 (11.1)	9 (25.7)	11 (20.8)
Renal function based on eGFR/CL_{CR}[1] (N, %)	Normal	16 (88.9)	26 (74.3)	42 (79.2)
	Mild	1 (5.6)	6 (17.1)	7 (13.2)
	Moderate	0	1 (2.9)	1 (1.9)
	Severe	0	0	0
	Missing	1 (5.6)	2 (5.7)	3 (5.7)
Hepatic impairment[2] (N, %)	No	18 (100.0)	32 (91.4)	50 (94.3)
	Yes	0	0	0
	Missing	0	3 (8.6)	3 (5.7)

[1] Classification of renal function based on estimated CL_{CR} calculated according to the Cockcroft-Gault formula, with the following CL_{CR} categories: normal (≥90 mL/min), mild decrease in GFR (60-89 mL/min), moderate decrease in GFR (30-59 mL/min), and severe decrease in GFR (15-29 mL/min) [R10-2511]

[2] Defined as International Normalized Ratio ≥2.2 and total serum bilirubin >51.3 µmol/L;

The baseline GPPGA, GPPASI and other disease scores at baseline are shown in Table 17.

Table 17. GPPGA and GPPASI scores and JDA GPP severity index at baseline in trial 1368-0013 – RS

		Placebo	Spesolimab	Overall total
Number of patients (N, %)		18 (100.0)	35 (100.0)	53 (100.0)
GPPGA total score (N, %)	3	15 (83.3)	28 (80.0)	43 (81.1)
	4	3 (16.7)	7 (20.0)	10 (18.9)
GPPGA pustulation subscore (N, %)	2	5 (27.8)	6 (17.1)	11 (20.8)
	3	7 (38.9)	16 (45.7)	23 (43.4)
	4	6 (33.3)	13 (37.1)	19 (35.8)
GPPASI total score				
Mean (SD)		24.056 (15.209)	27.789 (13.436)	26.521 (14.030)
Median (min, max)		20.90 (5.2, 68.8)	27.40 (7.5, 54.2)	27.20 (5.2, 68.8)
GPPASI pustules severity				
Mean (SD)		1.972 (0.826)	2.350 (0.841)	2.222 (0.847)
Median (min, max)		2.125 (0.75, 3.75)	2.250 (1.00, 4.00)	2.250 (0.75, 4.00)
Pain VAS score				
Mean (SD)		64.6 (27.6)	76.4 (16.8)	72.4 (21.6)
Median (min, max)		70.0 (0, 100)	79.8 (20, 100)	77.9 (0, 100)
PSS total score				
Mean (SD)		10.3 (3.1)	10.4 (3.6)	10.4 (3.4)
Median (min, max)		10.5 (2, 16)	11.0 (3, 16)	11.0 (2, 16)
FACIT-Fatigue score				
Mean (SD)		19.0 (14.9)	18.1 (14.2)	18.4 (14.3)
Median (min, max)		18.0 (0, 49)	14.0 (1, 49)	15.0 (0, 49)
DLQI score				
Mean (SD)		19.1 (7.1)	19.6 (7.1)	19.4 (7.0)
Median (min, max)		19.5 (5, 30)	19.5 (2, 30)	19.5 (2, 30)
JDA GPP severity index	Mild (N, %)	5 (27.8)	9 (25.7)	14 (26.4)
	Moderate (N, %)	8 (44.4)	19 (54.3)	27 (50.9)
	Severe (N, %)	4 (22.2)	4 (11.4)	8 (15.1)
	Missing (N, %)	1 (5.6)	3 (8.6)	4 (7.5)
Mean (SD)		8.4 (2.8)	7.9 (3.0)	8.0 (2.9)
Median (min, max)		8.0 (4, 14)	8.0 (2, 14)	8.0 (2, 14)

At baseline, (i.e. initiation of randomised treatment), overall, 81.1% of patients had a GPPGA total score of 3, and 18.9% of patients had a GPPGA total score of 4 (severe). Thus, the majority had a moderate GPPGA total score with less than 20% having a severe GPPGA score. The majority of patients had a GPPGA pustulation subscore of 3 (43.4%) or 4 (35.8%). The proportion of patients with a subscore of 2 (overall: 20.8%) was slightly lower in the spesolimab group (17.1%) than in the placebo group (27.8%). Thus, for pustules, the study population were mainly at the moderate to severe end.

The mean and median GPPASI total scores were somewhat higher in the spesolimab group and pustules severity was slightly higher in the spesolimab group compared with the placebo group. The mean and median Pain VAS, PSS, FACIT-Fatigue, and DLQI scores were largely comparable across treatment groups, with slightly higher Pain VAS rating for spesolimab.

The disease characteristics based on the flare that led to randomisation (i.e. the current flare) are shown in Table 18.

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Table 18. Disease characteristics (current flare) in trial 1368-0013 – RS

		Placebo N (%)	Spesolimab N (%)	Overall total N (%)
Number of patients		18 (100.0)	35 (100.0)	53 (100.0)
Trigger event for flare		*N = 18*	*N = 34*	*N = 52*
Treatment withdrawal		9 (50.0)	11 (31.4)	20 (37.7)
Steroid withdrawal		1 (5.6)	1 (2.9)	2 (3.8)
Stress		1 (5.6)	4 (11.4)	5 (9.4)
Infection		1 (5.6)	1 (2.9)	2 (3.8)
Pregnancy		0	0	0
Other		6 (33.3)	17 (48.6)	23 (43.4)
Symptom and status available		*N = 18*	*N = 34*	*N = 52*
Pustules	Worsened	10 (55.6)	14 (40.0)	24 (45.3)
	Newly appeared	7 (38.9)	17 (48.6)	24 (45.3)
	No change	1 (5.6)	3 (8.6)	4 (7.5)
Erythema	Worsened	11 (61.1)	19 (54.3)	30 (56.6)
	Newly appeared	4 (22.2)	11 (31.4)	15 (28.3)
	No change	3 (16.7)	4 (11.4)	7 (13.2)
Scaling	Worsened	11 (61.1)	16 (45.7)	27 (50.9)
	Newly appeared	3 (16.7)	12 (34.3)	15 (28.3)
	No change	4 (22.2)	6 (17.1)	10 (18.9)
Systemic components	Worsened	8 (44.4)	12 (34.3)	20 (37.7)
	Newly appeared	4 (22.2)	12 (34.3)	16 (30.2)
	No change	6 (33.3)	10 (28.6)	16 (30.2)
CRP [mg/dL]		*N = 16*	*N = 31*	*N = 47*
	Mean (SD)	5.181 (6.194)	6.362 (6.508)	5.960 (6.360)
	Median (min, max)	2.555 (0.17, 21.9)	3.840 (0.15, 20.8)	3.240 (0.15, 21.9)
		N = 18	*N = 34*	*N = 52*
	<0.3 mg/dL	1 (5.6)	3 (8.6)	4 (7.5)
	0.3 to <7 mg/dL	11 (61.1)	17 (48.6)	28 (52.8)
	≥7 mg/dL	4 (22.2)	11 (31.4)	15 (28.3)
	Unknown	2 (11.1)	3 (8.6)	5 (9.4)
Leukocytes [1/µL]		*N = 16*	*N = 32*	*N = 48*
	Mean (SD)	11 345.625 (4154.533)	11 221.250 (3591.049)	11 262.708 (3744.021)
	Median (min, max)	10 950 (5540, 23 000)	10 605 (5970, 19 750)	10 680 (5540, 23 000)
		N = 18	*N = 34*	*N = 52*
	<10 000/µL	6 (33.3)	14 (40.0)	20 (37.7)
	10 000 to <15 000/µL	8 (44.4)	14 (40.0)	22 (41.5)
	≥15 000/µL	2 (11.1)	4 (11.4)	6 (11.3)
	Unknown	2 (11.1)	2 (5.7)	4 (7.5)
Albumin [g/dL]		*N = 16*	*N = 31*	*N = 47*
	Mean (SD)	4.125 (0.373)	4.077 (0.534)	4.094 (0.482)
	Median (min, max)	4.00 (3.5, 4.7)	4.10 (2.8, 5.1)	4.10 (2.8, 5.1)
		N = 18	*N = 34*	*N = 52*
	≥3.8 g/dL	14 (77.8)	23 (65.7)	37 (69.8)
	3 to <3.8 g/dL	2 (11.1)	7 (20.0)	9 (17.0)
	<3.0 g/dL	0	1 (2.9)	1 (1.9)
	Unknown	2 (11.1)	3 (8.6)	5 (9.4)
Temperature [°C]		*N = 18*	*N = 34*	*N = 52*
	<37.5°C	15 (83.3)	23 (65.7)	38 (71.7)
	37.5 to 38.5°C	3 (16.7)	7 (20.0)	10 (18.9)
	>38.5°C	0	4 (11.4)	4 (7.5)

The medical history for the GPP condition is shown in Table 19.

Table 19. Medical history for GPP in trial 1368-0013 – RS

		Placebo	Spesolimab	Overall total
Number of patients, N (%)		18 (100.0)	35 (100.0)	53 (100.0)
Time since first diagnosis				
≤1 year, N (%)		6 (33.3)	10 (28.6)	16 (30.2)
>1 to ≤5 years, N (%)		3 (16.7)	4 (11.4)	7 (13.2)
>5 to ≤10 years, N (%)		3 (16.7)	4 (11.4)	7 (13.2)
>10 years, N (%)		6 (33.3)	17 (48.6)	23 (43.4)
Diagnosis method to confirm GPP				
Histopathological confirmation, N (%)		2 (11.1)	5 (14.3)	7 (13.2)
Skin biopsy, N (%)		8 (44.4)	12 (34.3)	20 (37.7)
Other, N (%)		8 (44.4)	18 (51.4)	26 (49.1)
Average number of flares per year				
Mean (SD)		3.8 (3.4)	3.3 (3.6)	3.4 (3.5)
Median (min, max)		3.0 (1, 12)	2.0 (0, 14)	2.0 (0, 14)
Time with involved skin/with involved skin with pustules over the last year, N (%)				
	<1 week	2 (11.1)	2 (5.7)	4 (7.5)
	1-2 weeks	4 (22.2)	7 (20.0)	11 (20.8)
	3-4 weeks	4 (22.2)	4 (11.4)	8 (15.1)
	5-8 weeks	1 (5.6)	4 (11.4)	5 (9.4)
	9-12 weeks	0	2 (5.7)	2 (3.8)
	>12 weeks	5 (27.8)	8 (22.9)	13 (24.5)
	Missing	2 (11.1)	8 (22.9)	10 (18.9)
Time with completely clear skin over the last year, N (%)				
	<1 week	5 (27.8)	8 (22.9)	13 (24.5)
	1-2 weeks	1 (5.6)	0	1 (1.9)
	3-4 weeks	1 (5.6)	4 (11.4)	5 (9.4)
	5-8 weeks	0	2 (5.7)	2 (3.8)
	9-12 weeks	2 (11.1)	0	2 (3.8)
	>12 weeks	6 (33.3)	10 (28.6)	16 (30.2)
	Missing	3 (16.7)	11 (31.4)	14 (26.4)

Table 20. Most frequent baseline conditions/medical history (reported for at least 3 patients [5.7%] overall on dictionary-derived term level) in trial 1368-0013 – RS

Primary System Organ Class Dictionary-Derived Term	Placebo N (%)	Spesolimab N (%)	Overall total N (%)
Number of patients	18 (100.0)	35 (100.0)	53 (100.0)
Patients with at least 1 baseline condition/medical history	16 (88.9)	32 (91.4)	48 (90.6)
Skin and subcutaneous tissue disorders	6 (33.3)	14 (40.0)	20 (37.7)
Psoriasis[1]	5 (27.8)	12 (34.3)	17 (32.1)
Infections and infestations	7 (38.9)	10 (28.6)	17 (32.1)
Hepatitis B	1 (5.6)	2 (5.7)	3 (5.7)
Metabolism and nutrition disorders	5 (27.8)	11 (31.4)	16 (30.2)
Diabetes mellitus	1 (5.6)	4 (11.4)	5 (9.4)
Hyperlipidaemia	4 (22.2)	1 (2.9)	5 (9.4)
Hyperuricaemia	1 (5.6)	2 (5.7)	3 (5.7)
Musculoskeletal and connective tissue disorders	8 (44.4)	7 (20.0)	15 (28.3)
Psoriatic arthropathy	3 (16.7)	2 (5.7)	5 (9.4)
Arthralgia	1 (5.6)	2 (5.7)	3 (5.7)
Osteoporosis	3 (16.7)	0	3 (5.7)
Vascular disorders	7 (38.9)	6 (17.1)	13 (24.5)
Hypertension	7 (38.9)	5 (14.3)	12 (22.6)
Hepatobiliary disorders	3 (16.7)	6 (17.1)	9 (17.0)
Hepatic steatosis	2 (11.1)	4 (11.4)	6 (11.3)
Social circumstances	4 (22.2)	5 (14.3)	9 (17.0)
Menopause	4 (22.2)	4 (11.4)	8 (15.1)
Blood and lymphatic system disorders	4 (22.2)	3 (8.6)	7 (13.2)
Anaemia	1 (5.6)	2 (5.7)	3 (5.7)
Respiratory, thoracic and mediastinal disorders	4 (22.2)	2 (5.7)	6 (11.3)
Pulmonary mass	2 (11.1)	1 (2.9)	3 (5.7)
Immune system disorders	1 (5.6)	4 (11.4)	5 (9.4)
Drug hypersensitivity	0	3 (8.6)	3 (5.7)
Seasonal allergy	1 (5.6)	2 (5.7)	3 (5.7)

[1] Most patients were reported with psoriasis vulgaris and plaque psoriasis by the investigator

An overview of genotyping results is shown in Table 21.

Table 21. Genetic mutations based on genotyping – RS

	Placebo N (%)	Spesolimab N (%)	Overall total N (%)
Number of patients	18 (100.0)	35 (100.0)	53 (100.0)
Presence of potential pathogenic variation on any of IL-36RN, CARD14, AP1S3			
No	12 (66.7)	20 (57.1)	32 (60.4)
Yes	2 (11.1)	9 (25.7)	11 (20.8)
DNA sequencing not done	4 (22.2)	6 (17.1)	10 (18.9)
Presence of potential pathogenic IL-36RN variation			
No	12 (66.7)	24 (68.6)	36 (67.9)
Yes	2 (11.1)	5 (14.3)	7 (13.2)
DNA sequencing not done	4 (22.2)	6 (17.1)	10 (18.9)
Presence of potential pathogenic CARD14 variation			
No	14 (77.8)	24 (68.6)	38 (71.7)
Yes	0	5 (14.3)	5 (9.4)
DNA sequencing not done	4 (22.2)	6 (17.1)	10 (18.9)
Presence of potential pathogenic AP1S3 variation			
No	14 (77.8)	28 (80.0)	42 (79.2)
Yes	0	1 (2.9)	1 (1.9)
DNA sequencing not done	4 (22.2)	6 (17.1)	10 (18.9)

Includes all genotyping data available by the final DBL (01 Apr 2021). Complete genotyping data, including data that became available afterwards, are reported outside of this CTR.

For the primary endpoint, the risk difference between spesolimab and placebo was **42.9%** (95% CI 8.1%, 66.0%) for patients without a potential pathogenic IL-36RN variation (nominal 1-sided p-value = 0.0060) and **70.8%** (95% CI 12.6%, 96.0%) for patients with a potential pathogenic IL-36RN variation (nominal 1-sided p-value = 0.0075). For the key secondary endpoint, the risk difference between spesolimab and placebo was **19.5%** (95% CI -15.1%, 45.4%) for patients without a potential pathogenic IL-36RN variation (nominal 1-sided p-value = 0.1580) and **58.3%** (95%CI 1.8%, 90.2%) for patients with a potential pathogenic IL-36RN variation (nominal 1-sided p-value = 0.0215).

Retrospective data were also collected in trial 1368-0013 on the natural course of flares and treatment responses.

Table 22. Historical information – Characteristics of most severe, typical, and longest flare based on retrospective data collected from patients in trial 1368-0013

		Most severe flare Overall total N (%)	Typical flare Overall total N (%)	Longest flare Overall total N (%)
Number of patients for whom information was requested		53 (100.0)	53 (100.0)	53 (100.0)
Reported intensity of previous flare	*Patients with available data*	*N = 31 (100.0)*	*N = 37 (100.0)*	*N = 14 (100.0)*
	Mild	0	5 (13.5)	1 (7.1)
	Moderate	8 (25.8)	13 (35.1)	3 (21.4)
	Severe	23 (74.2)	14 (37.8)	9 (64.3)
	Unknown	0	5 (13.5)	1 (7.1)
Hospitalization	*Patients with available data*	*N = 31 (100.0)*	*N = 37 (100.0)*	*N = 14 (100.0)*
	No	8 (25.8)	20 (54.1)	5 (35.7)
	Unknown	0	4 (10.8)	0
Yes, duration of hospitalization	<1 week	1 (3.2)	4 (10.8)	0
	1-2 weeks	14 (45.2)	5 (13.5)	4 (28.6)
	3-4 weeks	8 (25.8)	4 (10.8)	5 (35.7)
	5-8 weeks	0	0	0
	9-12 weeks	0	0	0
	>12 weeks	0	0	0
Duration of flare	*Patients with available data*	*N = 31 (100.0)*	*N = 35 (100.0)*	*N = 14 (100.0)*
	<1 week	1 (3.2)	4 (11.4)	0
	1-2 weeks	8 (25.8)	11 (31.4)	2 (14.3)
	3-4 weeks	10 (32.3)	12 (34.3)	4 (28.6)
	5-8 weeks	8 (25.8)	4 (11.4)	4 (28.6)
	9-12 weeks	0	0	0
	>12 weeks	4 (12.9)	4 (11.4)	4 (28.6)
Pustules	*Patients with available data*	*N = 31 (100.0)*	*N = 37 (100.0)*	*N = 14 (100.0)*
	Worsened	18 (58.1)	9 (24.3)	8 (57.1)
	Newly appeared	12 (38.7)	22 (59.5)	3 (21.4)
	No change	1 (3.2)	2 (5.4)	1 (7.1)
	Unknown	0	4 (10.8)	2 (14.3)
Pustules completely clear	*Patients with available data*	*N = 28 (100.0)*	*N = 30 (100.0)*	*N = 11 (100.0)*
	<1 week	3 (10.7)	5 (16.7)	0
	1-2 weeks	3 (10.7)	12 (40.0)	1 (9.1)
	3-4 weeks	13 (46.4)	7 (23.3)	3 (27.3)
	5-8 weeks	4 (14.3)	3 (10.0)	4 (36.4)
	9-12 weeks	1 (3.6)	0	2 (18.2)
	>12 weeks	4 (14.3)	3 (10.0)	1 (9.1)
Erythema completely clear	*Patients with available data*	*N = 27 (100.0)*	*N = 28 (100.0)*	*N = 11 (100.0)*
	<1 week	1 (3.7)	1 (3.6)	0
	1-2 weeks	3 (11.1)	12 (42.9)	1 (9.1)
	3-4 weeks	6 (22.2)	6 (21.4)	0
	5-8 weeks	8 (29.6)	1 (3.6)	4 (36.4)
	9-12 weeks	5 (18.5)	4 (14.3)	3 (27.3)
	>12 weeks	4 (14.8)	4 (14.3)	3 (27.3)
Scaling completely clear	*Patients with available data*	*N = 27 (100.0)*	*N = 29 (100.0)*	*N = 11 (100.0)*
	<1 week	2 (7.4)	2 (6.9)	1 (9.1)
	1-2 weeks	3 (11.1)	11 (37.9)	0
	3-4 weeks	9 (33.3)	9 (31.0)	1 (9.1)
	5-8 weeks	6 (22.2)	1 (3.4)	4 (36.4)
	9-12 weeks	2 (7.4)	1 (3.4)	3 (27.3)
	>12 weeks	5 (18.5)	5 (17.2)	2 (18.2)

Table 23. Historical information – Treatment of and systemic symptoms associated with previous flares (most severe, typical, and longest flare) provided by the investigators for patients entered in trial 1368-0013

		Most severe flare Overall total N (%)	Typical flare Overall total N (%)	Longest flare Overall total N (%)
Number of patients for whom information was requested		53 (100.0)	53 (100.0)	53 (100.0)
Treatment	*Patients with available data*	*N = 31 (100.0)*	*N = 37 (100.0)*	*N= 14 (100.0)*
	No	1 (3.2)	1 (2.7)	0
	Yes	28 (90.3)	31 (83.8)	13 (92.9)
	Unknown	2 (6.5)	5 (13.5)	1 (7.1)
	Patients with treatment	*N = 28 (100.0)*	*N = 31 (100.0)*	N = 13 (100.0)
	Topical[1]	6 (21.4)	5 (16.1)	4 (30.8)
	Systemic[1]	22 (78.6)	26 (83.9)	9 (69.2)
CRP	*Patients with available data*	*N = 31 (100.0)*	*N = 27 (100.0)*	*N = 14 (100.0)*
	<0.3 mg/dL	0	1 (3.7)	0
	≥0.3 and <7.0 mg/dL	4 (12.9)	2 (7.4)	4 (28.6)
	≥7.0 mg/dL	14 (45.2)	7 (25.9)	4 (28.6)
	Unknown	13 (41.9)	17 (63.0)	6 (42.9)
Neutrophilia	*Patients with available data*	*N = 31 (100.0)*	*N = 27 (100.0)*	*N = 14 (100.0)*
	No	7 (22.6)	4 (14.8)	5 (35.7)
	Yes	13 (41.9)	7 (25.9)	4 (28.6)
	Unknown	11 (35.5)	16 (59.3)	5 (35.7)
Temperature	*Patients with available data*	*N = 30 (100.0)*	*N = 27 (100.0)*	*N = 13 (100.0)*
	37.5 to 38.5°C	11 (36.7)	11 (40.7)	4 (30.8)
	>38.5°C	12 (40.0)	5 (18.5)	6 (46.2)
	Unknown	7 (23.3)	11 (40.7)	3 (23.1)
Fatigue	*Patients with available data*	*N = 31 (100.0)*	*N = 27 (100.0)*	*N = 14 (100.0)*
	No	3 (9.7)	2 (7.4)	2 (14.3)
	Yes	23 (74.2)	20 (74.1)	11 (78.6)
	Unknown	5 (16.1)	5 (18.5)	1 (7.1)
Pain	*Patients with available data*	*N = 31 (100.0)*	*N = 27 (100.0)*	*N = 14 (100.0)*
	No	4 (12.9)	3 (11.1)	1 (7.1)
	Yes	23 (74.2)	17 (63.0)	13 (92.9)
	Unknown	4 (12.9)	7 (25.9)	0

[1] Information on the drug class/the international non-proprietary names was not collected

Information on the previous GPP history and treatments was presented, but not all patients provided information for this analysis. It can however be concluded that the severity, duration and presentation of GPP flares can be quite variable. For a typical flare, about 35% graded it as moderate and 38% as severe, the duration was 1-2 weeks in about 30% of respondents and 3-4 weeks in about 34% (few had a flare duration <1 week or ≥5 weeks). Pustule clearance took place in 1-2 weeks in 40% for a typical flare but it took 3-4 weeks or longer for most of the severest flares.

Systemic flare treatment had been used in the majority of the respondents previous flares (around 80%). The most frequently used GPP background medications were clobetasol propionate, acitretin, ciclosporin, betamethasone valerate, and methotrexate.

Biologic therapy for GPP was used by 24.5% of patients. Historical non-drug therapy for GPP was used by 18.9% of patients overall, with phototherapy (17.0%) being the most frequently used non-drug therapy.

Overall, both demographic and disease characteristics were fairly balanced between the treatment groups, with slight imbalances for some factors.

Numbers analysed

The numbers of patients included in different analysis sets are shown in Table 24. The main analysis set for the efficacy analyses was the Randomised Set (RS); sensitivity analyses for efficacy were performed on the PPS. Safety analyses were performed on the SAF. One patient randomised to spesolimab was excluded from the PPS due to violation of inclusion criteria ("GPP per CTP was not confirmed").

Table 24. Patient analysis sets – RS

	Placebo N (%)	Spesolimab N (%)	Overall total N (%)
Randomized Set (RS)	18 (100.0)	35 (100.0)	53 (100.0)
Safety analysis set (SAF)	18 (100.0)	35 (100.0)	53 (100.0)
Per-protocol set (PPS)	18 (100.0)	34 (97.1)	52 (98.1)
Not in PPS	0	1 (2.9)	1 (1.9)

Outcomes and estimation

General comments about estimands and analyses

Different estimand concepts have been used in the efficacy analyses. Under the primary composite estimand EN applied for binary and continuous endpoints, any use of escape medication (SoC), open-label spesolimab at Day 8, or rescue medication with spesolimab before observing the endpoint represent "intercurrent events". When using the primary composite estimand strategy EN, all efficacy measurements observed after such intercurrent events were considered as non-response in the analysis of the endpoint outcome.

The number of patients who used escape medication (SoC), open-label spesolimab on Day 8, and spesolimab rescue medication during the trial is shown in Table 25. As shown in this table, 14 patients (40.0%) in the spesolimab group and 16 patients (88.9%) in the placebo group had received escape medication before Week 1 or open-label spesolimab on Day 8 for worsening, insufficient response, or non-response. These patients were thus treated as non-responders at any time points after Week 1. Overall, 15 patients (42.9%) in the spesolimab group and 16 patients (88.9%) in the placebo group had received escape medication, open-label spesolimab on Day 8, or rescue treatment with spesolimab by Week 4.

In addition, in the spesolimab group, 1 patient had prematurely discontinued. This means that only 2 of 18 patients in the placebo group and 19 of 35 patients in the spesolimab group contributed observed data for the analysis using the estimand EN. Hence, the interpretation of the prespecified efficacy analyses at Week 4 is limited. Several predefined sensitivity analyses were performed using different estimand strategies and imputation methods.

Additionally, over time data were analysed using the estimand EN-ID8 and the OC-IR approach. The composite estimand (EN-ID8) takes any values after the open-label spesolimab at Day 8 also into account, whereas any values after use of escape medication (SoC) or use of rescue medication with spesolimab are considered as non-response.

The treatment policy estimand (OC-IR) approach analyses observed cases including also values after intercurrent events, representing the intent-to-treat principle. Hence, the OC-IR approach evaluates all observed cases irrespective of any use of escape medication, open-label spesolimab on Day 8, or spesolimab rescue medication after Day 8.

The primary imputation strategy of missing values for binary endpoints was Non-Response Imputation (NRI). This strategy assumes that withdrawal (or missing data due to any other reason) are related to treatment failure. For continuous endpoints, the last observation carried forward (LOCF) method was applied to impute the missing or censored values. This imputation strategy assumes that the last observed value before censoring or missing would sustain until the end of the trial.

Table 25. Use of escape medication (standard of care at investigator's discretion), open-label spesolimab on Day 8, or spesolimab rescue medication (after Day 8) in trial 1368-0013

		Placebo (N = 18)	Spesolimab (N = 35)
Before Week 1, N (%)	Escape medication[1]	1 (5.6)	2 (5.7)
Before Week 4, N (%)	Open-label spesolimab on Day 8	15 (83.3)[2]	12 (34.3)
	Escape medication[1]	4 (22.2)	4 (11.4)
	Spesolimab rescue medication	0	1 (2.9)
	Total (any of the above)	16 (88.9)	15 (42.9)
	None of the above	2 (11.1)	20 (57.1)[2]
Within treatment phase (including before Week 4), N (%)	Escape medication[1]	5 (27.8)	6 (17.1)
	Spesolimab rescue medication	2 (11.1)[3]	4 (11.4)[4]

[1] Standard of care at the investigator's discretion
[2] 1 patient in the spesolimab group discontinued the trial before Week 1 and 1 patient in the placebo group discontinued the trial before Week 4
[3] 1 patient not treated and 1 patient treated with OL spesolimab on Day 8
[4] 2 patients not treated and 2 patients treated with OL spesolimab on Day 8 (i.e. 2 patients received 3 doses of spesolimab)

Primary endpoint

GPPGA pustulation subscore of 0 at Week 1

The study met its primary endpoint; the proportion of patients who achieved a GPPGA pustulation subscore of 0 at Week 1 was significantly higher for patients who received a single 900 mg i.v. dose of spesolimab (19 of 35 patients, 54.3%) compared with patients who received placebo (1 of 18 patients, 5.6%), leading to a risk difference of 48.7% (1-sided p = 0.0004).

Table 26. Proportion of patients with a GPPGA pustulation subscore of 0 at Week 1 in trial 1368-0013 – RS (EN-NRI)

				Comparison to placebo		
Treatment	n/N		(95% CI)[1]	Risk difference	(95% CI)[2]	p-value[3]
Placebo	1/18	0.056	(0.010, 0.258)			
Spesolimab	19/35	0.543	(0.382, 0.695)	0.487	(0.215, 0.672)	0.0004

EN = any values after use of escape medication (SoC), open-label spesolimab at Day 8, or rescue medication with spesolimab represent non-response; NRI = non-response imputation for any missing data
[1] Calculated using the method of Wilson
[2] Calculated using the method of Chan and Zhang
[3] Calculated using Suissa-Shuster Z-pooled test (1-sided p-value)

Key secondary endpoint

GPPGA total score of 0 or 1 at Week 1

The key secondary endpoint was also met; the proportion of patients who achieved a GPPGA total score of 0 or 1 was significantly higher in the spesolimab group (15 of 35 patients, 42.9%) compared with the placebo group (2 of 18 patients, 11.1%), leading to a risk difference of 31.7% (1-sided p-value=0.0118).

Table 27. Proportion of patients with a GPPGA total score of 0 or 1 at Week 1 in trial 1368-0013 – RS (EN-NRI)

				Comparison to placebo		
Treatment	n/N		(95% CI)[1]	Risk difference	(95% CI)[2]	p-value[3]
Placebo	2/18	0.111	(0.031, 0.328)			
Spesolimab	15/35	0.429	(0.280, 0.591)	0.317	(0.022, 0.527)	0.0118

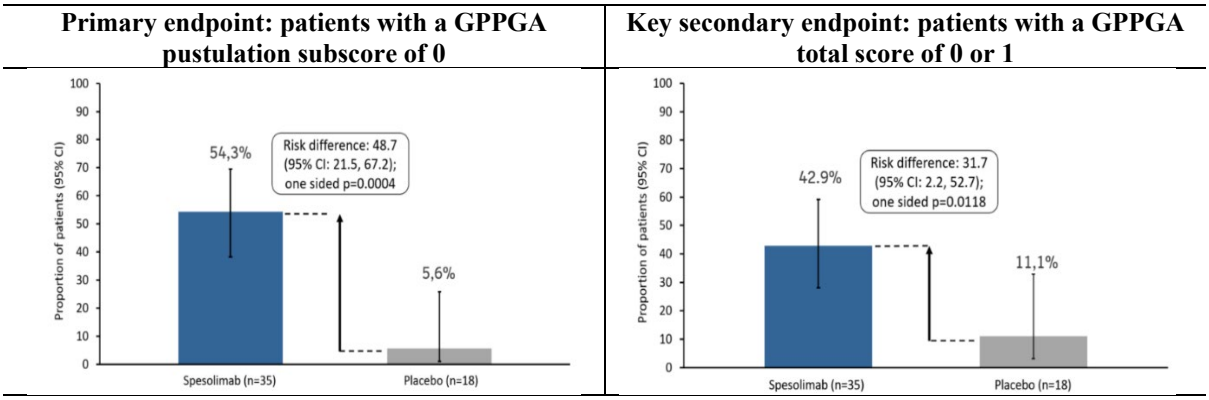
EN = any values after use of escape medication (SoC), open-label spesolimab at Day 8, or rescue medication with spesolimab represent non-response; NRI = non-response imputation for any missing data

[1] Calculated using the method of Wilson

[2] Calculated using the method of Chan and Zhang

[3] Calculated using Suissa-Shuster Z-pooled test (1-sided p-value)

The results of the primary and key secondary endpoints are also shown in the figure below.



The denominator for percentages and proportions is the number of patients in the analysis set. 95% CIs are calculated using the method of Wilson. EN = any values post escape medication represent non-response; NRI = non-response imputation for any missing data

Figure 15. Results of the primary and key secondary endpoints in trial 1368- 0013 – RS (EN-NRI)

Further results for the GPPGA endpoints (pustulation subscore of 0 and total score of 0 or 1), for instance the response rates over time, are shown below.

Secondary endpoints included in the hierarchical testing strategy

The results for the four multiplicity-controlled endpoints are summarised in Table 28 and also described further below.

Table 28. Results of the secondary endpoints included in the hierarchical testing strategy in trial 1368-0013 – RS

				Comparison to placebo		
	n/N		(95% CI)[1]	Risk difference	(95% CI)[2]	p-value[3]
Secondary endpoint: Proportion of patients with a GPPASI 75 at Week 4 – EN-NRI						
Placebo	2/18	0.111	(0.031, 0.328)			
Spesolimab	16/35	0.457	(0.305, 0.618)	0.346	(0.058, 0.554)	0.0081
	Failures		Median (Q1, Q3)	Estimate of difference (median)[4]	(95% CI)[4]	p-value[5]
	n/N	(%)				
Secondary endpoint: change from baseline in Pain VAS score at Week 4 – EN-LOCF						
Placebo	16/18	(88.9)	NR			
Spesolimab	15/35	(42.9)	-22.45 (-70.41, NR)	NC	NC	0.0012
Secondary endpoint: change from baseline in PSS score at Week 4 – EN-LOCF						
Placebo	16/18	(88.9)	NR			
Spesolimab	15/35	(42.9)	-2.00 (-9.00, NR)	NC	NC	0.0044
Secondary endpoint: change from baseline in FACIT-Fatigue score at Week 4 – EN-LOCF						
Placebo	16/18	(88.9)	NR			
Spesolimab	15/35	(42.9)	3.00 (NR, 30.00)	NC	NC	0.0012

NC = not calculable, NR = non-response

Mean (SD) baseline values: Pain VAS: spesolimab: 76.4 (16.8), placebo: 64.6 (27.6); PSS score: spesolimab: 10.4 (3.6), placebo: 10.3 (3.1); FACIT-Fatigue score: spesolimab: 18.1 (14.2), placebo: 19.0 (14.9)

[1] Calculated using the method of Wilson

[2] Calculated using the method of Chan and Zhang

[3] Calculated using Suissa-Shuster Z-pooled test (1-sided p-value)

[4] By modified Hodges-Lehmann method

[5] Based on Wilcoxon rank testing (1-sided p-value)

As shown in Table 28, the four secondary endpoints included in the hierarchical testing procedure (GPPASI 75, Pain VAS, PSS and FACIT-Fatigue score) showed significant results in favour of spesolimab.

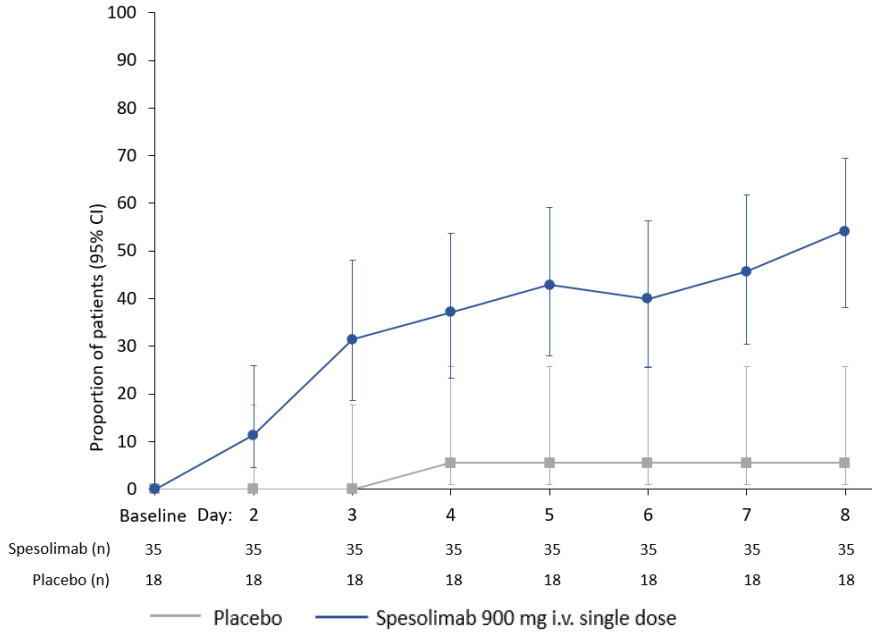
By Week 4, only 2 patients (11.1%) remained on placebo; in the spesolimab arm, 20 patients (57.1%) had not used any open-label spesolimab on Day 8, spesolimab as rescue medication, or escape medication by Week 4. These remaining patients (2 of 18 patients in the placebo group and 19 of 35 patients in the spesolimab group [1 patient had prematurely discontinued before Week 1]) contributed observed data for the Week-4 analyses.

Efficacy results over time (primary and key secondary endpoints)

GPPGA pustulation score 0, results up to Week 1

The proportion of patients with a GPPGA pustulation subscore of 0 over time up to Week 1 is presented in Figure 16. 14 patients (40.0%) in the spesolimab group and 16 patients (88.9%) in the placebo group had received escape medication before Week 1 or open-label spesolimab on Day 8. These patients were thus treated as non-responders at any time points after Week 1.

In the spesolimab group, all patients who reached pustular clearance after a single dose achieved this by Day 8 (19 patients, 54.3%) (EN-NRI). In the placebo group, 1 patient (5.6%) had spontaneous pustular clearance within the first week; afterwards, by Week 2 another patient had spontaneous pustular clearance, the remaining patients in the placebo group took rescue or escape medication.

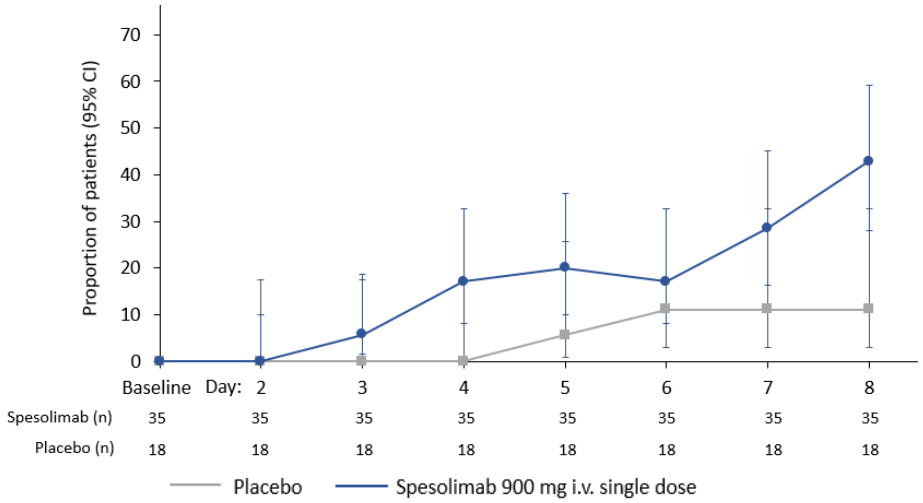


EN = any values after escape medication (SoC) represent non-response

Figure 16. Proportion (95% CI) of patients with a GPPGA pustulation subscore of 0 over time up to Week 1 in trial 1368-0013 – RS (EN-NRI)

GPPGA total score 0 or 1, results up to Week 1

The proportion of patients with a GPPGA total score of 0 or 1 over time up to Week 1 is presented in Figure 17. 14 patients (40.0%) in the spesolimab group and 16 patients (88.9%) in the placebo group had received escape medication before Week 1 or open-label spesolimab on Day 8. These patients were thus treated as non-responders at any time points after Week 1. Under the EN-NRI estimand, the curves for spesolimab and placebo separated early from Day 3 onwards. In the spesolimab group, most of the patients who had a response after a single dose, achieved this by Day 8 (15 patients, 42.9%) (EN-NRI). In the placebo group, 2 patients (11.1%) had spontaneous skin clearance, the remaining patients in the placebo group took rescue or escape medication.



EN = any values after escape medication (SoC) represent non-response

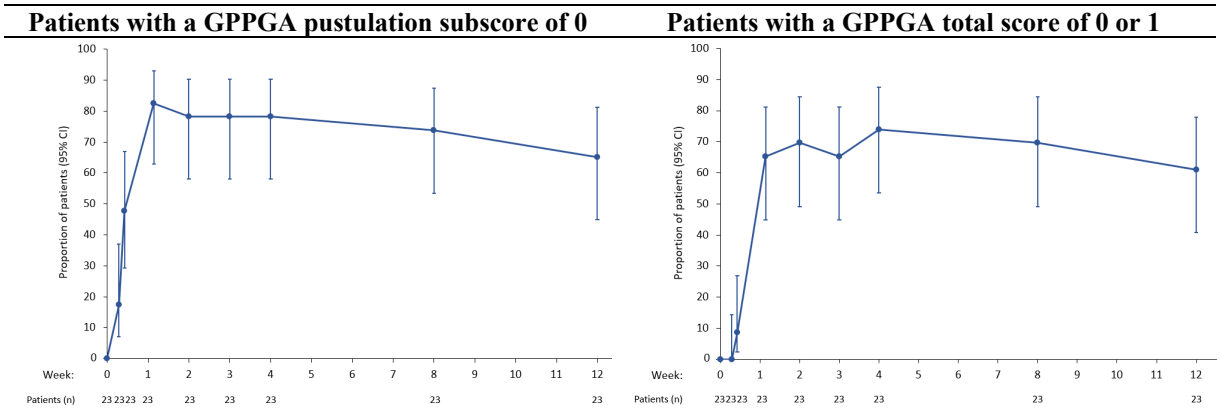
Figure 17. Proportion (95% CI) of patients with a GPPGA total score of 0 or 1 over time up to Week 1 in trial 1368-0013 – RS (EN-NRI)

GPPGA-related results over time up to Week 12

Pustular clearance and skin clearance (total GPPGA clear/almost clear) results after treatment with spesolimab are shown for the following groups up to the end of the trial:
- Patients randomised to spesolimab who received a single dose on Day 1 only (N=23)
- Patients randomised to spesolimab who received up to 2 doses (Day 1 ± Day 8, N=35)
- All randomised patients, following the intent-to-treat principle
  - --Patients randomised to spesolimab who received up to 3 doses (Day 1 ± Day 8 ± rescue medication) with or without escape medication (N=35)
  - --Patients randomised to placebo who received up to 2 doses of spesolimab (Day 8 ± rescue medication) with or without escape medication (N=18)

For the number of patients who received spesolimab on Day 1, on Day 8, or as rescue medication after Day 8 or who received escape medication (Standard of Care), see Table 25.

Of the 23 patients randomised to spesolimab who received a single 900 mg i.v. dose on Day 1 only, 15 patients (65.2%) had pustular clearance and 14 patients (60.9%) had a GPPGA total score of 0 or 1 by Week 12 (Figure 18).



EN-ID8 = any values after escape medication or spesolimab rescue medication represent non-response

Figure 18. Proportion (95% CI) of patients with a GPPGA pustulation subscore 0 (left) and GPPGA total score of 0 or 1 (right) over time – patients randomised to spesolimab who received a single dose on Day 1 only (N=23) in trial 1368 0013, RS (EN-ID8-NRI)

Of the 35 patients randomised to spesolimab who received up to 2 i.v. doses of spesolimab (Day 1 ± Day 8), 21 patients (60.0%) had pustular clearance and a GPPGA total score of 0 or 1 by Week 12 (Figure 19).

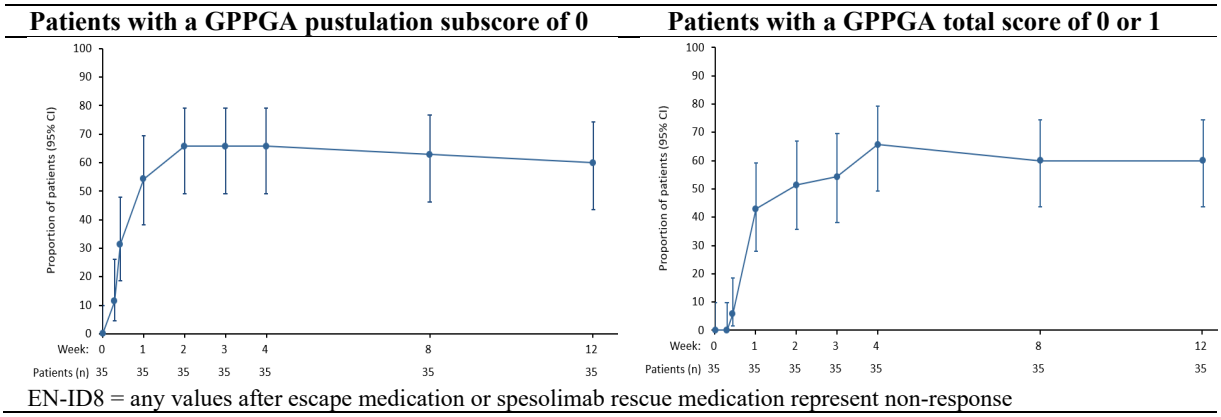
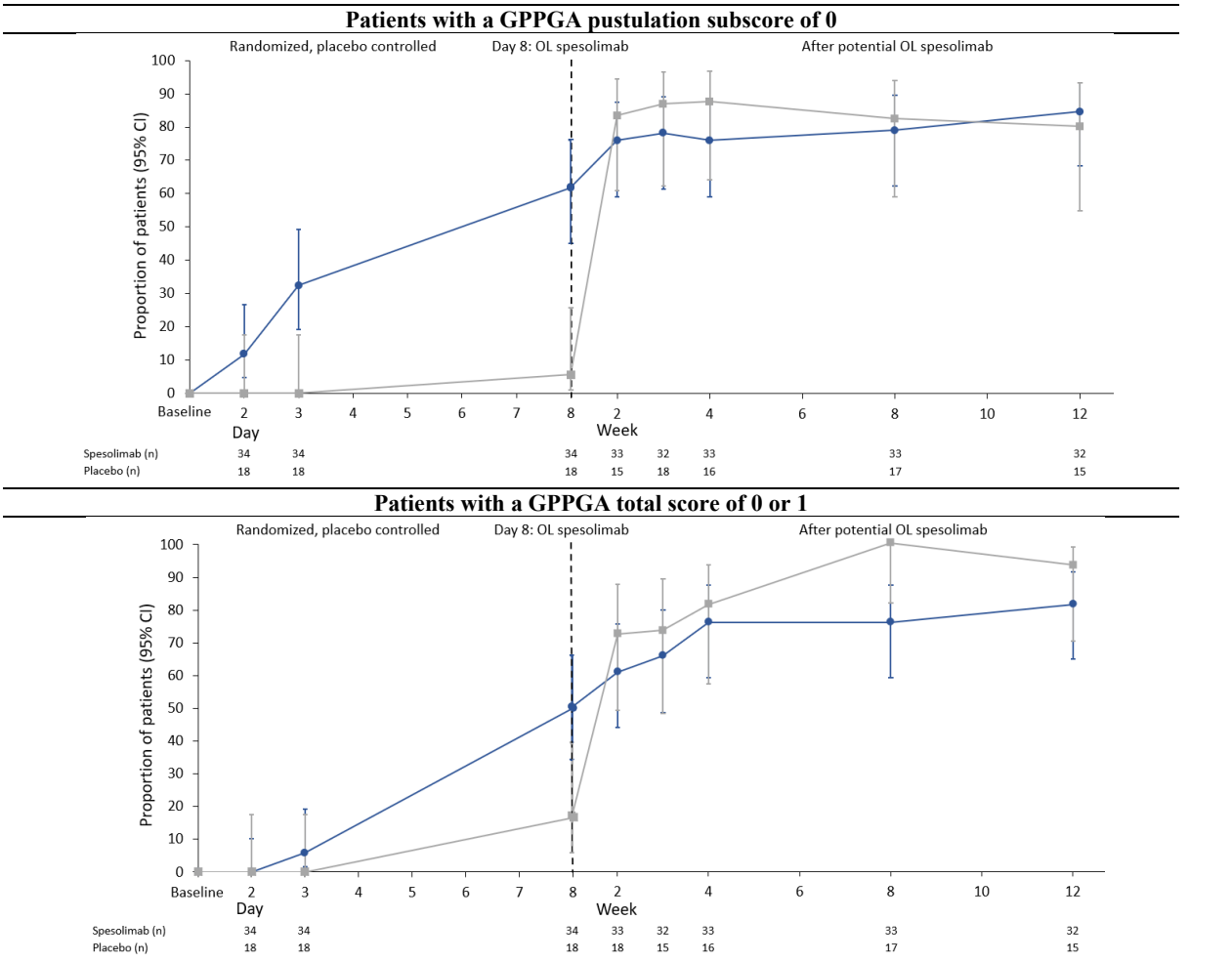


Figure 19. Proportion (95% CI) of patients with a GPPGA pustulation subscore 0 (left) and GPPGA total score of 0 or 1 (right) over time – patients randomised to spesolimab who received up to 2 doses (Day 1 ± Day 8, N=35) in trial 1368 0013, RS (EN-ID8-NRI)

For all randomised patients (intent-to-treat principle), the results are shown below. In the placebo arm, the steep increase of the curves of both endpoints post-Week 1 shows rapid response to treatment with open-label spesolimab on Day 8, which was used by 15 patients (83.3%) randomised to placebo.

From Week 2 onwards, the 2 curves converge and remain in the same range up to Week 12.

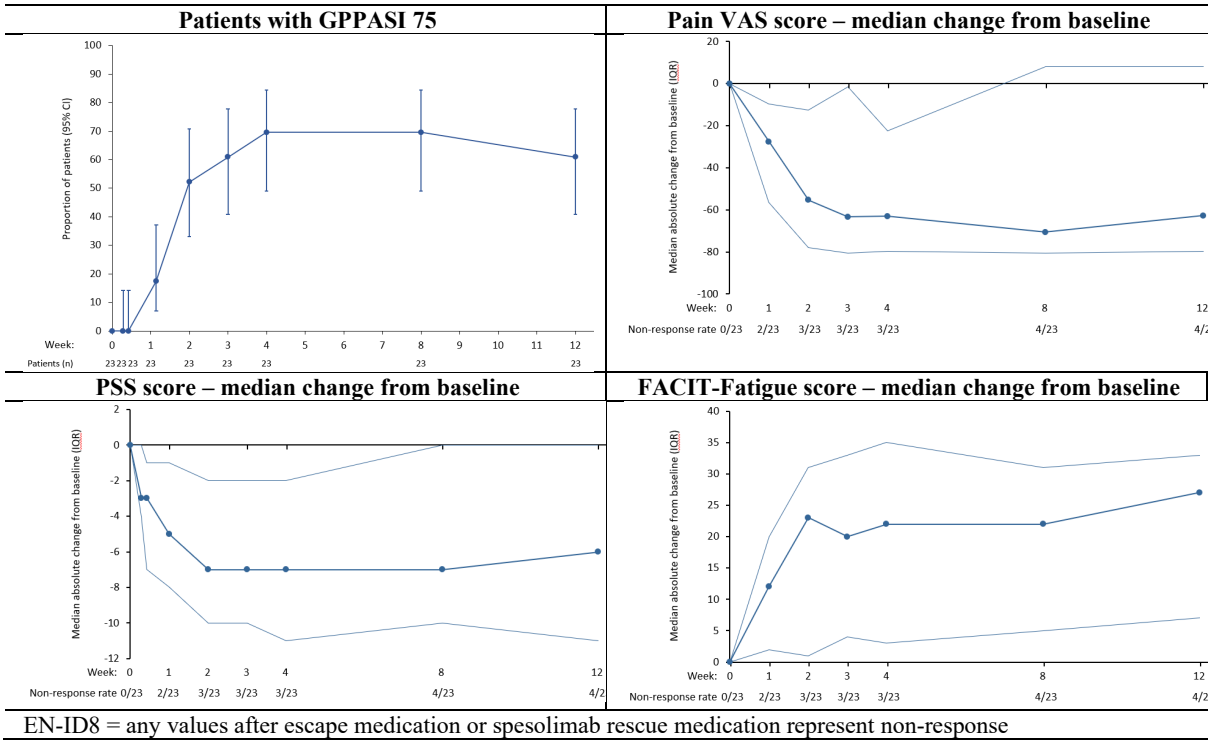


Please note that the scale of the x-axis is not linear but the first week (i.e. the part until the vertical dotted line) is stretched
OC-IR = all values regardless of escape medication, OL spesolimab on Day 8, or spesolimab rescue medication
The numbers of patients displayed are those with observed data at the corresponding time point; these are used as the denominator for the proportions.

Figure 20. Proportion (95% CI) of patients with a GPPGA pustulation subscore of 0 (top) and a GPPGA total score of 0 or 1 (bottom) over time – all randomised patients in trial 1368 0013, RS (OC-IR)

Efficacy results over time (other secondary endpoints)

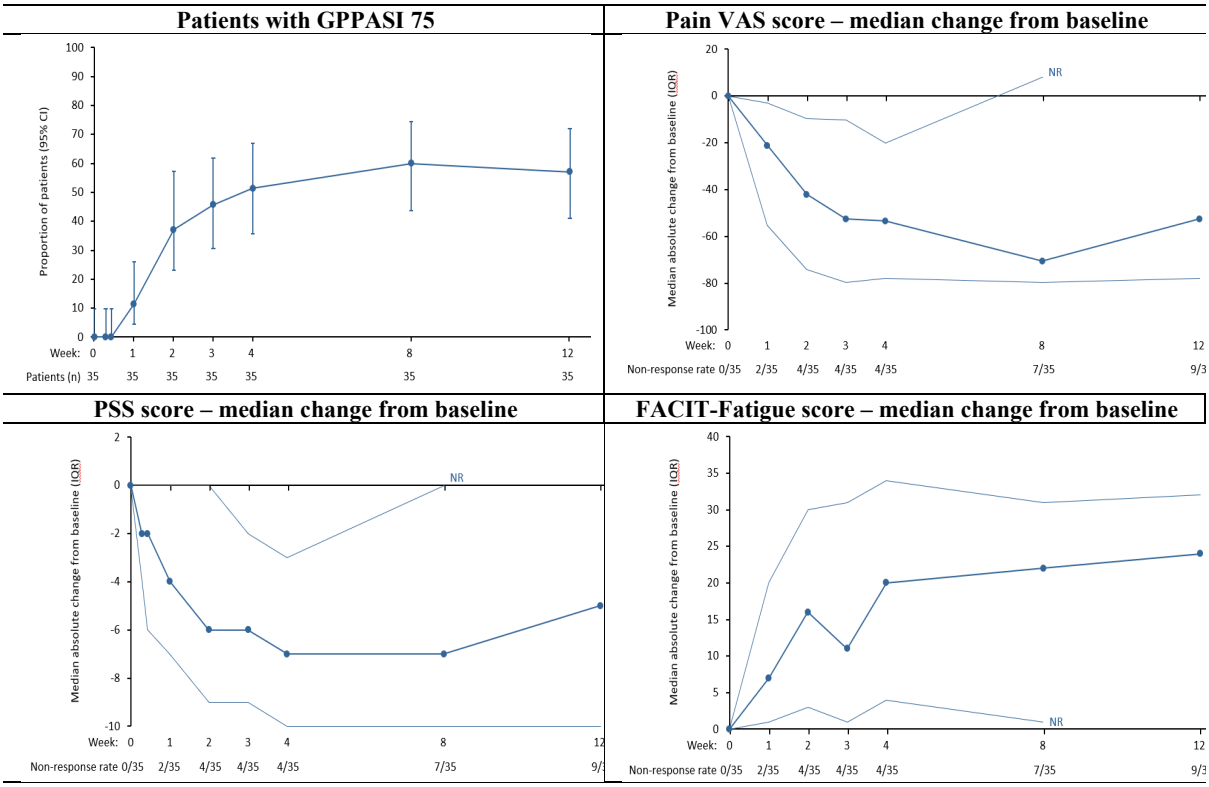
Results for GPPASI 75, Pain VAS score, PSS and FACIT-Fatigue score over time up to Week 12 are shown in figures below, based on the same categories as for the endpoints described above.



EN-ID8 = any values after escape medication or spesolimab rescue medication represent non-response

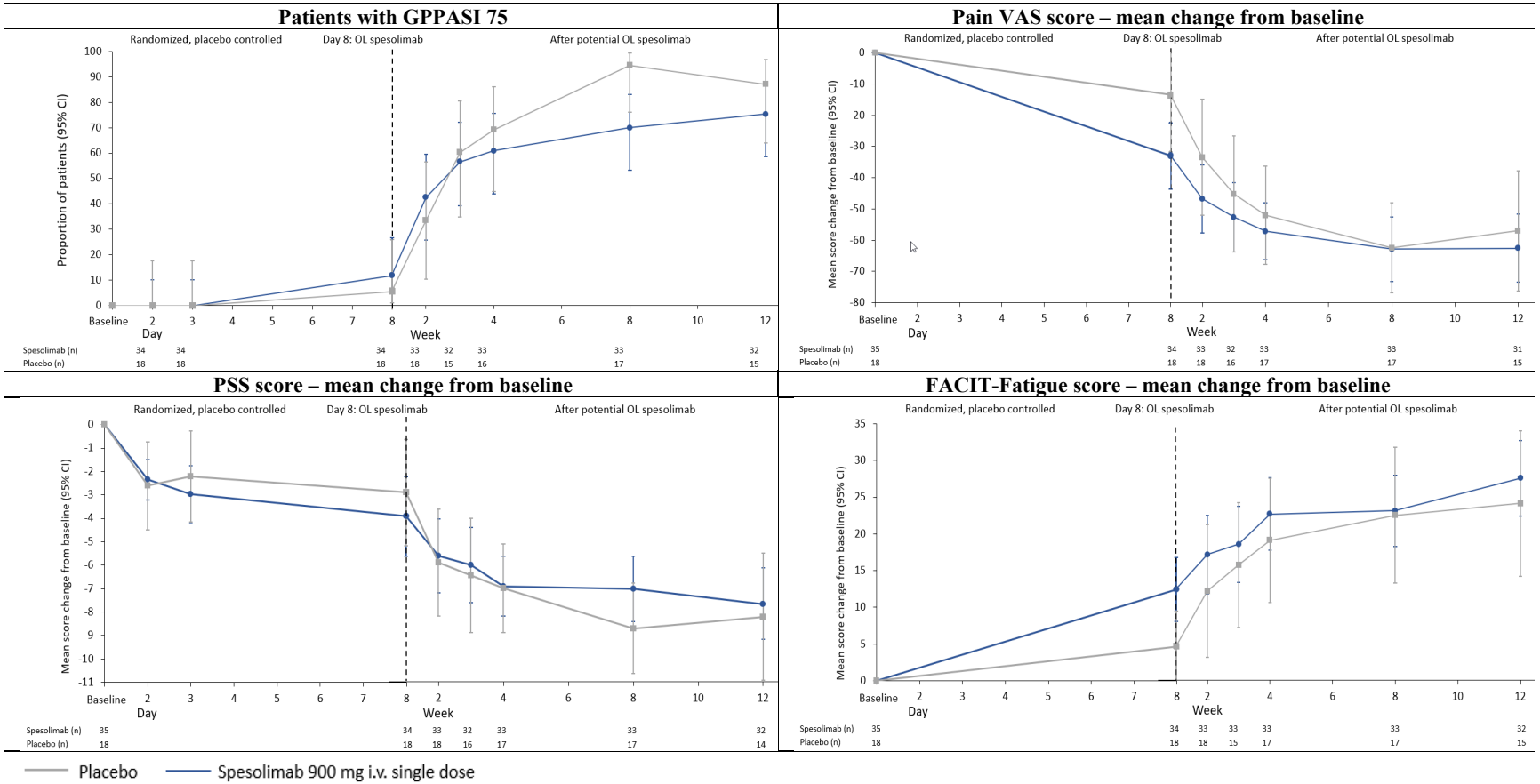
Figure 21 Proportion (95% CI) of patients with a GPPASI 75 (top, left) and median (Q1, Q3) absolute change from baseline in Pain VAS (top, right), PSS (bottom, left), and FACIT-

Fatigue (bottom, right) scores over time – patients randomizeised to spesolimab who received a single dose on Day 1 only (N=23) in trial 1368 0013, RS (EN-ID8-NRI/LOCF)



EN-ID8 = any values after escape medication or spesolimab rescue medication represent non-response

Figure 22. Proportion (95% CI) of patients with a GPPASI 75 (top, left) and median (Q1, Q3) absolute change from baseline in Pain VAS (top, right), PSS (bottom, left), and FACIT-Fatigue (bottom, right) scores over time – patients randomised to spesolimab who received up to 2 doses (Day 1 ± Day 8, N=35) in trial 1368 0013, RS (EN-ID8-NRI/LOCF)



Please note that the scale of the x-axis is not linear but the first week (i.e. the part until the vertical dotted line) is stretched.
OC-IR = all values regardless of escape medication, OL spesolimab on Day 8, or spesolimab rescue medication
The numbers of patients displayed are those with observed data at the corresponding time point. For the GPPASI 75, this number is used as the denominator for the proportion.

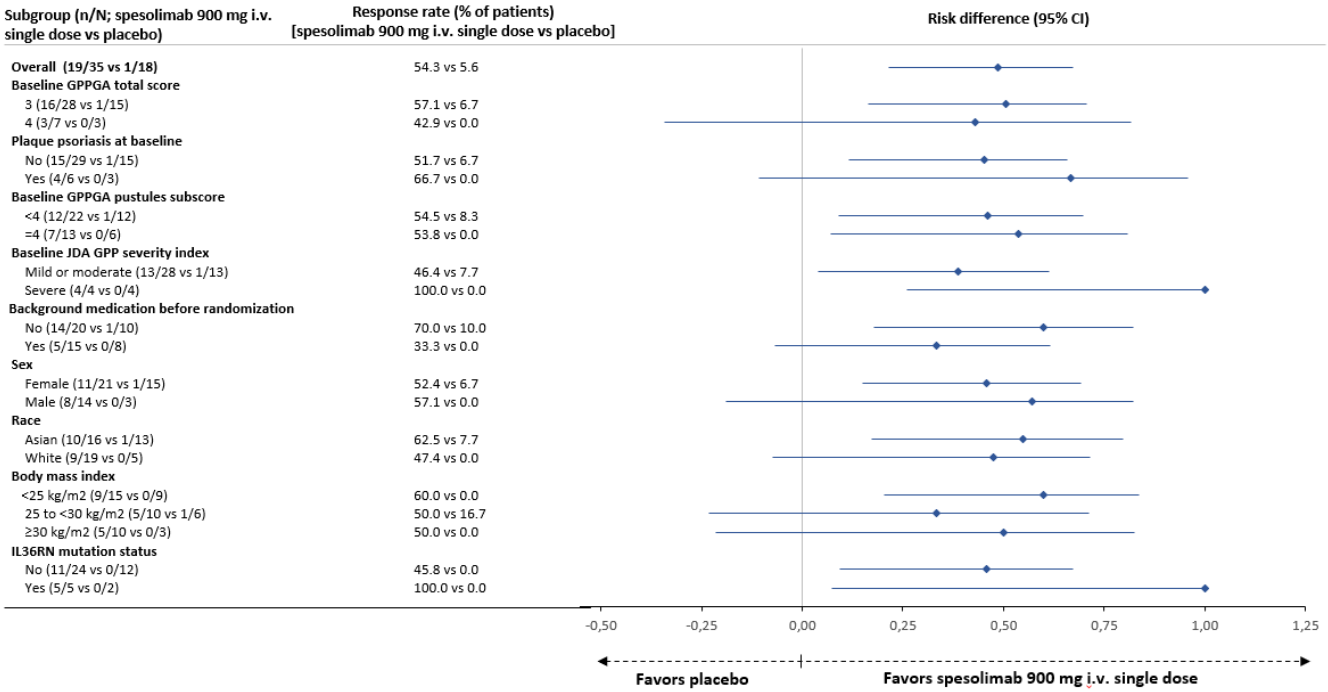
Figure 23. Proportion of patients with a GPPASI 75 and mean (95% CI) changes from baseline in Pain VAS, PSS, and FACIT-Fatigue scores over time – all randomised patients in trial 1368-0013, RS (OC-IR)

Ancillary analyses

Subgroup analyses

Subgroup analyses for the primary and key secondary endpoints were performed for predefined subgroups; sex, race, BMI category, GPPGA pustulation subscore at baseline, GPPGA total score at baseline, plaque psoriasis at baseline, background treatment prior to randomisation, JDA GPP severity score at baseline, and mutation status in IL-36RN.

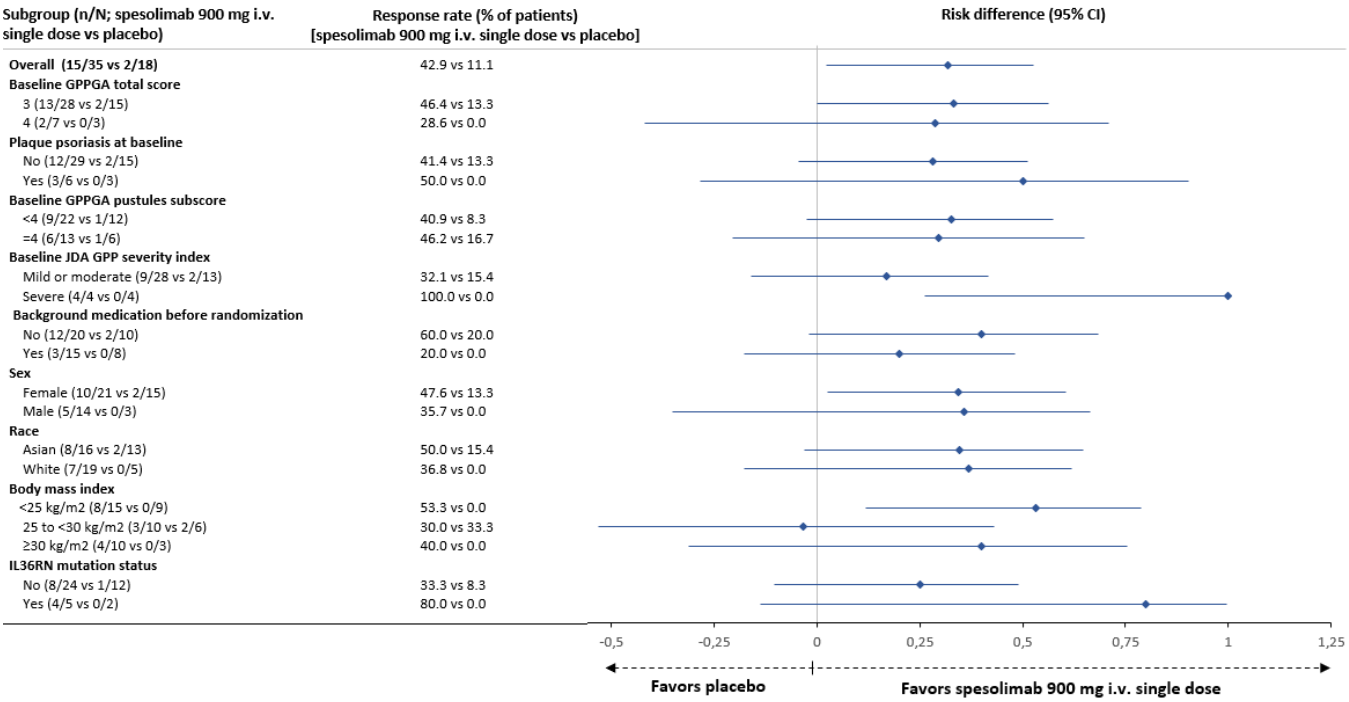
GPPGA pustulation subscore of 0 at Week 1



The denominator for proportions is the number of patients in the corresponding subgroup. 95% CIs are calculated using the method of Chan and Zhang. EN = any values after use of escape medication (SoC), open-label spesolimab at Day 8, or rescue medication with spesolimab represent non-response; NRI = non-response imputation for any missing data

Figure 24. Subgroup analyses for the primary endpoint proportion of patients with a GPPGA pustulation subscore of 0 at Week 1 in trial 1368-0013 – RS (EN-NRI)

GPPGA total score of 0 or 1 at Week 1



The denominator for proportions is the number of patients in the corresponding subgroup. 95% CIs are calculated using the method of Chan and Zhang. EN = any values after use of escape medication (SoC), open-label spesolimab at Day 8, or rescue medication with spesolimab represent non-response; NRI = non-response imputation for any missing data

Figure 25. Subgroup analyses for the key secondary endpoint proportion of patients with a GPPGA total score of 0 or 1 at Week 1 in trial 1368-0013 – RS (EN-NRI)

The results were largely consistent across the analysed subgroups for both a GPPGA pustulation subscore of 0 and GPPGA total score of 0 or 1 at Week 1. However, some groups were very small, resulting in wide CIs.

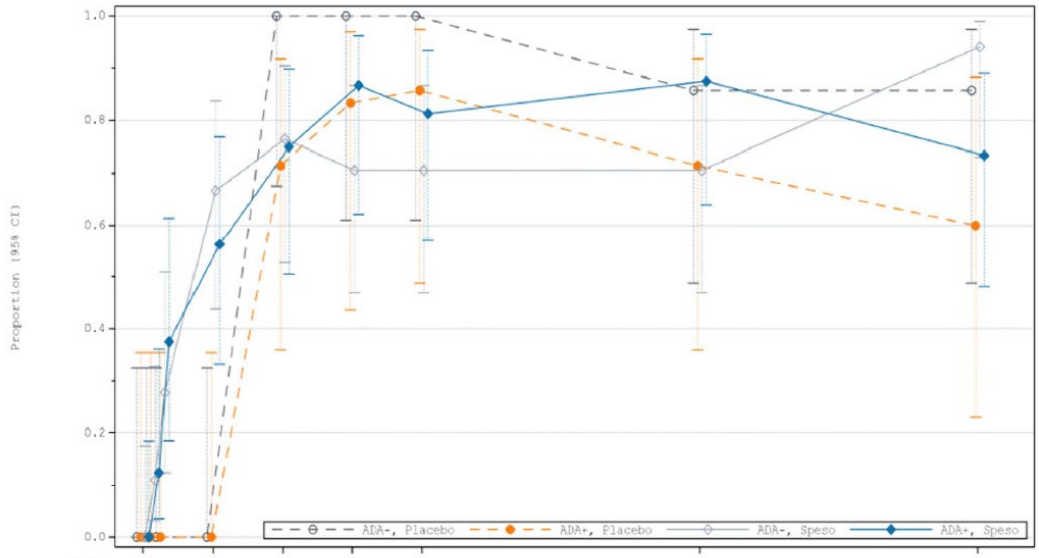
With respect to the mutation status in IL-36 RN, using updated genotyping data (including data that became available after the final database lock of trial 1368-0013), the subgroup analyses also showed consistent results.

Also for baseline GPP flare severity, sex, race (Asian vs. White) and BMI there seems to a clear effect of spesolimab even if the response rates sometimes differed to some extent.

Analyses of anti-drug antibodies or neutralizing antibodies and efficacy

ADA data are described also in the PK section above.

Data on the relationship of treatment-emergent ADA/NAb to efficacy in Study 1368-0013 have been presented. The proportion of patients with a GPPGA pustulation subscore of 0 over time for ADA-negative and ADA-positive patients and for NAb-negative and NAb-positive patients, respectively, are shown in the figures below.

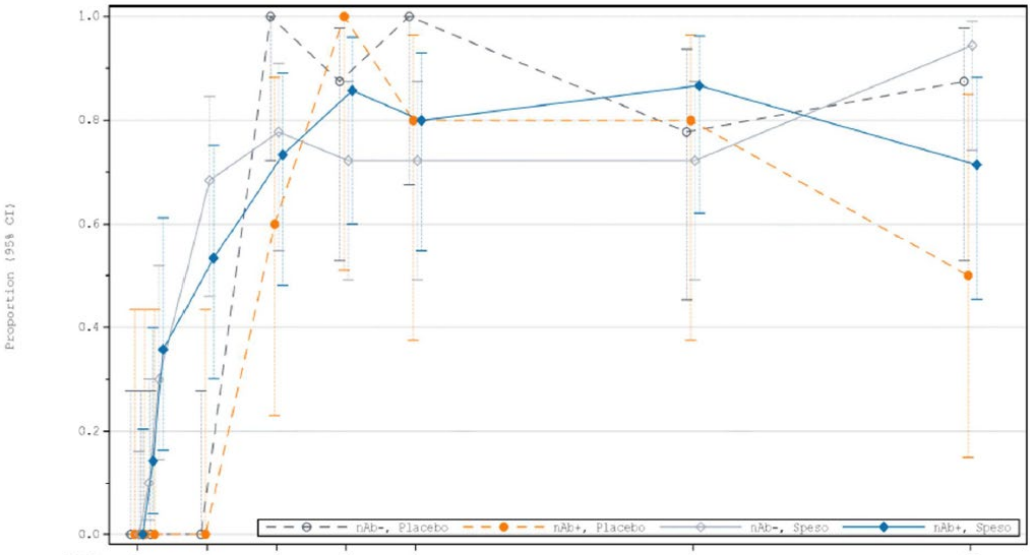


Week:	0	1	2	3	4	8	12
Number of patients:							
ADA-, Placebo	8	8	8	6	6	7	7
ADA+, Placebo	7	7	7	6	7	7	5
ADA-, Speso	18	18	17	17	17	17	17
ADA+, Speso	17	16	16	15	16	16	15

The denominator for percentages and proportions is the number of patients with observed data at the corresponding timepoint.
95% confidence intervals (CI) are calculated using the method of Wilson.
All values regardless of escape medication, or OL Spesolimab use at D8, or rescue medication with Spesolimab are included.

Patients in the placebo group who did not receive open-label spesolimab were excluded

Figure 26. Trial 1368-0013: Proportion of patients with GPPGA pustulation subscore 0 over time, by randomised arm and ADA status – RS(OC-IR)



Week:	0	1	2	3	4	8	12
Number of patients:							
nAb-, Placebo	10	10	10	8	8	9	8
nAb+, Placebo	5	5	5	4	5	5	4
nAb-, Speso	20	19	18	18	18	18	18
nAb+, Speso	15	15	15	14	15	15	14

The denominator for percentages and proportions is the number of patients with observed data at the corresponding timepoint.
95% confidence intervals (CI) are calculated using the method of Wilson.
All values regardless of escape medication, or OL Spesolimab use at D8, or rescue medication with Spesolimab are included.

Patients in the placebo group who did not receive open-label spesolimab were excluded

Figure 27. Trial 1368-0013: Proportion of patients with GPPGA pustulation subscore 0 over time, by randomised arm and NAb status – RS (OC-IR)

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial Effisayil™ 1

Table 29. Summary of Efficacy for trial Effisayil™ 1

	Title: Effisayil™ 1: Multi-center, double-blind, randomized, placebo-controlled, Phase II study to evaluate efficacy, safety and tolerability of a single intravenous dose of BI 655130 in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity		
Study identifier	1368-0013		
Design	Multi-centre, double-blind, randomised, placebo-controlled Phase II trial		
	Duration of screening phase: Duration of double-blind phase: Duration of treatment phase: Duration of extension phase:		Up to 6 months 12 weeks Single dose, with option of an open-label spesolimab dose on Day 8; afterwards, option of a dose of spesolimab as rescue medication if roll-over to open-label extension trial: 12 weeks, and up to 18 weeks, if spesolimab rescue medication given between Weeks 7 and 12 if no roll-over: 16 weeks after last i.v. dose (residual effect period), i.e. up to 28 weeks Not applicable
Hypothesis	Superiority of spesolimab over placebo		
Treatments groups	Spesolimab 900 mg i.v.		Spesolimab 900 mg i.v. Single dose, n (randomised) = 35
	Placebo		Matching placebo, n (randomised) = 18
Endpoints and definitions	Primary endpoint	GPPGA pustulation subscore of 0	Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0, indicating no visible pustules, at Week 1
	Key secondary endpoints	GPPGA total score of 0 or 1	GPPGA total score of 0 or 1 at Week 1
	Secondary endpoints included in the hierarchical testing strategy	GPPASI 75	Psoriasis Area and Severity Index for Generalized Pustular Psoriasis (GPPASI) 75 at Week 4
		Pain VAS	Change from baseline in Pain Visual Analog Scale (VAS) score at Week 4
		PSS	Change from baseline in Psoriasis Symptom Scale (PSS) score at Week 4
		FACIT-Fatigue	Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue score at Week 4
Database lock	21 Apr 2021		
	Results and Analysis		
	Analysis description	Primary Analysis The primary, key secondary, and 4 selected secondary endpoints were analyzed in a hierarchical testing strategy	

Analysis population and time point description	Randomised Set Week 1 for primary and key secondary endpoint; Week 4 for selected secondary endpoints included in hierarchical testing strategy		
Descriptive statistics and estimate variability	Treatment group	Spesolimab	Placebo
	Number of patients	35	18
	GPPGA pustulation subscore of 0		
	Number of responders	19	1
	n/N	0.543	0.056
	95% CI	(0.382, 0.695)	(0.010, 0.258)
	GPPGA total score of 0 or 1		
	Number of responders	15	2
	n/N	0.429	0.111
	95% CI	(0.280, 0.591)	(0.031, 0.328)
	GPPASI 75		
	Number of responders	16	2
	n/N	0.457	0.111
	95% CI	(0.305, 0.618)	(0.031, 0.328)
	Pain VAS		16
	Number of non-responders	15	Non-response (NR)
	Median	-22.45	
	(Q1, Q3)	(-70.41, NR)	NR
	PSS		
	Number of non-responders	15	16
	Median	-2.00	NR
	(Q1, Q3)	(-9.00, NR)	NR
	FACIT-Fatigue		
	Number of non-responders	15	16
	Median	3.00	NR
	(Q1, Q3)	(NR, 30.00)	NR
Effect estimate per comparison	Primary endpoint:	Comparison groups	Spesolimab vs. placebo

	GPPGA pustulation subscore of 0	Risk difference	0.487
		95% CI	(0.215, 0.672)
		P-value	0.0004
	Key secondary endpoint: GPPGA total score of 0 or 1	Comparison groups	Spesolimab vs. placebo
		Risk difference	0.317
		95% CI	(0.022, 0.527)
		P-value	0.0118
	Secondary endpoints included in the hierarchical testing strategy		
	GPPASI 75	Comparison groups	Spesolimab vs. placebo
		Estimate of difference (median)	0.346
		95% CI	(0.058, 0.554)
	Pain VAS	Comparison groups	Spesolimab vs. placebo
		Estimate of difference (median)	Not calculable (NC)
		95% CI	NC
	PSS	Comparison groups	Spesolimab vs. placebo
		Estimate of difference (median)	NC
		95% CI	NC
	FACIT-Fatigue	Comparison groups	Spesolimab vs. placebo
		Estimate of difference (median)	NC
		95% CI	NC
Notes	For the primary estimand concept applied to the primary and secondary endpoints, death, any use of escape medication (i.e. standard of care treatment of the investigator's choice if severity and progression of disease worsened), any use of open-label spesolimab on Day 8, or any use of rescue medication before observing the endpoint was considered a non-response. After Day 8, a large number of patients in both treatment groups were classified as non-responders due to an intercurrent event described above. For continuous endpoints, the non-responses were ranked as the worst values in the analysis and an estimate for the treatment difference was not calculable.		

2.6.5.3. Clinical studies in special populations

There were no dedicated studies in special populations. It is acknowledged that very few subjects aged above 65 years were included in the pivotal study 1368-0013. The applicant has completed the table on use in different age categories:

Table 30. Age distribution of spesolimab-treated patients in GPP clinical trials

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled trials			
1368-0013 (randomised, placebo-controlled trial)	2 / 53	0 / 53	0 / 53
Uncontrolled trials			
1368-0011 (open label, single arm trial)	0 / 7	0 / 7	0 / 7
1368-0025[1] (open label extension trial)	0 / 39	0 / 39	0 / 39
1368-0027[2] (open label cohort)	0 / 6	0 / 6	0 / 6

1 All patients rolled over from trial 1368-0013
2 All patients who flared and received open-label i.v. spesolimab

2.6.5.4. In vitro biomarker test for patient selection for efficacy

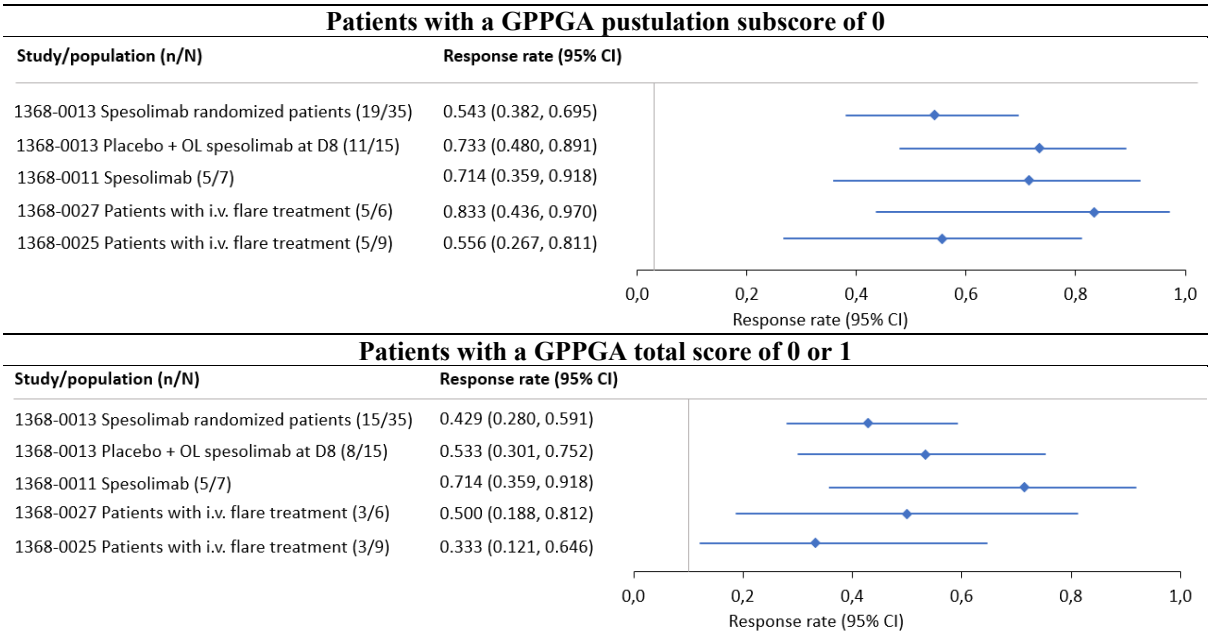
Spesolimab is an antibody acting as an antagonist towards the IL-36 receptor and a dysfunction related to this cytokine has been linked to GPP. In the clinical studies with spesolimab in GPP, the IL-36RN mutation status has been tested in the majority of patients.

An indication including a requirement for IL-36RN mutation status testing is not applied for and having an IL-36RN mutation was not required for inclusion in the pivotal (or any other) study. In study 1368-0013, a rather low proportion of the study population had an IL-36RN mutation; 7 in total. In subgroup analyses (see above), the mutation status did not seem to influence the response to spesolimab, even if the numbers are overall low. Also in the 1368-0013 biomarker report, a difference between treatment effects of spesolimab with or without IL-36RN mutation was not detected, however, this conclusion is limited due to the low number of patients (i.e. low statistical power) included in the analysis. Of note, the number of clinical responders were 7/8 (87.5%) and 9/21 (42.8%) in patients with or without IL-36RN mutation, respectively.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

The only study submitted as a pivotal study in this submission is the Phase 2 study 1368-0013 evaluating treatment of an acute GPP flare, as described above. Additional support comes from the open-label, uncontrolled Phase 1 Proof of concept study (1368-0011) as well as from the use of i.v. spesolimab for the treatment of acute GPP flares in Study 1368-0027 (SC prevention study, see below) and Study 1368-0025 (open-label extension study, see below).

Since these studies had different study design, pooling of data was not performed. Results from the respective studies have been presented side by side, as shown in Figure 28 below. Data from study 1368-0013 for patients randomised to placebo who received open label spesolimab on Day 8 are also included.



For all trials, the response rates 1 week after first spesolimab i.v. administration are reported (for the placebo arm in trial 1368-0013, the response rate 1 week after randomization was set as reference line).

Figure 28. Forest plot for GPPGA pustulation subscore of 0 and GPPGA total score of 0 or 1 after treatment with spesolimab i.v. across trials in patients with GPP

2.6.5.6. Supportive studies

Study 1368-0027 (Effisayil™ 2) is an ongoing study evaluating subcutaneous spesolimab for prevention of GPP flares, with IV spesolimab used as flare medication. Study 1368-0025 (Effisayil™-ON) is an open-label extension study in which IV spesolimab is also used as flare medication.

Study 1368-0027 Effisayil™ 2

Methods

This is a multi-centre, randomised, parallel group, double-blind, placebo-controlled, Phase IIb dose-finding study to evaluate efficacy and safety of spesolimab compared to placebo in preventing generalised pustular psoriasis (GPP) flares in patients with history of GPP.

The primary study objective is to demonstrate a non-flat dose response-curve and evaluate the dose-response relationship for 3 subcutaneous dosing regimens of spesolimab (with each regimen consisting of a single loading dose and a separate maintenance subcutaneous dosing regimen) versus placebo, on the primary endpoint, the time to the first GPP flare onset up to week 48.

The secondary objective is to demonstrate superiority versus placebo for each of spesolimab high dose (300 mg q4w) and spesolimab medium dose (300 mg q12w) on the primary endpoint, the time to the first GPP flare onset up to week 48, as well as the key secondary endpoint, the occurrence of at least one GPP flare up to week 48. Another objective is to evaluate safety and tolerability of multiple s.c. doses of spesolimab in patients with history of GPP.

The use of i.v. dose of BI 655130 for treating patients with onset of acute GPP flare is evaluated for safety and efficacy as an additional objective. Upon response of the flare, patients will continue receiving open label s.c. dose of spesolimab.

The Primary endpoint is the 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.

The Key Secondary Endpoint (for the secondary objective) is 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. Other secondary endpoints based on PSS, DLQI, etc. are also evaluated.

Included patients should have a known and documented history of GPP per ERASPEN criteria regardless of IL36RN mutation status, with at least 2 presentations of moderate to severe GPP flares with fresh pustulation (new appearance or worsening) in the past. They should have a GPPGA score of 0 or 1 at screening and randomisation. Patients who are on concomitant treatment regimen with retinoids and/or methotrexate and/or cyclosporine must stop at the day of randomisation. Male and female patients, aged 12 to 75 years at screening, are included. For all patients, a minimum weight of 40 kg is required.

Results

The study is still ongoing and some interim analysis have been provided.

Study 1368-0025

Methods

This is an open-label, non-randomised, multiple-regimen, long term, 5-year extension study to assess the safety and efficacy of spesolimab treatment in patients with GPP. Spesolimab treatment is offered for patients who completed their participation in the previous spesolimab trials with an aim to prevent reoccurrence of flares, if they are eligible to receive further spesolimab treatment.

The population included is male or female patients who have completed the treatment period without premature discontinuation in the previous spesolimab trial (1368-0013 or 1368-0027) and are willing and able to continue treatment in the current trial. Patients with evidence of flare symptoms of moderate or severe intensity at screening were excluded and other exclusion criteria were overall similar to those in the 0013 study.

The primary endpoint is the occurrence of treatment emergent adverse events (TEAEs) up to week 252 of maintenance treatment. Secondary endpoints are 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 and change from baseline in PSS score by visit.

The treatments are either:

Maintenance treatment with spesolimab s.c. q12w:

- patients who had not received any rescue treatment with open-label spesolimab i.v. in the previous trial, or:

Intensified maintenance treatment with spesolimab s.c. q4w or q6w:

- patients who had received rescue treatment with open-label spesolimab i.v. to treat GPP flare after achieving a clinical response in the previous trial.

In an event of GPP flare during maintenance s.c. treatment with either treatment schedule above, patients will receive i.v. dose of spesolimab as a rescue treatment. A recurrent GPP flare in this trial was defined as:

- Patients with GPPGA score 0 or 1 at screening: ≥2 point increase in the GPPGA score and the pustular component of GPPGA ≥2

- Patients with GPPGA score 2 at screening: ≥1 point increase in the GPPGA score and presence of fresh pustulation.

An amendment introduced the option to receive another flare treatment with open-label i.v. spesolimab 900 mg at Day 8 after the first dose of flare treatment, if specific criteria were met. This option was not fully implemented at the cut-off date for the interim analysis and none of the patients included in the interim analysis received a second dose of i.v. spesolimab after their first i.v. dose.

Results

The study is still ongoing and some interim analysis data have been provided.

Both in the flare prevention study 0027 and in the extension study 0025, i.v. spesolimab could be used as flare rescue treatment, in addition to the s.c. maintenance spesolimab treatment. Thus, these i.v. dose administrations will not reflect the posology as proposed in the current application, since no background s.c. spesolimab maintenance treatment is recommended. A discussion about the posology and a possibility to administer further spesolimab doses upon new, subsequent flares is provided below.

Patient Experience Dossier

Within the clinical development programme for spesolimab in GPP, the applicant has collected patient experience data in a variety of activities The objective was to summarise patient experience data collected to inform the applicant's approach to, and the overall benefit-risk assessment of, the GPP spesolimab programme.

I is concluded that for symptoms, pustules, pain, and itch were most frequently reported as the most burdensome ones and the symptom burden is overall greater in patients with GPP relative to patients with plaque psoriasis, e.g. for itch, pain, and fatigue. Patients report also stress and anxiety due to the unpredictable nature of the GPP flares and the overall burden of living with the chronic disease.

In the survey of GPP patients (n=66), flares were reported ≥2 times per year by 87% of respondents (n=57), 4 to 5 times annually by 20% (n=13), and >6 times annually by 26% (n=17). Thus, the majority of patients have at least 2 GPP flares per year and some have even more frequent flares. The most common cutaneous symptoms associated with flares were itching (76%), spreading of plaques (74%), increase in crust (67%), increase in pustules (62%), and increase in pain (59%). Thus, it is noted that itch was the reported most prominent symptom, however, it is not included as a dedicated endpoint in the pivotal study, e.g. assessed by an Itch NRS score. It is however, acknowledged that itch is part of the PSS (Psoriasis Symptom Scale) that was assessed as one of the secondary endpoints in study 1368-0013.

Concerning the period between flares, the majority of participants in the survey (n=50, 77%) reported persistent disease, with some degree of symptoms between periods of disease flare.

With respect to treatment experiences, participants reported trying a variety of treatments including topicals, non-biological disease modifying drugs, biologics, retinoids, and UV light therapy. Most reported trying multiple treatments over the years either consecutively and/or in combination, due to limited efficacy or loss of efficacy over time, or side effects.

In the survey (n=66), the most common current therapy was topical corticosteroids (56%), followed by methotrexate, IL-17i inhibitors, other topical treatments, oral steroids, infliximab, ustekinumab, cyclosporine, and UV light (in ≤20%). Less than one-third of the survey respondents (32%) reported their disease was well controlled by their current prescriptions or treatments.

Altogether, with the weaknesses mentioned above in mind (e.g. GPP diagnosis not confirmed by HCPs except in the registry data), the patient survey supports the view that GPP is a bothersome condition with large impact on patients' lives and with currently few satisfactory treatment alternatives.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The current application relates to flare treatment with spesolimab, using IV administration. This is supported by the single, pivotal Phase 2 study 1368-0013. Some support for the indication also comes from the small, uncontrolled PoC study (1368-0011). In the overall clinical programme for spesolimab in GPP, a study evaluating efficacy in prevention of GPP flares is also included (1368-0027; ongoing study) as well as a long-term, open-label extension study that is also ongoing (1368-0025).

CHMP Scientific Advice (EMEA/H/SA/3721/1/2017/III and EMEA/H/SA/3721/1/FU/1/2019/III) on the clinical development of spesolimab in GPP has been provided twice; in 2018 and in 2019. Overall, the CHMP advice have been followed, with some comments made where applicable (see below).

The applicant has confirmed that all trials were/are being performed in compliance with GCP and in accordance with applicable regulatory requirements and BI standard operating procedures.

Efficacy endpoints in GPP

There is no EMA guideline specifically describing the development of products for the treatment of GPP and very few products are approved in this indication which do not represent targeted therapy. In the spesolimab studies, the applicant has used endpoints resembling those commonly used in studies in plaque psoriasis, i.e. a global score (GPPGA; similar to PGA in plaque psoriasis) and a score evaluating different symptoms, severity and extent of lesions (GPPASI; similar to PASI in plaque psoriasis). In cooperation with GPP experts and dermatologists experienced in treating GPP, the applicant has developed and validated these GPP-specific endpoints. Validation reports were included in the dossier.

Given that the endpoint validation was performed within the study that is pivotal in this application, i.e. the Phase 2 1368-0013 (Effisayil 1) study; this approach was not considered appropriate by the CHMP since validation would be expected to be performed using an independent study/dataset. It may be that the 0013 study was initially intended as part of a clinical development plan for GPP overall (i.e. both flare treatment and prevention) and not as a single pivotal study in a MAA. Hence, even if not optimal, the approach was accepted, considering that the GPPGA/GPPASI (and other) endpoints are not entirely novel outcomes, but rather variants of Physician Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI) used in plaque psoriasis.

The GPPGA scale is used as the primary and key secondary endpoint in the pivotal GPP flare study 1368-0013. Both the intra- and inter-rater reliability showed acceptable results. For the GPPGA both the total score and the pustulation subscore (used as primary endpoint in the pivotal study 1368-0013) were evaluated. The GPPASI is used as one of the multiplicity-controlled secondary endpoints in the 0013 study.

Overall adequate validation exercises have been performed and the results show generally acceptable psychometric properties of the scales used, although some limitations were noted, e.g. due to challenges with the rather small sample size. This is acknowledged in a rare condition like GPP. It seems however that the GPPGA and GPPASI have been developed without any patient involvement, e.g. by performing focus interviews. This could have been expected since GPP represents a different population and condition (severity, predominant symptoms, time course, etc.) compared with 'conventional' plaque psoriasis. However, considering that the primary endpoints and highest ranked

secondary endpoints are based on GPPGA and GPPASI, both being endpoints related to lesion evaluation made by the physician without patient involvement, this is not deemed a critical issue.

Overall, the efficacy endpoints used in the spesolimab GPP studies are considered adequately supported and endorsed.

Study 1368-0011 (PoC study)

This was a multi-centre, open-label, single arm, phase I study to investigate safety, tolerability, pharmacokinetics, pharmacogenomics and efficacy of a single intravenous dose of spesolimab in patients with an active flare of generalised pustular psoriasis.

The inclusion and exclusion criteria stipulated that patients should have a known and documented history of GPP regardless of IL36RN mutation status, which was similar as in study 1368-0013. For inclusion, patients should be presenting with an acute GPP flare with a GPPGA total score of at least moderate (also similar to study 0013). The requirements for the affected body surface area (BSA) differed from the 0013 study (10% in the PoC study compared with 5% in the 0013 study) and the 0013 study included more specific requirements related to the presence of fresh pustules.

No control group was included. The participants received spesolimab at a dose of 10 mg/kg body weight administered as a single intravenous infusion over 60 min.

The primary endpoint was the number of patients with adverse reactions (i.e. drug-related AEs). Secondary endpoints included efficacy and PK endpoints, e.g. the percent change from baseline in GPPASI (GPP Area and Severity Index) total score, the proportion of patients with GPPGA (GPP Physician Global Assessment) total score of 0 or 1 and change from baseline in FACIT-Fatigue and Pain VAS scores, all four assessed at Week 2. Descriptive statistics were used to analyse safety, PK, and efficacy endpoints. Formal hypothesis testing was not planned or performed.

Dose finding

No formal dose response studies for spesolimab in GPP are included in the MAA.

The decision on the dosing scheme for the Phase 2 study 1368-0013 was informed by previous findings in healthy volunteers and in the proof-of-concept trial in GPP (1368-0011). In trial 1368-0011, a dose of 10 mg/kg body weight was shown to be efficacious and safe. In trial 1368-0013, a fixed rather than a weight-based spesolimab dose regimen was chosen. The selected 900 mg IV dose for trial 1368-0013 was chosen to target a similar efficacy to that in trial 1368-0011 and allow recruitment of patients with a body weight greater than 70 kg and of higher GPP severity than in trial 1368-0011. Thus, the dose in trial 1368-0013 was approximately 25% higher. A dosing regimen with an initial IV dose of 900 mg spesolimab followed by a second dose after 1 week in case of insufficient response was within the safety limits based on Phase I data.

The reasoning behind the dose regimen can be endorsed, even if not strongly supported by data. The use of a flat 900 mg dose and not a weight-based dosing was not extensively discussed and supported by the applicant. Nevertheless, available data indicate no cause for concern and adequate wording has been included in the SmPC (5.2) e.g. about the unknown clinical relevance of lower exposure in patients with body weight greater than 130 kg.

The acceptability of administration of a second IV dose 1 week after the first dose, as currently proposed by the applicant in the SmPC, is further discussed below. The possibility to administer spesolimab for new, recurrent flares occurring later in time was not addressed in the initially proposed SmPC and is also discussed further below.

Study 1368-0013, Effisayil™ 1 (pivotal study for GPP flare indication)

This was a multicentre, randomised, double-blind, placebo-controlled Phase II trial to assess the efficacy, safety, and tolerability of a single intravenous (i.v.) dose of spesolimab in patients with generalised pustular psoriasis (GPP) presenting with a flare of moderate to severe intensity. In addition, efficacy and safety of an open-label dose of spesolimab i.v. administered 1 week after the randomised treatment was evaluated in an exploratory fashion.

The enrolment into this study was made in a step-wise manner for most patients; i.e. first identifying patients with a diagnosis and history of GPP and then, upon experiencing a new acute flare, they were randomised and treatment was initiated. Patients could also be enrolled and randomised upon their first experience of an acute GPP flare event (with formal diagnosis performed later).

Both the diagnostic criteria (consensus diagnostic criteria by the European Rare and Severe Psoriasis Expert Network; ERASPEN) and the criteria for initiation of therapy are endorsed, i.e. patients presenting with an acute GPP flare of moderate to severe intensity, defined by emergence of a GPPGA total score of ≥3 (moderate), presence of fresh pustules (new appearance or worsening of pustules), a GPPGA pustulation subscore of ≥2 (mild), and ≥5% of Body Surface Area (BSA) covered with erythema and the presence of pustules. The total GPPGA score had to be at least 3 (moderate) while the pustulation subscore could be mild (≥2).

Patients could have been receiving background systemic treatment but were not required to for inclusion. Patients had to discontinue retinoids/methotrexate/cyclosporine prior to receiving the first dose of spesolimab or placebo. There were restrictions related to other treatments and washout required for e.g. biologics.

There was no requirement for an IL36RN mutation for inclusion as efficacy had been seen in GPP patients both with and without the IL-36RN mutation (early response to flare treatment with spesolimab in trial 1368.11), mutations in other genes linked to the IL-36 pathway have been described pointing to a general role of the IL-36 pathway as disease trigger/driver and since rapid treatment of flares is critical, patients could be included without the need for screening for mutation status. This is further discussed below in relation to baseline data and subgroup analyses.

Exclusion of other, specific forms e.g. SAPHO and primary erythrodermic psoriasis vulgaris, as well as drug-induced acute generalised exanthematous pustulosis (AGEP) is agreed. Also not including patients with an immediate, life-threatening flare of GPP or requiring intensive care treatment, is reasonable. This has been adequately reflected in the SmPC (section 4.4). Other exclusion criteria related to hepatic disease, infections, malignancies and other conditions are also reasonable.

The treatment in the study comprised one single IV dose of spesolimab, or placebo, on Day 1 (Week 1). For patients not responding satisfactorily, there were options for escape and/or rescue treatment.

Before Day 8 (Week 1), escape medication (standard of care, SoC), could be administered. The choice of the escape treatment (i.e. SoC) was left at the discretion of the investigator and was not defined in the study protocol.

On Day 8, patients who had not received escape treatment and who had a GPPGA ≥2 at Week 1 and a GPPGA pustulation subscore of ≥2 were eligible to receive treatment with a single open-label i.v. dose of 900 mg spesolimab. Thus, this was a second IV spesolimab dose for those in the spesolimab arm and a first IV spesolimab dose for those in the placebo arm, if needed based on GPPGA criteria.

Subsequently during the study, if a patient with a previous clinical response (GPPGA 0 or 1) experienced a recurrence of a GPP flare (defined as a ≥2-point increase in the GPPGA score and the pustular component of GPPGA ≥2 after achieving clinical response; i.e. GPPGA 0 or 1) after

Week 1/Day 8 and through the follow-up period, rescue treatment with a single i.v. dose of 900 mg spesolimab could be administered. This could occur anytime between after Day 8 and Week 12 and only 1 rescue dose with spesolimab for a flare recurrence was permitted. Subsequent flares were to be treated with escape treatment (SoC) per physician's discretion.

Thus, patients could be treated with one, two or three doses of spesolimab during the course of this study.

With respect to concomitant medications, different washout periods applied. Since screening (visit 1) and treatment/randomisation (visit 2) could take part quite far apart in time (depending on how soon after screening a subject experienced a flare qualifying for spesolimab treatment), it is not fully clear how this was handled in practise, though. Furthermore, more patients in the spesolimab treatment group were treated with biologics (ustekinumab, adalimumab and etanercept). Biologic treatment had to be discontinued 2 months before initiation of randomised treatment. Considering the 2-3 week T½ of the said biologics, it cannot be excluded that those patients were still impacted by the discontinued treatment, considering that 5 half-lives are needed for washout of a drug. The applicant was invited to discuss a potential impact on the efficacy and safety of spesolimab treatment in those patients and to summarise the time between screening visit and Visit 2 (treatment) for all patients, and clarify how concomitant treatments and washout was handled. Any implications for the SmPC should also be discussed (e.g. whether there should be a request for immediate withdrawal of background GPP therapy, or even a washout period, when spesolimab is given for a GPP flare). In the response, it was clarified that the time between the stop date of these biologics and administration of spesolimab i.v. on Day 1 was >14 weeks for all patients randomised to spesolimab and several months for the majority of patients. It therefore seems unlikely that the patients in the spesolimab group who took these drugs were still impacted by the discontinued treatment. It is agreed therefore that the washout periods according to the protocol have been kept, in some cases there was 'incomplete stop' of some medications, however, for these a 'worst case imputation' have been used, and discontinuation of biological drugs occurred so long before receiving spesolimab that it most likely did not influence efficacy of spesolimab (SmPC section 5.1).

It has been also clarified that 7 patients were enrolled and randomised upon their *first* experience of an acute GPP flare event (with formal diagnosis performed later). It has been clarified that blinded review by the external global expert committee was based on high resolution photographs of skin lesions (photo documentation) from both screening and baseline (randomisation) with the option to zoom in and out as well as on patients' detailed medical history, baseline demographics, and information on systemic symptoms and lab values. For the patients identified to have been randomised upon their first flare, the expert committee generally confirmed the diagnosis of GPP, but 1 patient was assessed as difficult to judge and considered to potentially have GPP with plaque psoriasis or plaque psoriasis with pustules. This seems adequate.

The primary objective of this trial was to evaluate efficacy, safety, and tolerability of a single i.v. dose of spesolimab compared with placebo in patients with Generalised Pustular Psoriasis presenting with a flare of moderate to severe intensity. Further objectives of this trial were to investigate the pharmacokinetics and anti-drug antibodies (ADA) of spesolimab as well as pharmacogenomics and specific biomarkers in patients with GPP presenting with a flare of moderate to severe intensity.

In a CHMP Scientific Advice (EMEA/H/SA/3721/1/2017/III and EMEA/H/SA/3721/1/FU/1/2019/III) the best option for a controlled study was discussed. This could be either a superiority study versus standard of care (acitretin, cyclosporine or methotrexate), a placebo-controlled study on top of standard of care, or a placebo-controlled study with escape criteria i.e. rescue medication. It was concluded that the option preferred and recommended by the CHMP would be a randomised, comparative, superiority trial vs. SOC. In a follow-up advice, it was noted that the advice of a

controlled study versus SoC had not been followed, however, other aspects were followed, e.g. not to use spesolimab as rescue therapy, at least up to the time point for assessment of the primary endpoint, i.e. week 1. The CHMP finally agreed that both pivotal studies (including study 0027 in prevention of flares) could support submission of MAA in GPP, despite the fact that, contrary to previous advice recommendation, placebo was chosen as the control arm for study 0013 instead of SoC. Thus, the design used for the flare treatment trial, with placebo control and option for rescue with spesolimab at Week 1, is considered adequate. It is agreed that due to the heterogenous SoC in GPP and lack of adequate information about its effects, a comparative study vs. SoC would have been difficult to plan.

The *primary efficacy endpoint* was a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0, indicating no visible pustules, at Week 1. This endpoint is an outcome reflecting a complete clearance of GPP pustules. This is a relevant outcome since pustule formation is the prominent symptom in the GPP condition. It was assessed already at Week 1, which is a relevant time point, since a rapid clearance of pustules is of importance and desirable.

The *key* secondary efficacy endpoint was a GPPGA total score of 0 or 1 at Week 1. Thus, this reflects also the other components of the GGPGA score, i.e. erythema and scaling/crusting. For this endpoint, a score of 0 or 1 was considered a response, which is reasonable considering that patients with severe erythema and scaling would not be expected to achieve a complete clearance for these components within 1 week. This endpoint was also assessed at Week 1, which is endorsed.

Secondary efficacy endpoints in this trial at Week 4 that were *included in the hierarchical testing strategy* were:

- A Psoriasis Area and Severity Index for Generalized Pustular Psoriasis (GPPASI) 75 at Week 4
- Change from baseline in Pain Visual Analog Scale (VAS) score at Week 4
- Change from baseline in Psoriasis Symptom Scale (PSS) score at Week 4
- Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue score at Week 4.

These are considered relevant secondary endpoints addressing different aspects, e.g. the extent of lesions (GPPASI), pain, psoriasis symptoms and assessment of fatigue. Evaluation of these endpoints at Week 4 is reasonable. However, the analyses are influenced by the fact that most patients in the placebo group and several subjects in the spesolimab group received a dose of spesolimab (‘rescue’) at Day 8, Week 1. Based on these uncertainties related to the secondary endpoints (except for the key secondary endpoint), further changes to the SmPC were requested and have now been introduced.

Other secondary efficacy endpoints were also evaluated in the study.

The impact of missing data and rescue medication on efficacy estimates were not entirely transparent: Escape/rescue medication coded as failure in the endpoint. This made it somewhat difficult to interpret the effect estimates, especially for the continuous endpoints. The applicant was also asked to provide more detailed information on number of patients intercurrent events and missing data. If data after intercurrent events are available, the applicant was asked to provide results based on a treatment policy type estimand.

In the response, the applicant has provided a detailed description of open label Spesolimab use, rescue and escape medication, and missing data. Graphs of change from baseline over time were also provided (data not presented). The applicant has also provided tipping point analyses where any data post-spesolimab-use were replaced with imputed values for patients randomised to placebo (data not presented).

At week 1 the occurrence of intercurrent events was balanced (1/18 in the placebo arm and 2/32 in the Spesolimab arm). There was one occurrence of missing data in the Spesolimab arm. This occurrence does not challenge the robustness of the results.

At the week 4 endpoints, 13 of the 18 placebo patients had open label Spesolimab use at day 8, and 1 patient had later escape/rescue medication without Spesolimab use at day 8. These patients are regarded failures at the week 4 endpoint. For continuous outcomes the primary estimand imputed these as the worst possible score. The study was blinded, so the need of open label Spesolimab at day 8 could be considered clinically relevant. However:

- The week 4 endpoints appear to be mainly driven by symptoms occurring at or before day 8 (triggering open label Spesolimab use at day 8) and can therefore not be considered to capture long term effects.

- The effect that is captured in the week 4 endpoints is "need of open label Spesolimab" rather than the results on the different scales.

Thus, it is concluded that Week 1 results are robust regarding intercurrent events and missing data. Week 4 endpoints lack in clinical interpretability.

For binary endpoint missing data was primarily imputed using failure imputation. For continuous endpoints, missing data were primarily imputed using the last observation carried forward (LOCF) method. It is not clear how the assumptions of LOCF, in combination with the missingness pattern in this study, have affected the estimated. Also, single imputation methods risk biasing the standard error downwards by ignoring the uncertainty of imputed values. Sensitivity analyses using MMRM were provided, although MMRM appears to have been implemented using a MAR assumption and is therefore unlikely to be conservative. In the primary endpoint only one subject had missing information. This subject was in the active group, and the imputation is therefore considered acceptable.

For the sample size estimation, a simulation-based power calculation was performed for sample size assessment on both the primary and key secondary endpoints. The applicant calculated power for the primary endpoint and the key secondary endpoint for a number of efficacy scenarios, for a sample size of 51 patients (2:1 ratio) and a 1-sided type I error of 0.025. The sample size was changed from 27 to 51 in amendment 1. At this amendment, the multiple testing procedure was also changed. Such changes may affect the type I error control, and some clarifications were requested. In the response it was clarified that no interim analysis was done before the CTP amendment. The updates to the multiple testing procedure and sample size were made when only 9 patients had been randomised and 8 patients had completed the week 1 Visit, and it is therefore considered unlikely that the changes were data driven.

The randomisation procedures appeared adequate. Stratification of randomisation was performed for Japan versus non-Japan. This stratification was implemented for operational purposes only and was not included in the analyses of efficacy endpoints. No other stratification factors were used.

The study procedures to maintain blinding is overall adequate.

Efficacy data and additional analyses

Study 1368-0011 (PoC study)

Out of 16 enrolled GPP patients, 7 patients entered the trial; all were included in the entered set, the treated set, and the full analysis set (FAS). Six patients were included in the per-protocol set (PPS); 1 patient was excluded due to a major protocol violation. No patient discontinued the trial prematurely.

No control group was included, which affects the interpretation of efficacy results. A fairly large mean reduction in GPPASI total score (around 73%) was observed at Week 2. Around 70% of subjects also

reached a GPPGA score of 0 or 1 at Week 2. In this study, the efficacy endpoints were evaluated at Week 2 (Week 1 in the pivotal study 1368-0013). Based on information about the duration of the historical GPP flares for the patients included (median 6 days for the shortest flare and median 10.5 days for the longest flare), the reductions may well (at least partly) reflect the natural course of recovery from a GPP flare. It should also be noted that all patients included had a flare of moderate (GPPGA total score of 3 at baseline) severity while none had a severe (GPPGA score of 4) flare.

Even if the primary evaluations of efficacy were performed at Week 2 in the 0011 study, it is noted that for instance for GPPGA, the response rate was similar at Week 1 and Week 2 (71.4%; 5 subjects, FAS, NRI). Also, for the GPPASI reduction, a mean percent reduction at Week 1 of 59.0% was observed (73.2% at Week 2). Therefore, it seems reasonable that spesolimab would have contributed although the lack of a control group hampers the assessment. Proof-of-concept for the use of spesolimab in GPP is supported based on this study.

Study 1368-0013, Effisayil™ 1

Out of 85 screened patients, 53 patients were randomised in a 2:1 ratio to receive a single dose of spesolimab 900 mg IV or placebo. A total of 32 patients were not randomised. The most common reason for not entering patients was "other" (17 patients), with global recruitment target achieved prior to patients having a flare being the main reason. The second most common reason was "failure to meet randomization criteria" (13 patients), with inclusion/exclusion criteria not met (e.g. absence of developing a flare within 6 months) being the main reason.

All randomised patients (spesolimab: 35 patients, placebo: 18 patients) were treated. A total of 27 patients (spesolimab: 12 patients, placebo: 15 patients) received open-label treatment with spesolimab on Day 8, and 6 patients (spesolimab: 4 patients, placebo: 2 patients) received rescue treatment with spesolimab after Day 8. A total of 11 patients (spesolimab: 6 patients, placebo: 5 patients) used escape medication within the treatment phase.

The rate of completion of the planned observation period was high (spesolimab: 32 patients, 91.4%, placebo: 17 patients, 94.4%). Withdrawal by patient was the main reason for premature discontinuation. There were no deaths. Almost three quarters of the patients overall (73.6%; spesolimab: 77.1%, placebo 66.7%) rolled over into the open-label extension trial 1368-0025.

This was a global study and enrolment took place in a total of 12 countries, at 26 centres across different regions. The largest groups of patients were from Malaysia (12 patients), France (10 patients), and Tunisia (7 patients). A total of 16 European patients were enrolled (calculated by assessor), of which one from Switzerland who discontinued the trial. The study was conducted 20 February 2019 to 05 January 2021.

Concerning protocol amendments, the Global amendment 1 included some major changes based on health authority recommendations, e.g. an increase in sample size from 27 to 51 patients and the former 2 co-primary endpoints were changed into a primary and a key secondary endpoint. Changes in statistical analyses, AE reporting, etc. were also performed. The Global amendment 2 introduced some additional analyses and endpoints, e.g. for evaluating efficacy of OL spesolimab on Day 8. The sample size adjustment and change of multiple testing procedure may have affected the type I error control. However, these changes were performed relatively early in the study (Amendment 1 19 July 2019, first patient randomised on 04 Mar 2019, last patient completed the trial on 05 Jan 2021), and the impact is thought not to have been substantial. The other changes in the amendments are not considered to have had a major influence on the conduct or analyses of the study.

Impact of the COVID-19 pandemic and procedures to address this were described as well as any actual disruptions in the study conduct. The trial was completed as planned despite the disruptions that

occurred (e.g. a pause in screening and site initiation, a need to delay and/or conduct some visits remotely) and the overall impact on the efficacy and safety results was considered minimal.

Concerning protocol deviations, a total of 13 patients (24.5%) had important protocol deviations. One related to violation of inclusion criteria ("GPP per CTP was not confirmed" leading to exclusion of this patient from the PPS) and 12 patients (22.6%) used prohibited (restricted) medications, which did not include the use of escape medication. All prohibited medications were administered after Week 1, i.e. after the assessment of the primary and key secondary endpoints, and thereby did not lead to exclusion of the patients from the PPS.

Compliance was not an issue since the primary treatment was a single dose administered at the study centre. The mean volume infused of the planned volume was high (99.6%).

With respect to baseline demographic characteristics, the main part of the study population was female (68% overall) and slightly more than half of the subject overall were Asian (55%). There were some imbalances, in that the placebo group had a larger proportion of females (83%) and Asian subjects (72%). The mean and median age and the age distribution were fairly similar across groups. Very few subjects aged ≥65 years were included (2 in the spesolimab group). The mean and median body weight was somewhat higher in the spesolimab group compared with the placebo group, which may be linked to the higher percentage of females and Asians in the placebo group. The groups were rather balanced with respect to smoking status (the majority had never smoked), renal function and hepatic function (both being normal in the majority of subjects).

At baseline, (i.e. initiation of randomised treatment), overall, 81.1% of patients had a GPPGA total score of 3, and 18.9% of patients had a GPPGA total score of 4 (severe). Thus, the majority had a moderate GPPGA total score with less than 20% having a severe GPPGA score.

The majority of patients had a baseline GPPGA pustulation subscore of 3 (43.4%) or 4 (35.8%). The proportion of patients with a subscore of 2 (overall: 20.8%) was slightly lower in the spesolimab group (17.1%) than in the placebo group (27.8%). Thus, for pustules, the study population were mainly at the moderate to severe end.

The mean and median baseline GPPASI total scores were somewhat higher in the spesolimab group and pustules severity was slightly higher in the spesolimab group compared with the placebo group. The mean and median Pain VAS, PSS, FACIT-Fatigue, and DLQI scores were largely comparable across treatment groups, with slightly higher Pain VAS rating for spesolimab.

With respect to the disease characteristics for the flare that led to randomisation (i.e. the current flare), these were overall comparable between the spesolimab group and the placebo group. In both treatment groups, the 2 most common trigger events for the flare were "treatment withdrawal" or "other" (with "unknown" being the most frequent entry for the category "other"). The majority of subjects had a worsening or new appearance of pustules, and similarly for erythema and scaling and systemic components (e.g. fever, malaise), in both treatment groups. More than 50% of patients had an elevated white blood cell count of ≥10 000/µL, and more than 20% of patients had an elevated CRP level of ≥7 mg/dL. Albumin levels and body temperature were normal for the majority of patients.

The medical history for the GPP condition showed that overall >40% (slightly more in the spesolimab group (48.6%) compared with the placebo group (33.3%)) had >10 years since first diagnosis of GPP. About 30% had ≤1 year since their GPP diagnosis. The diagnostic method to confirm GPP was by skin biopsy in overall 38% of subjects, by histopathological confirmation in 13% and 'other' in 49%. The mean number of GPP flares per year was 3 to 4. The time with completely clear skin over the past year differed quite a lot; about one fourth (24.5%) had <1 week with clear skin, whereas 30% had >12 weeks with clear skin the last year. The characteristics were overall well balanced between the treatment groups.

Concerning baseline conditions and medical history, around 90% had at least 1 baseline condition/medical history, with no major differences between groups. Around 32% had psoriasis (mainly psoriasis vulgaris and plaque psoriasis).

However, in the Baseline data on flare characteristics, it was not stated which mean or median body surface area that was affected in the patients evaluated. The applicant has explained that the exact percentage of body surface area affected by GPP was not collected. Based on indirect estimations from the GPPASI scores (which includes the extent of involvement of pustules, erythema and scaling), it was estimated that patients in study 1368-0013 had 30% to 50% of body surface area in the 4 body regions being affected by GPP.

Concerning IL-36RN mutation status, both historical data and genotyping data from analyses performed within the study were available. In both cases the number of patients with an IL-36RN mutation was low (spesolimab 7 or 5 patients; placebo 3 or 2 patients, respectively). The applicant has clarified the status of availability of IL-36RN mutation status. Overall, genotyping data are available for 46 patients in study 1368-0013 and are lacking for 7 subjects. The presence of potential pathogenic IL-36RN variation was shown for 14 patients in total (spesolimab: 8 patients, placebo: 6 patients; 26% of the study population) while 32 subjects in total (60%) had no such mutation. Patient characteristics (baseline disease severity, occurrence of flares) by the mutation status in IL-36RN were presented, as requested. Patients with or without IL-36RN mutation had similar baseline disease characteristics. There was a tendency to those with an IL-36RN mutation having higher baseline scores both for the GPPA total scores, the GPPGA pustulation subscore and GPPASI pustules severity. Based on the overall low numbers, firm conclusions are difficult to make, however, it is clear that having an IL-36RN mutation is not a determining factor in developing GPP and also subjects without an IL-36RN mutation can develop severe GPP. Subgroup analyses of efficacy endpoints by the mutation status in IL-36RN have also been presented. It is acknowledged that the sample sizes of the subgroups were very small. However, for both the primary and key secondary endpoints, the results were largely consistent across the 2 subgroups, although with somewhat larger treatment effects for this with a mutation.

Efficacy results

The study met its *primary endpoint*; the proportion of patients who achieved a GPPGA pustulation subscore of 0 at Week 1 was significantly higher for patients who received a single 900 mg IV dose of spesolimab (19 of 35 patients, 54.3%) compared with patients who received placebo (1 of 18 patients, 5.6%), leading to a risk difference of 48.7% (1-sided p = 0.0004).

The *key secondary endpoint* was also met; the proportion of patients who achieved a GPPGA total score of 0 or 1 was significantly higher in the spesolimab group (15 of 35 patients, 42.9%) compared with the placebo group (2 of 18 patients, 11.1%), leading to a risk difference of 31.7% (1-sided p-value=0.0118).

All *secondary endpoints included in the hierarchical testing procedure* (the GPPASI 75 plus 3 patient-reported outcome measures assessed at Week 4) showed significant results in favour of spesolimab. For instance, for the first of the hierarchically tested secondary endpoints "The proportion of patients with a GPPASI 75 at Week 4", the applicant claims that this proportion was higher in the spesolimab group (45.7%) than in the placebo group (11.1%), and that the risk difference between spesolimab and placebo of 34.6% was significant (p=0.0081). However, the interpretation of these pre-specified analyses is limited as a considerable number of patients had received open label spesolimab on Day 8, spesolimab rescue medication after Day 8, or escape medication, i.e. 13 of the 18 placebo patients had open label Spesolimab use at day 8, and 1 patient had later escape/rescue medication without Spesolimab use at day 8. Patients with these intercurrent events were treated as non-responders and assigned "worst outcome" in the rank analysis for the secondary continuous endpoints. Although it is acknowledged that ITT is used and the estimand strategy (EN-NRI), since the above calculation is

derived from data from only 2 patients in the placebo arm, the calculation should be interpreted with caution. The week 4 endpoints appear to be mainly driven by symptoms occurring at or before day 8 (triggering open label Spesolimab use at day 8), and can therefore not be considered to capture long term effects. Also, the effect that is captured in the week 4 endpoints is "need of open label Spesolimab" rather than the results on the different scales. For all the above described secondary endpoints the pattern is similar, with a separation of spesolimab and placebo during the first week and thereafter, the placebo group 'catching up' since a large proportion received open label spesolimab on Day 8. Therefore, the applicant agreed to remove all initially included data (text and graphics) in the SmPC section 5.1 related to the open-label period. This is endorsed.

Also, for endpoints assessed over time up to 12 weeks, the study design with possibility for escape as well as an extra spesolimab dose on Day 8 and rescue spesolimab at later time points, made the results at time points beyond Week 1 difficult to interpret. Due to the severity of the condition, it is acknowledged that other design options would have been difficult. For both a GPPGA pustulation score of 0 and for a total GPPGA score of 0 or 1, a separation of spesolimab and placebo during the first week is observed and thereafter, the placebo group 'catches up' since a large proportion received open label spesolimab on Day 8. For other secondary endpoints the pattern was similar.

Subgroup analyses

Subgroup analyses for the primary and key secondary endpoints were performed for predefined subgroups; sex, race, BMI category, GPPGA pustulation subscore at baseline, GPPGA total score at baseline, plaque psoriasis at baseline, background treatment prior to randomisation, JDA GPP severity score at baseline, and mutation status in IL-36RN. The subgroups analysed are deemed relevant.
A subgroup analysis for age was not possible or meaningful due to only two subjects being aged >65 years.

The results were largely consistent across subgroups for both a GPPGA pustulation subscore of 0 and GPPGA total score of 0 or 1 at Week 1. Some subgroups were very small, resulting in wide CIs.

With respect to the mutation status in IL-36 RN, using updated genotyping data (including data that became available after the final database lock of trial 1368-0013), the subgroup analyses also showed consistent results.

A discussion on potential differential baseline disease characteristics as well as treatment results related to the mutation status was provided. There were some tendencies to possibly more severe disease in those carrying an IL-36RN mutation and somewhat larger risk difference between spesolimab and placebo in terms of efficacy results, but the groups are small, which limits firm conclusions. Efficacy is demonstrated in the overall population (with and without mutation) as well as in the group not carrying an IL-36RN mutation. Hence, carrying a potential pathogenic IL-36RN variation does not appear to be a prerequisite either for developing GPP or for achieving an effect of spesolimab on a GPP flare. No updates of the posology, e.g. a requirement for obtaining information about the IL-36RN mutation status prior to treatment, are considered necessary.

Also, for baseline GPP flare severity, sex, race (Asian vs. White) and BMI there seems to be a clear effect of spesolimab even if the response rates for some comparisons differed to some extent. The impact of body weight on spesolimab exposure is not expected to be clinically meaningful up to approximately 130 kg. The clinical relevance of higher body weight greater than 130 kg is unknown (SmPC section 5.2).

With respect to the proposed indication wording, the applicant has not specified the GPP flare severity. Even if only about 20% of the study population had severe GPP, the subgroup analyses indicate similar response rates in moderate and severe GPP. Hence, an indication covering both severities is adequate.

The applicant was asked to clarify in the SmPC that patients with a life-threatening flare of GPP or requiring intensive care treatment were excluded from the study and have hence not been studied. A contraindication against use in such patients is not warranted, however, lack of information should be pointed out. This has now been added also in SmPC section 4.4 as requested: "There is no experience from the use of spesolimab in patients with an immediate, life-threatening flare of GPP or a flare requiring intensive care treatment".

Moreover, the currently proposed indication did not specify that spesolimab has been used as monotherapy in the treatment of a GPP flare. At CHMP's request, this has been reflected in SmPC section 4.1. In relation to this, the applicant was asked to discuss the doses and types of treatments for which data on concomitant use with spesolimab are available and how they overlap with management of GPP (to be able to judge the overlap/gaps with GPP treatment in clinical practice). Overall, 17 of 53 patients (32.1%) in trial 1368-0013 received concomitant biologics, other systemic immunomodulating treatments, or topical corticosteroids as GPP treatment concomitantly to spesolimab i.v. A detailed listing of these drugs (including their dose, route, and timing of administration) was provided. The additional GPP treatments are relevant to standard practice. Remaining comments on the PI in relation to co-treatment with other GPP medications have been resolved. The SmPC section 4.4 informs that "Concomitant use of other immunosuppressants and spesolimab is not recommended. At initiation of spesolimab treatment, other GPP treatments should be stopped and other treatments (e.g. with systemic immunosuppressants) should not be used concomitantly to treat the flare."

Analysis performed across trials

The only study submitted as a pivotal study in this submission is the Phase 2 study 1368-0013 evaluating treatment of an acute GPP flare, as described above. Additional support comes from the open-label, uncontrolled Phase 1 Proof of concept study (1368-0011) as well as limited data from the use of IV spesolimab for the treatment of acute GPP flares in Study 1368-0027 (SC prevention study, see below) and Study 1368-0025 (open-label extension study, see below).

Since these studies had different study design, pooling of data was not performed. Results from the respective studies have however been presented side by side. Data from study 1368-0013 for patients randomised to placebo who received open label spesolimab on Day 8 are also included. It is agreed that pooling of efficacy data is not adequate in this situation. Except for the pivotal study 1368-0013, the other studies only provided limited data and firm conclusions are difficult to make. Nevertheless, the reported responder rates are similar or higher compared with those observed in study 1368-0013.

Proposed posology

The currently proposed SmPC states that if flare symptoms persist, an additional 900 mg dose may be administered 1 week after the initial dose. This is based on data from a limited number of subjects (n=12) in the spesolimab arm who received a second dose on Day 8. This seemed to improve response for some of these patients; of the 12 patients, 5 patients (41.7%) achieved pustular clearance at Week 2, i.e. 1 week after the second dose administration. It is acknowledged from a safety point of view that data from multiple spesolimab dose administrations are available. The need for a second dose may imply that the initial dose was insufficient for these patients. The applicant was asked to analyse data (albeit limited) and discuss whether such patients could be identified. No specific factor could be identified and no updates of the posology in this respect are considered warranted.

Another point to address is whether there is a possibility to administer further spesolimab doses upon new, subsequent flares. This is a very likely scenario since GPP patients are expected to experience new flares at some point in time. This is now reflected in the SmPC sections 4.2 and 4.4.

ADA/NAb status

Concerning immunogenicity in relation to efficacy, the applicant states that the results for GPPGA pustulation subscore of 0 (and a GPPGA total score of 0 or 1) are similar regardless of ADA or NAb status. Patients who achieved response generally maintained this treatment effect of spesolimab over time, even in the presence of ADA.

In study 1368-0013, a large proportion of subjects (46%, 23/50) developed ADA by Week 12-17 with median onset time of 2.3 weeks and maximum titre at a median time of 11.7 weeks. A total of 24% of patients had a maximum ADA titre greater than 4000. NAb was detected at a median onset time of 6.7 weeks. Females appeared to have higher immunogenicity response. For the currently applied posology, i.e. one i.v. dose of spesolimab with a possibility to administer one additional dose at day 8, immunogenicity may not be of high importance from an efficacy point of view. With an ADA onset time of 2.3 weeks, the incidence of ADAs has no impact on the decision to administer a second dose at day 8. It may however have an impact in case of *recurrent* flares treated by spesolimab. The applicant claims that based on data from e.g. Study 1368-0025 that re-treatment of recurring flares with spesolimab i.v. was still efficacious. However, this is based on very few subjects. This was also rescue treatment on top of a s.c. maintenance (prevention) regime of spesolimab, which represents a different situation from occasional repetition of i.v. flare treatments. The SmPC section 4.4 now reports that "Very limited efficacy and safety data are available for re-treatment with spesolimab for a subsequent new flare. E.g., data are available for five patients with GPP who received re-treatment at a subsequent new flare and followed up for a minimum of 8 weeks."

PRO

The conduct of the patient surveys is noted and appreciated. A few limitations were however highlighted by the applicant in the report. For instance, a diagnosis-confirmation was not feasible to collect across all of the patient experience activities (diagnosis reported by patients in the patient surveys compared with diagnosis reported by HCP in the data obtained from the Corrona registry). This is a weakness, considering that GPP may not always be readily diagnosed, as also noted in the surveys based on patient histories (delayed diagnosis or misdiagnosis reported in many cases).

Additional efficacy data needed in the context of a conditional MA

Data on re-treatment is not considered comprehensive. The applicant proposes to conduct an additional open-label, single-arm post-authorisation study (trial 1368-0120) on the treatment of subsequent flares with spesolimab and submit the final study report to comply with a CMA.

Planned Specific Obligation Study

Title

An open-label, multicentre, single-arm, post-marketing trial to evaluate efficacy and safety and the impact of immunogenicity on efficacy, safety, and pharmacokinetics of spesolimab i.v. in treatment of patients with Generalized Pustular Psoriasis presenting with a recurrent flare following their initial GPP flare treatment with spesolimab i.v.

Rationale

Spesolimab has been approved in some countries as the treatment of flares in adult patients with GPP administered as an intravenous (i.v.) infusion. However, the data on the efficacy and safety of spesolimab i.v. in the treatment of recurrent flares (defined as subsequent new flares) is limited. Trial 1368-0120 is an open-label, single-arm, post-marketing trial to generate data on the efficacy and

safety and on the impact of immunogenicity on efficacy, safety, and pharmacokinetics (PK) of spesolimab i.v. in the treatment of recurrent flares following treatment of patients' initial flares with spesolimab i.v.

Objective

The main objective is to evaluate the response to recurrent flare(s) treatment with spesolimab i.v. after first flare treatment with spesolimab i.v.. A further objective is to evaluate the potential impact of immunogenicity on this response of recurrent flare treatment with spesolimab.

2.6.7. Conclusions on the clinical efficacy

An effect of spesolimab in the treatment of a single, acute GPP flare has been demonstrated vs. placebo. The data for spesolimab in GPP flare re-treatment was not regarded as comprehensive by the CHMP and the applicant was asked to propose how further data could be generated in a post marketing prospective study. This study, albeit small and uncontrolled, can provide further data on the efficacy, safety and immunogenicity for the treatment of repeated GPP flares with spesolimab.

The CHMP therefore considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

In order to confirm the efficacy and safety of spesolimab in the treatment of flares in adult patients with generalised pustular psoriasis (GPP), the MAH should conduct and submit the final results of study 1368-0120, an open-label trial in the treatment of recurrent flares in adult patients with generalised pustular psoriasis, conducted according to an agreed protocol by January 2028.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

The main analysis of safety in patients with GPP was based on the results of the pivotal, placebo-controlled Phase II trial 1368 0013, evaluating the efficacy and safety of a single IV dose of spesolimab (with the option of an additional open-label dose on Day 8 if symptoms persisted) in patients with a GPP flare. This trial included 53 subjects (of which 18 were treated with placebo with the option of crossover to spesolimab).

Supportive evidence in patients with GPP is provided from the completed Phase I proof-of-concept trial 1368 0011 and from open-label data from the ongoing GPP trials 1368 0025 and 1368 0027.

Supportive data were also obtained from trials in patients with diseases other than GPP as well as from trials in healthy volunteers. These trials comprised mainly all completed trials with spesolimab or trials with a completed primary analysis period, independent of administration route (intravenous [IV] or subcutaneous [SC]). For the other ongoing trials, the analysis of open-label data focused on the IV administration of spesolimab. Such trials were included if at least 8 patients had received at least one IV dose of open-label spesolimab.

For all ongoing trials included in this submission, an interim analysis with data reported up to a cut-off date of 08 Jan 2021 were included.

For SAEs, the applicant's global safety database, with a cut-off of 31 January 2022, was used as the data source.

Overall, there is data from 401 patients (GPP and non-GPP) and from 226 healthy volunteers who have been treated with at least one dose (IV or SC or both) of spesolimab. Thus, there is data from a total of 627 subjects who have received at least one dose of spesolimab. IV spesolimab was administered to a total of 252 patients and 148 healthy volunteers. This includes dose-finding studies with lower doses.

In the GPP trials, a total of 66 patients received at least one dose of spesolimab (SC or IV). Of these, 64 subjects received at least one dose via the IV route of administration, and 57 patients were exposed to at least one dose of 900 mg IV spesolimab.

In the pivotal trial 1368-0013, 13 patients received two doses and 2 patients received three IV doses of 900 mg spesolimab (including open-label on Day 8 and/or rescue spesolimab thereafter; Table 31).

In the ongoing trial 1368-0025, including 39 patients who all rolled over from trial 1368-0013, spesolimab is administered as s.c. maintenance treatment for prevention of GPP (300 mg q12w or 600 mg q6w). At the interim analysis, nine of the 39 patients had received flare rescue treatment (900 mg IV spesolimab). None of these patients had received more than one dose of rescue treatment within trial 0025. However, seven of them had previously been treated with IV spesolimab within trial 1368-0013. The remaining two had only received placebo in trial 0013.

In the ongoing trial 1368-0027, a total of six patients received one 900 mg dose of IV spesolimab for treatment of a GPP flare up to the cut-off date of 8 January 2021.

Table 31. Disposition of patients in the pivotal trial 1368-0013

1368-0013				
Treatment Day 1	N	Additional treatment on Day 8	N	Number of patients who received spesolimab i.v. rescue after Day 8
Spesolimab (Day 1)	35	Patients who also received open label spesolimab on Day 8 (total ***2*** doses in Days 1-8)	12	2[*)]
		Patients who did **not** receive open label spesolimab on Day 8 (total ***1*** dose in Days 1-8)	23	2
Placebo (Day 1)	18	Patients who received open label spesolimab on Day 8 (total ***1*** dose in Days 1-8)	15	1
		Patients who did **not** receive open label spesolimab on	3	1

		Day 8 (total ***0*** dose in Days 1-8)		
Total	53		53	6

*) these two patients received a total of 3 i.v. doses of spesolimab in the trial

In order to calculate the cumulative time at risk and relative exposure, the applicant defined the residual effect period (REP) as 16 weeks after the last dose of spesolimab. The median time at risk in the GPP trials was 3.1 months and ranged from 0.1 to 8.3 months in any of the Phase II GPP trials. The time at risk for patients in the placebo group was shorter than in the spesolimab groups: median 0.2 months (range 0.2 to 3.0 months). Note that Trial 0013 was the only GPP trial with a placebo control and patients were offered an open-label spesolimab dose at Day 8 if they did not show a sufficient response at this point in time. Across all placebo-controlled trials (i.e. also other diseases), the median time at risk was 2.8 months (range 0.1 to 6.7 months) for IV spesolimab and 3.7 months (range 1.0 to 3.7 months) for SC spesolimab. The time at risk was similar in the placebo groups: median 3.7 months (range 0.2 to 6.5 months).

2.6.8.2. Adverse events

A comparative AE analysis for spesolimab and placebo could primarily be made for week 1 after the first dose as after Day 8, most subjects in the placebo group (15 of 18 subjects) received rescue spesolimab.

For the Week-1 period, most patients reported any AE and a third of patients were reported with investigator-defined drug-related AEs with similar rates in the spesolimab and the placebo groups. Most AEs were mild (RCTC grade 1) or moderate (RCTC grade 2), while AEs of 2 patients in the placebo group (11.1%) and of 6 patients in the spesolimab group (17.1%) were classified as severe (RCTC grade 3). Serious adverse events (SAEs) were reported for 3 patients in the placebo group (16.7%) and 5 patients in the spesolimab group (14.3%). These are further described below. No AEs leading to death occurred in this trial. Altogether, the proportions of patients with any AE or SAE were comparable between the spesolimab and the placebo groups.

The *most frequently reported* events belonged to the SOCs skin disorders, general disorders, infections, and nervous system disorders (Table 32).

The proportions of patients and incidence rates were balanced between the two treatment groups for most SOCs except for infections. The frequencies and incidence rates of infections were higher in the spesolimab group than in the placebo group. All infections were categorized as mild or moderate intensity, but one event (urinary tract infection) in the spesolimab group was an SAE due to hospitalisation of the patient. The patient, however, also had other AEs that required hospitalisation.

The frequencies and incidence rates of skin disorders were balanced between groups and were mainly driven by the PT pustular psoriasis.

Table 32. AEs reported for more than 10% of patients in either treatment group on SOC or PT level up to Week 1 in trial 1368 0013

	Placebo		Spesolimab 900 mg IV	
	N (%)	Rate/100 Pt-yrs	N (%)	Rate/100 Pt-yrs
Number of patients	18 (100.0)		35 (100.0)	
Time at risk (Pt-yrs)	0.3		0.7	
Patients with any AE	12 (66.7)	6446	27 (77.1)	8651
Skin and subcutaneous tissue disorders	9 (50.0)	3612	18 (51.4)	3845
Pustular psoriasis	7 (38.9)	2720	13 (37.1)	2499
General disorders and administration site conditions	5 (27.8)	1756	9 (25.7)	1543
Pyrexia	4 (22.2)	1405	2 (5.7)	314
Infections and infestations	1 (5.6)	292	6 (17.1)	987
Nervous system disorders	3 (16.7)	961	4 (11.4)	655
Dizziness	2 (11.1)	619	0	0
Investigations	2 (11.1)	619	4 (11.4)	664
Musculoskeletal and connective tissue disorders	2 (11.1)	624	4 (11.4)	627
Metabolism and nutrition disorders	2 (11.1)	624	3 (8.6)	485
Blood and lymphatic system disorders	2 (11.1)	641	1 (2.9)	154

Including AEs starting or worsening from start of treatment to Day 8 or EoS, whatever was earlier.
MedDRA version 23.1 was used

On the PT level, the most frequently reported AEs during week 1 were pustular psoriasis, pyrexia, and headache. Pyrexia was reported more frequently in the placebo group than in the spesolimab group. All other PTs were reported for at most 3 patients overall (Table 33).

Table 33. Individual PTs reported within the most common SOCs during week 1 in Study 0013 (n=1 unless otherwise specified)

Placebo	Spesolimab
Skin and subcutaneous disorders	
Pustular psoriasis (n=7)	Pustular psoriasis (n=13), DRESS
General disorders and administration site conditions	
Pyrexia (n=4), Oedema peripheral, Asthenia, Chills	Pyrexia (2), Oedema peripheral (n=2), Fatigue (n=2), Asthenia (n=2), Chills, Infusion site haematoma, Injection site bruising, Non−cardiac chest pain
Infections and infestations	
Streptococcal infection	Urinary tract infection (n=2), Bacteraemia, Bacteriuria, Cellulitis, Herpes dermatitis, Oral herpes, Pustule, Upper respiratory tract infection
Nervous system disorders	
Dizziness (n=2), Headache	Headache (n=3), Presyncope
Investigations	
Alanine aminotransferase increased, Eosinophil count increased, Eosinophil percentage increased, Haematocrit decreased, Haemoglobin decreased, High density lipoprotein decreased, Protein total decreased	C−reactive protein increased (n=2), Blood creatinine increased, Blood pressure increased
Musculoskeletal and connective tissue disorders	
Pain in extremity, Myalgia	Pain in extremity (n=2), Arthralgia
Metabolism and nutrition disorders	
Decreased appetite, Hyperuricaemia	Dehydration, Hypercholesterolaemia, Hyperlipidaemia
Blood and lymphatic system disorders	
Anaemia, erythropenia	Anaemia

Additional analysis up to Week 12 and Week 16 (end or REP) indicated that the exposure-adjusted incidence rates of AEs on PT and SOC level were not increased compared with Week 1. The most commonly reported SOC after spesolimab treatment was still Infections (Table 34).

Table 34. AEs reported for more than 10% of patients in either treatment group on SOC or PT level by spesolimab use in trial 1368-0013 – All events (up to 16 weeks post-dose)

	Initial randomization (censored at first open-label use)[1]				All patients treated with spesolimab, irrespective of randomization (including data after open-label use)[2]	
	Placebo		Spesolimab 900 mg IV		Spesolimab 900 mg IV	
	N (%)	Rate/100 pt-years	N (%)	Rate/100 pt-years	N (%)	Rate/100 pt-years
Number of patients	18 (100.0)		35 (100.0)		51 (100.0)	
Time at risk	0.9		5.6		13.0	
Patients with any AE	13 (72.2)	3083	29 (82.9)	2391	47 (92.2)	1874
Infections and infestations	1 (5.6)	110	12 (34.3)	327	24 (47.1)	263
Blood and lymphatic system disorders	2 (11.1)	310	3 (8.6)	58	4 (7.8)	33
Metabolism and nutrition disorders	2 (11.1)	306	4 (11.4)	82	4 (7.8)	32
Nervous system disorders	3 (16.7)	464	5 (14.3)	102	7 (13.7)	61
Headache	1 (5.6)	150	4 (11.4)	78	5 (9.8)	42
Dizziness	2 (11.1)	226	0	0	0	0
Skin and subcutaneous tissue disorders	9 (50.0)	1857	22 (62.9)	797	33 (64.7)	582
Pustular psoriasis	7 (38.9)	969	18 (51.4)	530	27 (52.9)	367
General disorders and administration site conditions	5 (27.8)	961	9 (25.7)	199	13 (25.5)	128
Pyrexia	4 (22.2)	533	2 (5.7)	36	5 (9.8)	41
Investigations	2 (11.1)	304	7 (20.0)	167	7 (13.7)	62
ALT increased	2 (11.1)	273	1 (2.9)	18	1 (2.0)	8

[1] Patients were censored if they received open-label spesolimab (i.e. for non-responders on Day 8 or as rescue treatment later). For patients who did not receive open-label spesolimab, events are included until Day 113 (i.e. including a 16-week residual effect period after double-blind treatment), EoS, or treatment in the extension trial, whichever was earlier.

[2] This includes patients who received at least 1 dose of spesolimab (i.e. double-blind, open-label on Day 8, or as rescue treatment later). Events are included from first spesolimab dose until 16 weeks after last spesolimab administration, EoS, or treatment in the extension trial, whichever was earlier.

MedDRA version 23.1 was used

Acknowledging the low number of patients receiving more than one dose of spesolimab in this study (2 doses n=13; 3 doses n=2), overall, the exposure-related incidence rates of AEs on PT and SOC level did not increase with increasing number of doses of spesolimab.

Other GPP trials

The overall pattern of adverse events in other trials in patients with GPP (as IV flare treatment or SC maintenance treatment), were generally in line with Week 1 data in trial 0013. Thus, most patients treated with spesolimab reported at least one AE, while the number of patients with severe or serious AEs was low. In placebo-controlled trials, the overall profile (number of AEs, treatment-related AEs, severe and serious AEs) was comparable between treatment groups. AEs were most commonly reported within dermatological disorders and infections. The reported AEs of pustular psoriasis likely represented the reporting of the initial GPP flare, or further flares in the maintenance trials.

Other dermatological indications

The safety profile of spesolimab in all available PPP and AD trials was generally comparable with the profile in patients with GPP, with a low number of severe or serious cases. Common adverse events

across trials were (worsening of) the disease under study and other skin disorders, uncomplicated infections, and injection site reactions.

Across trials, AEs in approximately 30-50% of patients were considered drug-related by the investigator, with no clear differences between the placebo-treated and spesolimab-treated groups.

Ulcerative colitis

In the placebo-controlled trials 0005 and 0010, the proportions of patients reported with at least 1 AE were comparable between the spesolimab groups and the placebo groups. The proportions of patients with AEs assessed as drug-related by the investigator were higher in the spesolimab groups (17% to 26%) than in the placebo groups (9-14%). Adverse events were of mild or moderate intensity for the majority of patients. The most frequently reported SAE was ulcerative colitis, and was reported with comparable frequencies across the treatment groups. On the PT level, the most frequently reported AEs were ulcerative colitis, anaemia, nasopharyngitis, rash, acne, eczema, and headache.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

Except for SAEs reflecting worsening of the underlying condition, the reported SAEs across studies were of various nature and the individual PTs were often reported only in single patients. Most SAEs were not considered treatment-related, including SAEs within the user-defined adverse event categories (UDAECs). Among the latter, only the infections and the hypersensitivity reactions (excluding DRESS), were assessed as treatment-related, as there were other risk factors or alternative explanations for the remaining UDAEC reactions.

For SAEs, the applicant's global safety database, with a cut-off of 31 January 2022, was used as the data source. At the 31 January 2022 cut-off, across studies a total of 164 SAEs were reported in 119 patients.

Of these 164 SAEs, 77 were related to the disease under study, pre-existing co-morbidity or unrelated accident/injury.

Across studies, there was a total of 27 SAEs of infection, of which 4 occurred after placebo and 2 after blinded treatment. These cases are described in section on UDAECs.

There were 11 SAEs describing malignancies or neoplasms, nine of which were diagnosed in patient who had been treated with spesolimab. These cases are described in section on UDAECs. None of the cases were considered treatment-related.

A total of 13 SAEs reported from spesolimab trials were coded with MedDRA PTs from the SMQs Hypersensitivity (narrow), Angioedema (narrow) or Anaphylactic reaction (narrow): Infusion-related reaction (2), Dermatitis exfoliative generalised (2), Drug eruption (2), Henoch-Schönlein purpura (1), Dermatitis atopic (1), Hypersensitivity (1), Angioedema (1), Circulatory collapse (1) and DRESS (1). One of the 2 events of Dermatitis exfoliative generalised and the event of Dermatitis atopic were manifestations/exacerbations of the underlying disease. The case of DRESS and one case of Drug eruption are described in section on UDAECs. These events had other plausible explanations (concomitant medications). Both SAEs of infusion-related reaction and the SAE hypersensitivity occurred after placebo. In the case of suspected angioedema, the onset latency of 6 days and event resolution without discontinuation of the suspected medication. In the case of circulatory collapse, the event occurred after and over-night fast and before administration of study treatment. In the case

describing drug eruption and palpitations, there was an immediate temporal association to COVID-19 vaccination.

There were 7 SAEs within neurological disorders, including 3 cases reporting Guillain-Barré Syndrome (GBS) or peripheral neuropathy. An expert panel, however, assessed two of these cases as not being GBS. The third case was considered GBS at low level certainty. In this latter case, which was fatal, Covid-19 infection was an alternative explanation. The remaining SAEs of neurological disorders were heterogenous in nature and either plausibly explained by pre-existing disorders (seizure in a patient with a known history of epilepsy and hypertensive encephalopathy in a patient with untreated hypertension) or were incidental, idiopathic events (VIth nerve paralysis and Bell's palsy).

There were 7 SAEs of thromboembolic events. The reported events were heterogeneous in nature, occurred in variable temporal association to initiation of trial medication and in a pattern consistent with what would be expected during longer-term observation of the trial populations, and were all assessed as unrelated to trial medication by the investigator. Cardiovascular risk factors (including in 1 case the underlying ulcerative colitis itself) were reported in all cases.

There were 5 SAEs relating to depression or suicidality. Most of the above cases appear to describe exacerbation of known pre-existing psychiatric illness in the context of worsening of the dermatological disease under study.

There were 5 SAEs of anaemia or iron deficiency anaemia. Four of these SAEs occurred in patients with ulcerative colitis, including 3 patients who had received spesolimab and one patient who received placebo. Onset latency from initiation of trial treatment ranged from approximately 2 weeks to 20 months. The investigator considered the event to be unrelated to trial medication in each of these cases, and the anaemia was expressly attributed to the underlying inflammatory condition of ulcerative colitis in 3 cases. Anaemia was also reported as medical history in 2 of these cases. The 5th SAE was worsening of pre-existing anaemia preceded by menorrhagia, and occurred in a female patient with GPP who had anaemia reported as medical history.

There were an additional 13 isolated SAEs that could not be grouped together. In each of these cases, the investigator considered that there was no reasonable possibility for a causal relationship between trial medication and the event.

Deaths

In the clinical programme of spesolimab in GPP, no death was reported. In the entire spesolimab clinical trial programme, 1 fatal case occurred in a patient with ulcerative colitis participating in trial 1368-0017 (maintenance treatment with SC spesolimab 600 mg q6w). This patient was reported with SARS-CoV-2 pneumonia and Guillain-Barre syndrome (GBS) 20 days after the last administration of trial medication. The patient was hospitalized and died 12 days later. The event occurred in a hospital different from the investigational site and therefore, the complete detailed information was not directly available to the trial investigator and sponsor. Based on the information received, the sponsor concluded that the clinical course in this patient may be reflective of a Covid-19 infection with neurological complications and that a contribution of spesolimab seems unlikely.

A second fatal case was reported within the spesolimab compassionate use programme, and occurred in a 7x-year-old male patient, who was treated with a single dose spesolimab for a GPP flare. The patient rapidly deteriorated and died three days after administration of spesolimab. The patient had multiple co-morbidities, including COPD, type II diabetes mellitus, peripheral arterial disease, atrial fibrillation, cardiac pacemaker insertion, coronary artery disease, and squamous cell bronchial carcinoma that was in remission. The patient was taking multiple chronic medications. The patient had

signs of renal impairment before administration of spesolimab. Initially, the cause of death was reported as hypoxia and aspiration of blood from an oral bleeding, however, this was later revised as the oral bleeding (due to mucositis) was minimal and unlikely to have caused death by aspiration. Due to a temporal association between administration of spesolimab and a raise in liver transaminases, the dermatologist suspected liver injury to be causally related to spesolimab. The critical care specialist, however, assessed the cause of death rather as multi-organ failure, possibly due to lactic acidosis or sepsis, with no evidence for a hepatic cause of death. Overall, the case is highly confounded by the patient's complex and grave medical history, his age and co-medications.

Adverse events of special interest – User-defined Adverse Event categories UDAECs

Across studies in different diseases, SMQs and BI-customized MedDRA Queries (BIcMQs) were defined, which collapse multiple MedDRA PTs into clinically relevant categories. These were selected in accordance with the expected safety profile of spesolimab in the indication of GPP and other potential indication-specific symptoms.

At time of submission, all studies were analysed for the following user-defined adverse event categories (UDAECs):

- Systemic hypersensitivity reactions
- Infections (severe, serious or opportunistic)
- Malignancies
- Cardiac safety
- Hepatic injury

Further, for the GPP trials 1368-0013, 1368-0025, and 1368-0027, the following AESIs were defined in the clinical trial protocols (CTPs):

- Hepatic injury, defined by the following elevations of hepatic laboratory parameters:
  -- AST and/or ALT and/or AP ≥3×ULN plus 2×baseline value, combined with total bilirubin ≥2×ULN plus 1.5×baseline value, measured in the same blood draw sample
  -- ALT and/or AST elevations ≥10×ULN
- Systemic hypersensitivity, including infusion reactions and anaphylactic reactions
- Severe infections (according to Rheumatology common toxicity criteria [RCTC] grading 3 or 4)
- Opportunistic and mycobacterium tuberculosis infections

For the GPP trial 1368-0011 and the healthy volunteer trials, hepatic injury was the only protocol-specified AESI.

Systemic hypersensitivity reactions

Studies in GPP

In the pivotal **Trial 0013,** one patient was reported with hypersensitivity in the placebo group *before* any spesolimab infusion, and 5 patients were reported in the spesolimab group after any (double-blind or open-label) spesolimab infusion, with AEs belonging to one of the subsearch categories angioedema or hypersensitivity, while no cases in the grouping of anaphylactic reactions were reported (Table 35).

Two events initially reported as DRESS were serious, one of them was life-threatening. Independent external expert assessment by the principal collaborator of the RegiSCAR consortium was undertaken in both cases. In summary, in case 1, the RegiSCAR score and temporal course were not consistent with DRESS related to spesolimab. Upon follow-up, the SAE term was changed to Drug eruption. In case 2, while DRESS was possible, on the basis of rechallenge, spiramycin is considered a plausible

alternative explanation. Based on a post-hoc AE analysis using the SMQ DRESS, no further possible DRESS cases were identified in this trial or any other spesolimab trials up to the cut-off date of 08 Jan 2021.

Table 35. Hypersensitivity events in trial 1368-0013

UDAEC PT	Up to Week 1 (double-blind period)				Patients initially randomized to spesolimab (censored at first open-label use)[1]		All patients treated with spesolimab, irrespective of randomization (including data after open-label use)[2]	
	Placebo		Spesolimab		Spesolimab		Post any spesolimab[2]	
	N (%)	Rate/100 Pt-yrs	N (%)	Rate/100 Pt-yrs	N (%)	Rate/100 Pt-yrs	N (%)	Rate/100 Pt-yrs
Number of patients	18 (100.0)		35 (100.0)		35 (100.0)		51 (100.0)	
Hypersensitivity "all"	1 (5.6)	289.9	3 (8.6)	478.5	4 (11.4)	87.9	5 (9.8)	42.3
DRESS	0	0	1 (2.9)	154.1	2 (5.7)	41.8	2 (3.9)	15.9
Urticaria	0	0	1 (2.9)	154.1	1 (2.9)	20.0	2 (3.9)	15.9
Eye oedema	0	0	1 (2.9)	154.1	1 (2.9)	20.9	1 (2.0)	7.8
Dermatitis	0	0	0	0	1 (2.9)	20.8	1 (2.0)	7.8
Allergic dermatitis	1 (5.6)	289.9	0	0	0	0	0	0

[1] Patients were censored if they received OL spesolimab (i.e. on Day 8 or as rescue treatment later). For patients who did not receive OL spesolimab, events are included until Day 113 (i.e. including a 16-week REP after double-blind treatment), EoS, or treatment in the extension trial, whichever was earlier.

[2] This includes patients who received at least 1 dose of spesolimab (i.e. double-blind, OL on Day 8 or as rescue treatment later). Events are included until 16 weeks after last spesolimab administration, EoS, or treatment in the extension trial, whichever was earlier.

In **Trial 0011**, 3 patients had AEs belonging to the sub-search category hypersensitivity. The reported PTs were eczema for 2 patients (non-serious, moderate intensity, not related) and infusion-related reactions for 1 patient (non-serious, mild intensity, related).

In **Trial 0025**, 3 patients had AEs belonging to the sub-search category hypersensitivity (all non-serious), while no cases in the groupings of angioedema, infusion reactions, or anaphylactic reactions were reported. No AESI of hypersensitivity was reported.

Studies in other diseases

AEs grouped to UDAEC systemic hypersensitivity were reported in all non-GPP trials, mostly with unspecific PTs like rash or eczema, and mostly in similar frequencies across treatment groups in the placebo-controlled trials. An exception was trial 1368-0016 in PPP, where the frequency of patients with hypersensitivity events was higher in a low-dose spesolimab treatment regimen than in all other treatment groups, mainly with PTs eczema and injection site reaction.

In study 0005 (UC) one SAE of was reported as 'infusion-related reaction' but was listed as 'anaphylaxis' in the list of AESIs and was classified as life-threatening by the investigator. This case was reported in a patient treated with placebo.

The occurrence of hypersensitivity events was also analysed in relation to ADA and NAb formation. In short, the review concluded that it was unlikely that the hypersensitivity events were related to ADA/NAb development. This is further described below.

Infections (severe, serious, opportunistic)

The systematic searches for infections focused on severe, serious, opportunistic, and tuberculosis infections. In the pivotal **trial 0013,** the number of such infections was low. In total, 3 patients were reported, 1 in the placebo group following open-label spesolimab infusion (i.e. after 1 spesolimab dose) and 2 in the spesolimab group (1 each before and after open-label spesolimab infusion). The PTs were urinary tract infection, influenza (both classified as serious due to hospitalisation), and non-serious latent tuberculosis (which was also reported as AESI). None of these infections were graded as severe (RCTC Grade ≥3). The patient with serious urinary tract infection was also reported with DRESS on the same day as the urinary tract infection.

Overall, a higher proportion of patients with infections was noted after spesolimab than placebo treatment. Nevertheless, infections were generally mild to moderate and non-serious. There was no indication for a higher proportion of patients with severe, serious, or opportunistic infections in spesolimab-treated patients.

At the 31 January 2022 cut-off, across all studies, the following 21 serious infections (SAEs) were reported during or after treatment with spesolimab: pneumonia (3 SAEs), COVID-19 pneumonia (2 SAEs), staphylococcal bacteraemia (2 SAEs), COVID-19 (2 SAEs), urinary tract infection (2 SAEs), and 1 SAE each of sepsis, paraspinal abscess, influenza, cellulitis, device related infection, appendicitis, encephalitis viral, hepatitis C, endocarditis and gastroenteritis. Four SAEs of infection occurred during or after placebo treatment, including 1 SAE each of cholecystitis, cholecystitis acute, clostridium difficile colitis and peritonsillar abscess. Trial medication is currently blinded for 1 SAE each of cellulitis and pneumonia.

For the 21 SAEs in spesolimab-treated patients, onset latency from trial medication initiation ranged from 2 days to more than 14 months (median, 147 days). Onset latency for the serious infections reported from placebo-treated patients ranged from 20 days to 5.5 months (median, 149 days). The only serious infection (MedDRA PT) reported more than twice was pneumonia (4 SAEs). In addition, 2 SAEs of COVID-19 pneumonia were reported. This includes the reports of pneumonia, which were heterogeneous in terms of the reported clinical context, pathogen and temporal association. The higher number of serious infections reported from patients whose (last) prior treatment was spesolimab can be explained by the substantially higher number of patients who were randomized to spesolimab, patients who received spesolimab as rescue treatment in accordance with respective trial procedures, and the longer follow-up of spesolimab-treated patients in uncontrolled trials or trial periods. Confounding risk factors for infection such as underlying diabetes mellitus, GPP flares, and/or hospitalisation were reported in several cases. No SAEs from the SMQ Opportunistic infections (narrow) have been reported.

Opportunistic infections

No cases of opportunistic infections were reported in any of the trials when defined as narrow SMQ. A search for opportunistic infections using broad SMQ resulted in a few cases in almost all GPP trials. Frequencies were similar between treatment groups in the placebo-controlled part of trial 1368-0013.

The most frequently reported PT in GPP trials was influenza (3 patients treated with spesolimab in trial 1368-0013). No cases of herpes zoster were reported in GPP trials. One case of influenza was serious (hospitalisation). None of the other opportunistic infections in GPP trials were SAEs or severe (defined as RCTC grade 3 or 4).

In trials in other dermatological diseases, the most frequently reported PTs were herpes zoster (4 patients in trial 1368-0016, 1 [2.3%] in the placebo and 3 [2.0%] in the spesolimab treatment group), oral herpes (3 patients overall: 1 patient in trial 1368-0015 and 2 patients in trial 1368-0016), COVID-

19 (3 patients in trial 1368-0016), erysipelas (2 patients overall, 1 patient each in trials 1368-0016 and 1368-0032), and staphylococcal skin infection (2 patients in trial 1368-0032, 1 each in the placebo [5.6%] and spesolimab [3.0%] group); all other PTs were single occurrences. None of the opportunistic infections were serious or severe.

In the UC trials, the most frequently reported PTs were herpes zoster (1 patient each in trials 1368-0005, 1368- 0017 [flare treatment], and 1368-0017 [re-induction]; all in the spesolimab groups) and influenza (1 patient each in trials 1368-0005 and 1368-0017 [re-induction]; all in the spesolimab groups), all other PTs were single occurrences and, in many cases, related to the underlying disease. The case of clostridium difficile colitis was both serious and severe. None of the other opportunistic infections were SAEs or severe.

Malignancies

Per cut-off date of the day 121 response, 11 SAEs in 11 cases describing malignancies or neoplasms were reported. The events were reported from trials in the indications PPP (6 SAEs), ulcerative colitis (3 SAEs) and GPP (2 SAEs).

Nine malignancies / neoplasms were diagnosed in patients who were receiving or had previously received spesolimab, including colon cancer (2 patients), squamous cell carcinoma of skin (2 patients), adenocarcinoma of colon, basal cell carcinoma, breast cancer, large intestine polyp and adenocarcinoma (likely lung cancer). Onset latency from trial medication initiation ranged from 1 month to more than 2 years (median, 77 days). One case each of prostate cancer and carcinoid tumour of the small bowel were reported from patients treated with placebo. In these 2 cases, onset latency from trial medication initiation was 12 weeks and approximately 8 months, respectively. Risk factors were identifiable in all cases occurring during or after spesolimab treatment, including underlying ulcerative colitis in 2 cases of colon cancer, long-term sunlight exposure in the case of basal cell carcinoma and 1 of the cases of squamous cell skin carcinoma, acrodermatitis continua of Hallopeau in the other case of squamous cell skin carcinoma, current or former smoking in the case describing adenocarcinoma (presumably lung cancer) and 1 of the cases of colon cancer, family history and gastric polyps in the case of large intestine polyp, and breast cancer history in the case of breast cancer. The reported malignancies mostly corresponded to the location of the disease under study (e.g. all cancers diagnosed in ulcerative colitis studies were gastrointestinal cancers; all skin cancers were diagnosed in patients with GPP or PPP), suggesting that disease- or trial-specific diagnostic procedures might have increased the likelihood for incidental diagnosis of the respective cancer.

None of the reported malignancies were considered related to trial medication and there was no discernible pattern to suggest a causal relationship between spesolimab exposure and the development of the reported malignancies. All of the patients reporting malignancies while taking spesolimab had underlying relevant risk factors.

Cardiac safety

A broad scope of the UDAEC 'Torsade the point' was in the pivotal trial 0013, reflected by the report of a (non-serious) syncope in patient. 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. There were no reports of AEs within the UDAEC Torsade de points in the other GPP studies.

There were 1 or 2 cases per trial in trials 1368-0015, 1368-0016, and 1368-0005. In all of the cases, the PT was (non-serious) syncope, except one serious case grouped to 3-point MACE (PT cerebral infarction). Both parents of the patient had a history of stroke. The event was assessed as not drug-related by the investigator and did not lead to treatment discontinuation.

Overall, there is no indication for an adverse effect of spesolimab on the cardiovascular system.

Hepatic injury

In the pivotal trial 0013, one patient in the spesolimab group was reported with AESI hepatic injury by the investigator (PTs DRESS and DILI) after 1 spesolimab dose. The hepatic injury was considered serious due to hospitalisation and was assessed as drug-related by the investigator. Despite not meeting RegiSCAR criteria for DRESS, the patient had evidence of an acute drug reaction resulting in hepatic injury in the form of DILI. However, in light of the time course of transaminase elevations and the patient's history of prior reaction to cephalosporins, the co-administered cefuroxime is a potential suspect medication for having caused DILI in this case.

No patients were reported within AESI hepatic injury in GPP trials 0011 or 0025.

In almost all trials, a few patients (1-3 per treatment group) were reported 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 patients had a marked elevation in AP or total bilirubin, therefore no patient was categorized as a potential Hy's law case.

2.6.8.4. Laboratory findings

In the Pivotal trial 0013, the evaluation of clinical laboratory values focused primarily on the time period of up to Week 12 (including REP, but censored at use of any open-label spesolimab). A total of 6 patients were identified with markedly elevated ALT or AST values, all of them before open-label spesolimab use: 3 patients (16.7%) in the placebo group (all with an elevation of ≥3x ULN but <5x ULN) and 3 patients (8.6%) in the spesolimab group (2 with an elevation of ≥3x ULN but <5x ULN and 1 with an elevation ≥10x ULN (this patients is described above as DILI). None of these patients had a marked elevation in AP or total bilirubin, therefore no patient was categorized as a potential Hy's law case.

No marked effects were observed in the other GPP trials.

In the PPP trial 0015, a total of 2 patients were identified with markedly elevated ALT or AST values: 1 patient (4.8%) in the placebo group (with an elevation of ≥5x ULN but <10x ULN) and 1 patient (5.3%) in the 300 mg spesolimab group (with an elevation of ≥3x ULN but <5x ULN). In PPP trial 0016, 1 patient (4.5%) in the medium-high dose group was reported with an elevation of ≥3x ULN but <5x ULN. In the AD trial 0032, during the first 16 weeks of the trial, no patient was identified with markedly elevated ALT or AST values. During the open-label part of the trial, 3 patients (14.3%) were reported with elevations: 2 patients with an elevation of ≥3x ULN but <5x ULN and 1 patient with an elevation of ≥5x ULN but <10x ULN. In the UC trial 0005 2 patients were identified with markedly elevated ALT or AST values: 1 patient (4.3%) in the placebo group and 1 patient (4.2%) in the spesolimab group, both with an elevation of ≥3x ULN but <5x ULN. None of these patients had a marked elevation in AP or total bilirubin, therefore no patient was categorized as a potential Hy's law case.

In the UC trial 0004, there were 4 patients (50.0%) with possibly clinically significant abnormality (PCSA) values developed during treatment. However, medical review confirmed that no clinically relevant trends in any laboratory variables were observed.

Trials 1368-0001 and 1368-0002 in healthy volunteers included an in-depth ECG evaluation and the other trials in healthy volunteers included routine ECG measurements. Exposure-response analyses of spesolimab plasma concentrations and relationship to QTcF, QT interval, and heart rate change from baseline were performed in study 0001 and Study 0002. The data do not indicate relevant effects of spesolimab on QTc interval.

Safety information supporting the proposed label

To identify ADRs for spesolimab in patients with GPP, the complete set of available safety data for completed and ongoing trials at the cut-off date (08 Jan 2021) were considered.

The complete dataset was screened for designated medical events, but the PTs identified did not lead to the identification of any ADR due to the existence of relevant confounders. All laboratory data were analysed and reviewed.

In addition, double-blind placebo-controlled trials were analysed systematically for imbalances between the spesolimab and the placebo treatment group. The focus was on the 1368-0013 trial and other trials of at least similar size with regard to patients treated in the verum group.

Specifically, the safety results for the spesolimab and placebo groups of trial 1368 0013 at Week 1 and Week 12 were compared. In addition, data from placebo-controlled, double-blind clinical trials with at least 35 patients treated with spesolimab in other diseases were taken as supportive evidence (trial 1368 0005 in UC, trial 1368 0015 in PPP, trial 1368 0016 in PPP [up to Week 16], and trial 1368 0032 in AD [up to Week 16]). A screening algorithm with numerical thresholds was applied to each PT using the numerical criteria outlined in Table 36:

Table 36. Screening algorithm for identification of potential ADRs

Trials to be considered			**Data to be considered**	
GPP pivotal trial (1368-0013)			Week 1	AE frequency for spesolimab > than for placebo
			Week 12	AEs in ≥3 patients for spesolimab + rate difference >0 for spesolimab vs. placebo
Non-GPP double-blind, placebo-controlled trials[1]	≥100 patients treated with spesolimab	(1368-0016 Week 16)	AE frequency ≥5% + rate ratio ≥1 for spesolimab vs. placebo AE frequency ≥2% + rate ratio ≥2 for spesolimab vs. placebo	
	≥35 to <100 patients treated with spesolimab	(1368-0005, -0015, -0032 Week 16)	AE frequency ≥5% + rate ratio ≥2 for spesolimab vs. placebo	
All trials included in the MAA dossier			AEs, Designated Medical Events, UDAECs	

[1] Trial or trial period completed

All terms identified by this screening algorithm were subject to further integrated medical evaluation, considering all sources of safety data, such as individual case medical content, seriousness, investigator-reported relatedness, and, if applicable, clinical laboratory and vital sign data.

Based on these methods the following reactions were identified as potential ADRs for spesolimab in the treatment of GPP flares:

- urinary tract infection,
- upper respiratory tract infection,
- pruritus,
- injection site reactions (including injection site erythema, injection site swelling, injection site pain, injection site induration, and injection site warmth),
- and fatigue.

No trial studying the effects on the ability to drive or operate machinery were performed. Based on available safety data from the completed and ongoing trials with spesolimab, no indication of an increased frequency of AEs related to dizziness, fall, road accidents or of low blood pressure recorded as vital signs was observed. Therefore, it was concluded that spesolimab has no influence on the ability to drive and use machines.

A search of the clinical trial data showed that no cases of overdose of spesolimab (i.e. dose higher than foreseen in the protocol) were reported. Safety results from a higher dose than the therapeutic dose of 900 mg IV (plus an optional 900 mg dose 1 week after the initial dose) are available from trial 1368-0002 in healthy volunteers, where 6 healthy volunteers received a single IV dose of spesolimab 20 mg/kg body weight (translating into administered doses of 1448 mg to 2108 mg) and another 6 volunteers received multiple doses (4 times) once weekly spesolimab IV 20 mg/kg bodyweight (translating into total doses administered of 1492 mg to 6896 mg). There were no relevant differences in frequencies of subjects with local tolerability findings between these and the lower dose treatment groups, and no dose-dependency was observed. One drug-related injection-site reaction AE was reported in the highest dose spesolimab treatment groups of this trial.

Two pregnancies were reported across all trials. One of the patients was treated with spesolimab in trial 1368-0032 (AD) and reported a miscarriage approximately 11 weeks after the last administration of trial medication, at a gestational age of approximately 12 weeks. She did not report any abnormalities during the course of pregnancy. It was not known if there were any causes known for the miscarriage. It was not known if reported baseline condition trichomoniasis may have triggered a miscarriage. It is unknown whether there was a family history of miscarriage. The patient used condoms as contraception during trial before she got pregnant. The patient reported medical marijuana intake. It was confirmed that the last pregnancy was normal with a spontaneous delivery around the estimated delivery date. The second patient was treated with spesolimab in trial 1368-0016 (PPP) and was reported with maternal exposure during pregnancy; however further dates and outcomes were not available. As a precautionary measure, it is recommended to avoid the use of spesolimab in pregnancy, unless the expected clinical benefit clearly outweighs the potential risks.

2.6.8.5. Safety in special populations

Adverse event data from the pivotal trial 1368-0013 were analysed by different subgroups. No patient with hepatic impairment was included in the trial, therefore the analysis by hepatic impairment status was not performed. There were only 2 patients older than 65 years, therefore the analysis by age was not performed. For other subgroups (sex, race [Asian/White], BMI, GPPGA score at baseline, mutation status in IL-36RN, renal function [normal renal function/mild renal impairment]) the trends in frequencies and incidence rates of most types of AEs were generally consistent with those of the overall population of the trial, with the limitation of small group sizes for some subgroups.

Across trials, the number of patients ≥65 years was small. Table 37 gives an overview of exposure across all placebo-controlled trials or trial periods by age group (<65/≥65 years). Table 38 gives an overview of exposure in the uncontrolled trials/trial periods by age group (<65/≥65 years).

Table 37. Placebo-controlled trials/trial periods: Overview of exposure by age group

Trial number	Condition/ route of administration	Number of patients			
		Age group <65 years		Age group ≥65 years	
		Placebo	Spesolimab	Placebo	Spesolimab
1368-0013 (up to Week 12)	GPP/i.v.	18	33	0	2
1368-0015 (up to end of residual effect period)	PPP/i.v.	20	39	0	0
1368-0016 (up to Week 16)	PPP/s.c.	32	92	11	17
1368-0032 (up to Week 16)	AD/i.v.	18	30	0	3
1368-0005 (up to Week 12)	UC/i.v.	22	69	1	5
1368-0010 (up to end of residual effect period)	UC/i.v.	7	15	0	0

Table 38. Uncontrolled trials/trial periods: Overview of exposure by age group

Trial number	Condition/ route of administration	Number of patients	
		Age group <65 years	Age group ≥65 years
1368-0013 (overall spesolimab)	GPP/i.v.	49	2
1368-0011	GPP/i.v.	7	0
1368-0025 (flare treatment)	GPP/i.v.	9	0
1368-0025 (maintenance treatment)	GPP/s.c.	39	0
1368-0027 (flare treatment)	GPP/i.v.	6	0
1368-0027 (maintenance treatment)	GPP/s.c.	6	0
1368-0004 (on-treatment period)	UC/i.v.	7	1
1368-0017 (re-induction period)	UC/i.v.	53	4
1368-0017 (first flare treatment)	UC/i.v.	16	0
1368-0016 (including post-Week 16 data)	PPP/s.c.	122	25
1368-0032 (re-allocation treatment period)	AD/i.v.	21	1

Data included up to end of REP, last contact date, first treatment in next trial period or extension trial, or submission cut-off (08 Jan 2021), whatever was earlier.

In placebo-controlled trials/trial periods, the overall frequency of AEs was generally similar in older and younger patients in both treatment groups. The frequencies of treatment-related AEs as well as of AEs leading to treatment discontinuation were also similar in older and younger patients in both treatment groups. Rates of serious and severe AEs tended to be numerically higher among older than younger patients. This was, however, apparent in both treatment arms in placebo-controlled trials/trial periods. Moreover, the serious or severe AEs reported from patients ≥65 years of age were mostly disorders that would be expected to occur more frequently in an older population. Thus, overall, no evidence of an increased frequency, greater severity, or different pattern of adverse events in older patients compared with younger patients was identified where a causal role of spesolimab might be reasonably suspected. The observed differences were plausibly explained by the age difference itself.

2.6.8.6. Immunological events

Immunogenicity of spesolimab was tested through sampling and analysis for anti-drug antibodies (ADAs) in the healthy volunteer trials. In the trials in patients with GPP and other diseases, ADAs and

neutralising antibodies (NAbs) were tested. The analysis methods for ADAs and NAbs are described in the PK assessment report.

Population PK analysis indicated that ADA titres > 4000 may lead to decreased plasma concentrations of spesolimab (see PK assessment).

In most trials, the frequency of patients positive for ADAs was relatively high. In GPP trials, following administration of IV spesolimab 900 mg, 46% patients developed ADA by Week 12-17 with median onset time of 2.3 weeks. A total of 24% of patients had a maximum ADA titre greater than 4000. Females appeared to have higher immunogenicity response. The ADA incidence rate and percentage of patients with titre greater than 4000 were 58% and 30% in females, and 24% and 12% in males, respectively. The maximum ADA titres were observed to be lower in patients who received 2 doses of IV spesolimab within the first 8 days compared with patients who received only 1 IV dose. Following administration of IV and SC administration of spesolimab, 64% patients developed ADA while 28% patients had a maximum titre greater than 4000 in patients who rolled over from 1368-0013 to 1368-0025. Females continued to have higher immunogenicity response. The ADA incidence rate and percentage of patients with titre greater than 4000 were 75% and 38% in females, and 42% and 8% in males, respectively. In patients with GPP, the NAb status appeared to be associated with the titre value. All ADA samples with titre value greater than 4000 were also NAb positive.

Compared with patients with GPP, the formation of ADA appeared later in patients without GPP with a median onset time ranging 8-11 weeks after dosing across trials, similar to healthy volunteers. In patients with PPP, the immunogenicity response was comparable between IV and SC administration, as well as between female and male patients. After IV spesolimab, the ADA incidence trended higher in the females compared with males in patients with AD or UC. In patients with UC, concomitant use of immunosuppressants or oral corticosteroid appeared to decrease the formation of ADA. The ADA incidence rate was 21% in patients on spesolimab alone, compared with 6% or 9% in patients on background treatments of immunosuppressants and oral corticosteroid, respectively.

Across studies, the frequency and incidence rate of hypersensitivity events was suggested to be comparable before and after ADA/NAb development (Figure 29). Many of the reactions reported as hypersensitivity reactions were considered unlikely to be related to ADA or NAb formation, due to e.g. type of event and/or timing of the event.

An increased rate of hypersensitivity events after detection of ADAs was seen in study 0016 (in PPP) and in study 0032 (in AD). In study 0016, apart from some serious events that were considered unrelated to spesolimab (and occurring before detection of ADAs) the nature of the events was overall similar before and after ADA development, while the rate of primarily eczema and rash increased after detection of ADAs. These reactions were generally mild to moderate in intensity. In study 0032 (patients with AD), the increase in hypersensitivity reactions after development of ADAs was primarily due to an increased rate of events of AD.

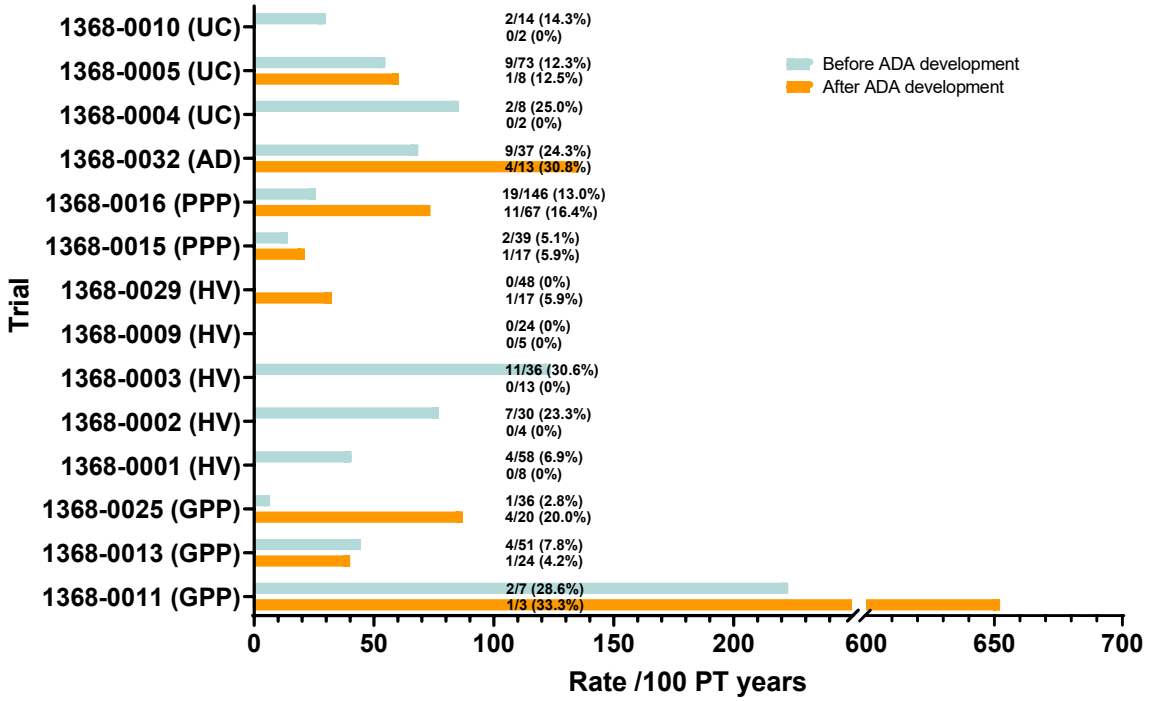


Figure 29. Summary of proportion and incidence rate of hypersensitivity events by ADA development across spesolimab trials

2.6.8.7. Safety related to drug-drug interactions and other interactions

No formal drug interaction trials with spesolimab have been performed, which the applicant suggests is justifiable for the MAA of spesolimab for the short-term treatment of patients with a GPP flare.

Based on the immune-modulating nature of spesolimab, attenuated live vaccines should not be given concurrently.

Limited data indicate no worsening of the safety profile of spesolimab with concomitant administration of other immunosuppressants, other than what would be expected from the added medication by itself. In study 0013, there were restrictions regarding the concomitant use of medications for the treatment of GPP, in order not to confound the efficacy and safety evaluation. However, during the trial, investigators could treat patients with any treatment of their choice (escape medication) if GPP worsened. Such use occurred in a total of 19 subjects; 9 in the placebo arm and 10 in the spesolimab arm. Based on these analyses (Use of immunosuppressants, yes/no), there were no apparent differences in the AE profile (Table 39).

In the UC trials, almost all patients used concomitant immunosuppressants, and within-study comparisons of other immunosuppressants yes/no cannot be reliably made (Table 40). However, across studies in all indications, the safety profile of spesolimab appeared similar and manageable without indications of an increased rate of e.g. Serious infections.

Limited data from study 0032 (AD) showed an increased rate of hypersensitivity reactions and infections in patients with concomitant immunosuppressants (n=11) than without (n=40). However, the increased rate with concomitant immunosuppressants was seen to the same extent in patients treated with placebo (n=7) as in patients treated with spesolimab (n=4).

Table 39. Summary of exposure to concomitant immunosuppressive therapy in trial 0013

	Trial 1368-0013 Week 1[1]		Trial 1368-0013 (any spesolimab) [2]
	Placebo N (%)	Spesolimab N (%)	Spesolimab N (%)
Number of patients	18	35	51
Subpopulation taking immunosuppressants	9 (100.0)	10 (100.0)	19 (100.0)
Any AE	6 (66.7)	8 (80.0)	18 (94.7)
AE leading to discontinuation	0	0	0
Investigator-defined drug-related AE	4 (44.4)	5 (50.0)	13 (68.4)
SAE	2 (22.2)	2 (20.0)	5 (26.3)
SOC Infections and infestations	0	2 (20.0)	8 (42.1)
UDAEC Infections	0	0	0
UDAEC Hypersensitivity	0	1 (10.0)	1 (5.3)
Subpopulation not taking immunosuppressants	9 (100.0)	25 (100.0)	32 (100.0)
Any AE	6 (66.7)	19 (76.0)	29 (90.6)
AE leading to discontinuation	0	0	0
Investigator-defined drug-related AE	2 (22.2)	7 (28.0)	19 (59.4)
SAE	1 (11.1)	3 (12.0)	8 (25.0)
SOC Infections and infestations	1 (11.1)	4 (16.0)	16 (50.0)
UDAEC Infections	0	1 (4.0)	3 (9.4)
UDAEC Hypersensitivity	1 (11.1)	2 (8.0)	4 (12.5)

1 Including AEs starting or worsening from start of treatment to Day 7 or EoS, whatever was earlier.
2 This includes patients who received at least 1 dose of spesolimab (i.e. double-blind, open-label on Day 8, or as rescue treatment later). Events are included from first spesolimab dose until 16 weeks after last spesolimab administration, EoS, or treatment in the extension trial, whichever was earlier. Events included in the Week 1 randomized period are duplicated.

Table 40. Summary of exposure to concomitant immunosuppressive therapy in UC trials

	Trial 1368-0005		Trial 1368-0010		Trial 1368-0004
	Placebo N (%)	Spesolimab N (%)	Placebo N (%)	Spesolimab N (%)	Spesolimab N (%)
Number of patients	23	74	7	15	8
Subpopulation taking immunosuppressants					
Number of patients	22 (100.0)	66 (100.0)	7 (100.0)	15 (100.0)	8 (100.0)
Any AE	14 (63.6)	40 (60.6)	6 (85.7)	14 (93.3)	8 (100.0)
AE leading to discontinuation	2 (9.1)	6 (9.1)	1 (14.3)	2 (13.3)	2 (25.0)
Investigator-defined drug-related AE	2 (9.1)	14 (21.2)	1 (14.3)	3 (20.0)	6 (75.0)
SAE	3 (13.6)	7 (10.6)	1 (14.3)	1 (6.7)	2 (25.0)
SOC Infections and infestations	2 (9.1)	17 (25.8)	3 (42.9)	8 (53.3)	6 (75.0)
UDAEC Infections	1 (4.5)	0	1 (14.3)	0	1 (12.5)
UDAEC Hypersensitivity	1 (4.5)	8 (12.1)	1 (14.3)	2 (13.3)	2 (25.0)
Subpopulation not taking immunosuppressants					
Number of patients	1 (100.0)	8 (100.0)	0	0	0
Any AE	1 (100.0)	8 (100.0)	0	0	0
AE leading to discontinuation	0	0	0	0	0
Investigator-defined drug-related AE	0	2 (25.0)	0	0	0
SAE	1 (100.0)	0	0	0	0
SOC Infections and infestations	0	2 (25.0)	0	0	0
UDAEC Infections	0	0	0	0	0
UDAEC Hypersensitivity	0	2 (25.0)	0	0	0

2.6.8.8. Discontinuation due to adverse events

There were no discontinuations due to AEs during week 1 in the pivotal trial 0013. There were also no discontinuations due to AEs in GPP trial 0011 (n=7). One patient in each of the GPP trials 0025 and 0027 discontinued due to AEs, the reported PTs were adenocarcinoma and erythema, respectively.

In the PPP trial 0015, 3 patients (14.3%) in the placebo group, 1 patient (5.3%) in the 300 mg spesolimab group and 3 patients (15.8%) in the 900 mg spesolimab group discontinued due to AEs. The reported PTs were palmoplantar pustulosis (n=2) and psoriatic arthropathy in the placebo group, VIth nerve paralysis in the 300 mg spesolimab group and syncope, vitreous floaters, palmoplantar pustulosis and psoriasis in the 900 mg spesolimab group. In the PPP trial 0016, 10 patients (6.6%) discontinued due to AEs up to week 16, 5 of which were in the placebo group. The reported reactions included prostate cancer, palmoplantar pustulosis (n=2), psoriasis, and pustulotic arthro-osteitis in the placebo group and arthritis, palmoplantar pustulosis (n=3) and retinal artery embolism in spesolimab-treated patients.

In the AD trial 0032, 3 (16.7%) and 7 patients (21.2%) discontinued treatment due to AE in the placebo and spesolimab groups, respectively. The only PT reported for more than 1 patient was worsening of AD (placebo: 2 patients, 11.1%; spesolimab: 4 patients, 12.1%). Other events were hypersensitivity (placebo), anaemia, depression, and dermatitis exfoliative generalised (spesolimab). Two additional patients (12.5 %) discontinued treatment due to AE in the re-allocation period, both were worsening of AD.

In Study 0004 (UC) two patients discontinued treatment due to AE, both reported as Worsening of UC. In Study 0005 (UC), 8 patients (8.5%) discontinued treatment due to AE, the frequencies ranged in the spesolimab groups from 0% to 14.8% compared with 8.7% in the placebo group. The most frequently reported PTs were colitis ulcerative, reported for 3 patients in the spesolimab groups, and infusion related reaction, reported for 1 patient each in the spesolimab 300 mg and in the placebo groups; all other PTs were individual occurrences (diarrhoea, arthritis, genital tract fistula).

2.6.8.9. Post marketing experience

NA

2.6.9. Discussion on clinical safety

The number of patients treated with 900 mg IV spesolimab for a GPP flare in the pivotal trial 0013 is limited (n=51). The duration of treatment/number of treatment cycles are also a limitation of the safety database in the applied indication. The safety assessment is therefore highly dependent on supportive data from other GPP trials, as well as from studies in other diseases and in healthy volunteers. Altogether, 627 subjects had received at least one dose of spesolimab up to the data cut-off for the initial MAA (08 Jan 2021). The heterogeneity of the data, with different patient populations, dosing regimens (maintenance SC dosing vs. intermittent IV doses) and dose levels, has made the assessment somewhat difficult. The safety assessment was further hampered by the fact that in the pivotal study, the patients in the placebo group were offered rescue spesolimab after the first week. The data on concomitant treatment with other immunosuppressants in GPP patients, which may be expected in the real-life situation, is also limited.

Nevertheless, the safety profile appeared largely similar and manageable across studies and indications (with the exception of AEs that could be considered related to the underlying disease). In placebo-controlled trials there were few notable differences between treatment groups, with the exception of infections, which was more commonly reported in spesolimab-treated patients, also during the 1 week

in the pivotal trial 0013. The infections were generally mild to moderate in severity. Across studies, the reported SAEs were few and of various nature and, overall, not largely concerning. Most SAEs were assessed as unrelated to spesolimab.

Thus, altogether, the safety assessment has not given raise to any major safety concerns regarding the administration of one or two doses of 900 mg IV spesolimab for the treatment of a GPP flare.

Data supporting re-treatment of patients with spesolimab at a new GPP flare is very sparse. The safety data from the study of spesolimab treatment of GPP flares beyond one GPP episode cannot, therefore, be considered comprehensive.

Given the severity of the condition, the unmet medical need, the supportive safety data from other indications and the likely scenario of recurrent flares, a conditional MA is considered appropriate. The applicant has committed to the collection of relevant post authorisation data on re-treatment of new flares and long-term maintenance of efficacy and safety (e.g. impact of ADA, hypersensitivity reactions, infections, safety of concomitant treatment) in the planned SOB study 1368-0120.

In the pivotal study, patients were required to discontinue systemic and topical therapy for GPP, prior to receiving spesolimab. The indication has therefore been restricted to spesolimab monotherapy and the SmPC informs that data supporting combination treatment is absent. Safety data on concomitant treatment with other immunosuppressants are available from studies in other indications. In PPP and AD studies, a higher frequency of AEs overall were reported in the patients with other immunosuppressants than in those without, but this might be expected with added therapy. These differences were seen to a similar extent in the placebo-treated and the spesolimab-treated patients, indicating that the observed higher frequency of AEs reflect the safety profile of the concomitant therapy rather than spesolimab. However, the number of patients was, in many studies, too small to allow definite conclusions. There were no clear differences in the safety profile observed in UC patients receiving concomitant immunosuppressive therapy (biologicals or non-biologicals), compared with that in patients with dermatological indications without concomitant immunosuppressive therapy. The available data do not give raise to immediate concern regarding the safety of spesolimab in combination with other immunosuppressants, but the overall increased risk for AEs with a higher drug burden needs to be considered. Furthermore, it should be kept in mind that the assessment is based on small datasets, between-study comparisons and on other indications than GPP.

As an immunosuppressant, spesolimab may be expected to increase the risk for serious, severe or opportunistic infections. Infection (serious/severe or opportunistic) is listed in the RMP as an important potential risk. Across studies, the rate of mild to moderate infections was higher in spesolimab-treated patients than in placebo-treated patients. Although the applicant notes that most cases were mild and uncomplicated, and the frequency of severe or serious infections were largely similar across groups and trials, due to very short follow up period and no real placebo control beyond 1 week, infections are still considered an identified risk and serious or opportunistic infections are important potential risk. It is agreed that the available data does not, presently, suggest that severe/serious infection should be listed as an ADR in section 4.8 of the SmPC.

There was one case of herpes zoster during ulcerative colitis flare treatment with spesolimab. Cases of 'oral herpes' has been reported in other studies. It is agreed that the data are currently not sufficient to suggest an increased risk for opportunistic infection, including herpes zoster, with spesolimab treatment. There were few cases across studies, and the events occurred with largely similar frequencies in spesolimab-treated and placebo-treated patients. Based on the mechanism of action of spesolimab, however, 'Serious or opportunistic infection' remains listed as an important potential risk in the RMP, and will be monitored in the PASS and in PSURs.

Two fatalities have been reported within the spesolimab clinical programme. The first case was a

patient treated with SC spesolimab 600 mg q6w for UC, who was reported with SARS-CoV-2 pneumonia and Guillain-Barre syndrome (GBS). This event was considered unrelated to spesolimab. The second fatal case was a 70-year old patient with multiple co-morbidities who was treated with a single dose spesolimab for a GPP flare. The patient's condition rapidly deteriorated and cause of death was suggested to be multi-organ failure. This case was highly confounded by significant co-morbidity and concomitant medications, and the event was suggested unrelated to spesolimab.

In addition to the fatal case of Covid-19 and GBS, two other cases that were originally coded as GBS have been reported. However, these cases were re-assessed and the diagnosis of GBS was questioned. The applicant suggests the symptoms were more in line with peripheral neuropathy, which has been added as an important potential risk in the list of safety concerns in the RMP and will be monitored in the PASS and in PSURs. This is acceptable.

Systemic hypersensitivity reaction is listed in the RMP as an important potential risk. Across studies with spesolimab, most reactions reported as 'hypersensitivity' appeared to be unspecific (such as rash, eczema, urticaria) and were of mild to moderate severity. Frequencies were overall similar in placebo- and spesolimab-treated groups. Severe or life-threatening hypersensitivity to the active substance or to any of the excipients is a contraindication in the PI. Systemic hypersensitivity reaction will be monitored in the PASS and in PSURs.

The descriptive statistics of hypersensitivity parameters does not signal AEs to be related to ADA or NAb formation upon limited exposure in short term and in monotherapy.

Hepatic injury has been evaluated as an AESI across studies with spesolimab. One case of DILI was reported, but the case did not meet Hy's law. The applicant suggests that due to the short time to onset of the reaction (acute drug reaction) after administration of spesolimab and based on the mode of action of spesolimab it is unlikely to be the causative agent. Furthermore, the patient was treated with cefuroxime and paracetamol prior to the reaction and had had prior reactions against cephalosporins. It is agreed that data is not sufficient to suggest a causal relationship between spesolimab and DILI. Based on laboratory data there are no apparent indications of a hepatotoxic potential of spesolimab.

There is *in vitro* and *in vivo* data indicating a potential tumour suppressive role after IL-36 receptor activation. Spesolimab, as an IL-36 inhibitor, therefore, bears the potential to promote tumour proliferation. Review of malignancies reported from spesolimab trials as SAEs has not identified additional, serious ADRs that should be included in the ADR table of the SmPC. Malignancy is listed as an important, potential risk in the RMP and will be monitored in the PASS and in PSURs.

A subgroup analysis based on age was not possible in Trial 0013, as there were only two subjects above 65 years of age in the study. Some data are, however, available from other studies that do not indicate a different safety profile in the elderly. Given the age distribution of GPP patients, additional data for the currently applied indication will likely be difficult to retrieve. It is therefore accepted that elderly should not be a Missing information topic in the RMP.

Subgroup analyses for safety by the mutation status in IL-36RN were also briefly presented. Even if these did not indicate major differences proportions of patients with any AE or with SAEs, conclusions are very difficult to make based on the low numbers.

From the safety database all the adverse reactions reported in clinical trials <and post-marketing> have been included in the Summary of Product Characteristics.

Additional safety data needed in the context of a conditional MA

The data on long-term safety at repeated treatment of recurrent GPP flares cannot be considered comprehensive and are planned to be provided in the planned post-marketing study 1368-0120. This is agreed upon by the CHMP.

2.6.10. Conclusions on the clinical safety

The safety database for spesolimab treatment of GPP flares is very small, however, the observed safety profile across studies, also in other indications and with maintenance treatment, appeared overall manageable. The data on long-term safety at repeated treatment of recurrent GPP flares cannot be considered comprehensive. Given the severity of the condition, the unmet medical need, the supportive safety data from other indications and the likely scenario of recurrent flares a conditional MA is considered appropriate. The applicant has committed to the collection of relevant post authorisation data on re-treatment of new flares and long-term maintenance of efficacy and safety (e.g. impact of ADA, hypersensitivity reactions, infections, safety of concomitant treatment) in the planned SOB study 1368-0120. The applicant has also included a PASS (category 3) as an additional PV activity in the RMP to address existing safety concerns..

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

In order to confirm the efficacy and safety of spesolimab in the treatment of flares in adult patients with generalised pustular psoriasis (GPP), the MAH should conduct and submit the final results of study 1368-0120, an open-label trial in the treatment of recurrent flares in adult patients with generalised pustular psoriasis, conducted according to an agreed protocol by January 2028.

2.7. Risk Management Plan

2.7.1. Safety concerns

Important identified risks	None
Important potential risks	Serious or opportunistic infections Systemic hypersensitivity reaction Malignancy Peripheral neuropathy
Missing information	Pregnant or breast-feeding women

2.7.2. Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
A 5-year active surveillance, post-authorisation safety study to characterise the safety of spesolimab for flare treatment in patients with GPP. Planned	To evaluate the risks serious or opportunistic infections, systemic hypersensitivity reaction, malignancy, and peripheral neuropathy in adult patients (aged ≥18 years) experiencing a GPP flare who are treated with spesolimab or other treatments in the routine clinical care setting.	Serious or opportunistic infections, systemic hypersensitivity reaction, malignancy, peripheral neuropathy	Protocol submission Final report	30 Jun 2023 30 Sep 2029

2.7.3. Risk minimisation measures

Safety concern	Routine risk minimisation activities
Important identified risks	
None	
Important potential risks	
Serious or opportunistic infections	*Routine risk communication* EU-SmPC sections 4.3, 4.4; PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Spesolimab is available as a prescription-only medicine. Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases.
Systemic hypersensitivity reaction	*Routine risk communication* EU-SmPC sections 4.3, 4.4; PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk*

	None *Other routine risk minimisation measures beyond the Product Information* Spesolimab is available as a prescription-only medicine. Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases.

PV.Table 1 (cont'd) Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important potential risks (cont'd)	
Malignancy	*Routine risk communication* None *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Spesolimab is available as a prescription-only medicine. Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases.
Peripheral neuropathy	*Routine risk communication* EU-SmPC section 4.4, PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Spesolimab is available as a prescription-only medicine. Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases.
Missing information	
Pregnant or breast-feeding women	*Routine risk communication* EU-SmPC section 4.6; PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Spesolimab is available as a prescription-only medicine. Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 1 September 2022. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Spevigo (spesolimab) is included in the additional monitoring list as

- it is a medicinal product authorised in the EU that contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;

- it is granted a conditional marketing authorisation (Article 14-a of Regulation (EC) No 726/2004))

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

GPP is a rare, severe, neutrophilic skin disease characterised by episodes of widespread eruptions of sterile, macroscopically visible pustules that can occur with systemic inflammation. Flares are characteristic of the clinical course of GPP, with some patients having a relapsing disease with recurrent flares and others having a persistent disease with intermittent flares.

The prevalence of GPP varies across geographical regions. It is more prevalent in females than in males, with a reported female to male ratio of 2:1 and a mean age of onset of about 41 years (range 21 to 81 years).

GPP flares, which may be idiopathic or triggered by external stimuli (e.g. infection, corticosteroid use or withdrawal, stress, or pregnancy), may cause significant morbidity and mortality. All flares have the potential to progress to a life-threatening status, requiring hospitalisation for inpatient medical management and monitoring. A goal of treatment is to find therapies that are effective in rapidly resolving flares, thus, minimizing potential risk. The all-cause mortality for patients hospitalized with a GPP flare was estimated to be 2.5% within 4 weeks after the flare. The reported mortality rates due to GPP or associated treatment ranged between 2% and 16%.

A GPP flare consists of the acute onset of rapidly disseminating painful skin manifestations (including aseptic pustules), which can be accompanied by systemic symptoms, such as high fever and extreme fatigue, as well as acute phase response (with increased C-reactive protein). Whilst the severity of GPP flares can vary, GPP flares can lead to failure in multiple organ systems, e.g. lung (acute respiratory distress syndrome), liver/kidney, cardiovascular/shock, and possibly to sepsis. Aside from the potential risk of hospitalisation, GPP flares are also associated with significant burden on patient's lives.

The current application for spesolimab concerns an indication for the acute treatment of GPP flares as monotherapy. The aim of the treatment is to achieve a fast clearance of GPP pustules and other skin manifestations with an anticipation of a recovery also from the systemic manifestations of a GPP flare.

3.1.2. Available therapies and unmet medical need

To date, there are no approved therapies specifically indicated for the treatment of GPP flares. For the use of the non-targeted immunomodulatory therapies (e.g. methotrexate, ciclosporin, retinoids, systemic corticosteroids) to treat GPP flares, there is limited evidence on the efficacy and safety. Most of these therapies used in clinical practice are associated with toxicities that make them inappropriate for continuous use. The limitation in efficacy and safety data also applies to the use of biologic treatment options in GPP, including TNF inhibitors (adalimumab, infliximab, and certolizumab pegol), IL-17 inhibitors (secukinumab, brodalumab, and ixekizumab), and IL-23 inhibitors (risankizumab and guselkumab). The approval of these biologics in Japan for the treatment of GPP is based on evidence from endpoints assessing any improvement (without the need for complete pustular clearance) at late time points (e.g. 12 to 16 weeks) in small (<12 patients), open-label, single-arm trials only. Thus, there is a lack of data on the impact of these biologics on flare treatment (e.g. time to pustular clearance and sustainability).

In a recent publication on the treatment response of 86 patients with GPP receiving 201 treatment courses for their disease in dermatology centres in Germany, the most frequently administered drugs were methotrexate (20.9% of treatment courses), acitretin (13.9%), fumaric acid esters (9.5%), etanercept and infliximab (9.0% each), as well as adalimumab and ciclosporin (8.5% each).

Therefore,, there is a high need for treatments that rapidly resolve the symptoms associated with GPP flares and prevent reoccurrences of flares with an acceptable safety profile.

3.1.3. Main clinical studies

This application is mainly supported by the pivotal Phase 2 study 1368-0013 evaluating efficacy in GPP flare treatment. Some support for the flare indication also comes from the small (n=7), uncontrolled PoC study 1368-0011.

The overall clinical development programme for spesolimab contains also a study evaluating efficacy in prevention of GPP flares (1368-0027; ongoing study). A long-term, open-label extension study is also ongoing (1368-0025). In both of these studies, spesolimab is administered subcutaneously with a possibility to administer i.v. spesolimab as flare rescue treatment.

Study 1368-0013 (EffisayilTM1) is a multi-centre, randomized, double-blind, placebo-controlled Phase II trial to assess the efficacy, safety, and tolerability of a single intravenous (i.v.) dose of spesolimab in patients with GPP presenting with a flare of moderate to severe intensity. In addition, efficacy and safety of an open-label dose of spesolimab i.v. administered 1 week after the randomized treatment was evaluated in an exploratory fashion.

A total of 53 patients were randomized in a 2:1 ratio to receive 900 mg i.v. spesolimab or placebo. Efficacy was primarily evaluated at Week 1 and at that time point, patients not responding adequately could receive rescue treatment with a dose of 900 mg i.v. spesolimab (thus a first dose in placebo patients and a second dose in non-responding spesolimab patients). Due to the severity of the condition, escape medication with standard of care medication (not protocol-defined) could also be administered during the course of the study if needed and administration of one rescue dose of spesolimab at time points beyond Week 1 was also allowed. The study duration was 12 weeks after which patients could enter the long-term, open-label study 1368-0025.

Efficacy has been evaluated with endpoints resembling those commonly used in studies in plaque psoriasis, i.e. a global score (GPPGA; similar to PGA in plaque psoriasis) and a score evaluating different symptoms, severity and extent of lesions (GPPASI; similar to PASI in plaque psoriasis). These endpoints were developed and validated by the applicant.

3.2. Favourable effects

Study 1368-0013 met its primary endpoint; the proportion of patients who achieved a GPPGA pustulation subscore of 0 at Week 1 was significantly higher for patients who received a single 900 mg i.v. dose of spesolimab (19 of 35 patients, **54.3%**) compared with patients who received placebo (1 of 18 patients, **5.6%**), leading to a risk difference of 48.7% (1 sided p = 0.0004).

The key secondary endpoint was also met; the proportion of patients who achieved a GPPGA total score of 0 or 1 was significantly higher in the spesolimab group (15 of 35 patients, **42.9%**) compared with the placebo group (2 of 18 patient s, **11.1%**), leading to a risk difference of 31.7% (1-sided p-value=0.0118).

All secondary endpoints included in the hierarchical testing procedure (the GPPASI 75 plus three patient-reported outcome measures assessed at Week 4) showed significant results in favour of

spesolimab. Also, for endpoints assessed over time up to 12 weeks, efficacy of spesolimab appeared to be maintained.

Subgroup analyses performed for the primary and key secondary endpoints for predefined subgroups (sex, race, BMI, GPPGA pustulation and total score at baseline, plaque psoriasis at baseline, background treatment prior to randomisation, JDA GPP severity score at baseline, and mutation status in IL-36RN) showed largely consistent results for both a GPPGA pustulation subscore of 0 and GPPGA total score of 0 or 1 at Week 1.

In the small number (n=12) of patients in the spesolimab arm who received a second dose on Day 8 in the pivotal study, 5 patients (41.7%) achieved pustular clearance at Week 2, i.e. 1 week after the second dose administration. This has been included as information in the SmPC in sections 4.4 and 5.1.

The small uncontrolled PoC study 1368-001 showed a mean reduction in GPPASI total score of 73% at Week 2 (primary endpoint) and 59% at week 1. Around 70% of subjects reached a GPPGA score of 0 or 1 both at Week 1 and 2.

3.3. Uncertainties and limitations about favourable effects

The basis for the proposed dose of spesolimab, a flat 900 mg i.v. dose, was considered somewhat arbitrary. The conduct of a formal dose finding study is not deemed feasible though, due to both the rarity and urgency of the condition. A proportion of patients needed a second spesolimab dose 1 week after the initial dose, which has also been reflected in the proposed posology.

The submission is based on a single pivotal small study with only 53 patients randomised, together with some support from the even smaller (n=7) uncontrolled PoC study 1368-0011.

The pivotal study is essentially placebo-controlled only up to week 1, since a large proportion of patients in the placebo arm received open-label rescue spesolimab at Week 1, based on the study design. Hence, interpretation of results of secondary endpoints assessed at Week 4 and all endpoints evaluated up to week 12 is affected by the fact that a considerable number of patients received open label spesolimab on Day 8, but also spesolimab rescue medication after Day 8, or escape medication. Patients with these intercurrent events were treated as non-responders and assigned "worst outcome" in the rank analysis for the secondary continuous endpoints. By Week 4, only 2 patients (11.1%) remained on placebo; in the spesolimab arm, 20 patients (57.1%) had not used any open label spesolimab on Day 8, spesolimab as rescue medication, or escape medication by Week 4. These remaining patients (2 of 18 patients in the placebo group and 19 of 35 patients in the spesolimab group [1 patient had prematurely discontinued before Week 1]) contributed observed data for the Week-4 analyses. Thus, it is concluded that while the Week 1 results are robust regarding intercurrent events and missing data, the Week 4 endpoints lack in clinical interpretability. Labelling claims for data beyond Week 1 have been removed from the SmPC.

The study population includes primarily patients with a moderate GPP flare, while less than 20% of the study population had a severe GPP flare. No patients with a mild GPP flare were included. Patients with a very severe, life-threatening GPP flare or a flare requiring intensive care were excluded. This has been reflected in the SmPC in sections 4.4 and 5.1.

Due to the small study population, some subgroups became very small, resulting in wide CIs for the response estimates. No subgroup analysis for age could be performed due to low numbers. Slightly more than half of the study population overall were Asian (55%) with approximately 30% of patients overall being from Europe.

The proposed SmPC recommends that if flare symptoms persist, an additional 900 mg spesolimab dose may be administered 1 week after the initial dose. Data supporting this recommendation are limited to 12 patients in the spesolimab arm who received a second dose (SmPC section 4.2 and 4.4).

The initial SmPC did not advice on the possibility to receive further spesolimab doses upon new, subsequent flares. It has been shown that formation of anti-spesolimab antibodies occurs to rather high extent (46% in study 1368-0013). This may lead to decreased plasma concentrations of spesolimab, which raises concern regarding the treatment of new GPP flares in patients previously exposed to spesolimab. The prevalence of GPP is higher in women (2:1 ratio) and a higher immunogenicity response was also observed in female patients during the pivotal study. There is very limited efficacy data supporting treatment of further flares; in the ongoing GPP prevention study (1368-0027), 6 patients have received i.v. spesolimab for an acute flare and in the open-label study 1368-0025, 9 patients did. A few patients in the pivotal study also received a third spesolimab dose as rescue medication at some time point during the study period. There is no further data available on re-treatment of new flares. In order to address the uncertainties, the applicant will conduct the post-authorisation study 1368-0120 to provide comprehensive data on spesolimab re-treatment of additional flares, including data on efficacy, safety and antibody formation as a Specific Obligation.

3.4. Unfavourable effects

The safety assessment is based on the 53 patients in the pivotal trial 0013 (spesolimab n=35; placebo n=18), and on the overall safety database of 627 patients with GPP, patients with other dermatological diseases or ulcerative colitis, or healthy volunteers who have received at least one dose of spesolimab (IV or SC, single doses or maintenance treatment) in different studies. A total of 129 patients received placebo in placebo-controlled studies.

During the first week after the first dose in the pivotal trial 0013, AEs were most commonly reported within the SOCs skin and subcutaneous disorders (spesolimab: 51.4%, placebo: 50.0%), general disorders (spesolimab: 25.7%, placebo: 27.8%), and infections and infestations (spesolimab: 17.1%, placebo: 5.6%). The most commonly reported PTs were Pustular psoriasis (spesolimab: 37.1%, placebo: 38.9%), pyrexia (spesolimab: 5.7%, placebo: 22.2%) and headache (spesolimab: 8.6%, placebo: 5.6%). Thus, there were no clear differences between the treatment groups with the exception of AEs within SOC infections and infestations, which were more commonly reported in the spesolimab group than in the placebo group.

At the week 12 and week 16 analyses of Trial 0013, a comparison with placebo was not relevant, as the majority of subjects initially randomised to placebo had received rescue spesolimab on Day 8. At week 16, AEs within SOCs Skin and dermatological disorders and Infections and infestations remained the most common, reported in 64.7% and 47.1% of patients, respectively, after any dose of spesolimab. The dermatological AEs were driven primarily by pustular psoriasis. The infections were generally mild-moderate in severity.

A total of 6 patients were identified with markedly elevated ALT or AST values: 3 patients (16.7%) in the placebo group and 3 patients (8.6%) in the spesolimab group.

Most patients were reported with mild (RCTC grade 1) or moderate (RCTC grade 2) AEs. The most commonly reported Grade 3 events and SAEs were pustular psoriasis, with similar frequencies in the two treatment groups. SAEs that were considered possibly related to spesolimab by the investigator were two cases reported as DRESS (RCTC Grade 4 and Grade 2, respectively), one case of DILI (RCTC Grade 2), and one case of urinary tract infection (Grade 2). These cases were, however, not considered treatment-related by the Sponsor, as there were other likely explanations to the events.

Also in other GPP trials, the most commonly reported AEs were pustular psoriasis and non-severe infections.

There were overall few reports of serious or severe infections across the trials with spesolimab. The following 21 serious infections were reported during or after treatment with spesolimab: pneumonia (3 SAEs), COVID-19 pneumonia (2 SAEs), staphylococcal bacteraemia (2 SAEs), COVID-19 (2 SAEs), urinary tract infection (2 SAEs), and 1 SAE each of sepsis, paraspinal abscess, influenza, cellulitis, device related infection, appendicitis, encephalitis viral, hepatitis C, endocarditis and gastroenteritis.

Hypersensitivity reactions observed in the studies were generally unspecific (such as rash, eczema, urticaria, eye oedema) and were of mild to moderate severity. As mentioned above there were two cases reported as DRESS (SAEs) and assessed as treatment-related by the investigator,. There was no apparent trend in terms of hypersensitivity reactions in patients who were positive for spesolimab antibodies.

Two deaths have been reported in the spesolimab trials and compassionate use programs; the first death was suggested due to Covid-19 sequelae (SARS-CoV-2 pneumonia and Guillain-Barre syndrome) in a subject with UC, and it was considered unrelated to spesolimab. A second fatal AE (reported cause of death: "hypoxia and aspiration of blood from an oral bleeding" and "liver injury") occurred within the spesolimab compassionate use programme, in a patient treated for a GPP flare. Upon further investigation, the Sponsor suggested the cause of death was rather multi-organ failure in a patient with several significant co-morbidities, possibly exacerbated by the GPP flare. The case was thus highly confounded.

Across studies, the rate of SAEs varied between 0 and 20%, and there were no notable rate differences between placebo-treated and spesolimab-treated subjects during the placebo-controlled periods. Except for SAEs likely reflecting worsening of the underlying condition, the reported SAEs were of various nature and the individual PTs were often reported only in single subjects. The following SAEs within the User-defined adverse event categories/Adverse events of special interest were reported: DRESS (n=2), infusion-related reaction, anaphylaxis (in a placebo-treated patient), hypersensitivity reaction, urinary tract infection, influenza, pneumonia, drug-induced liver injury (DILI, n=1), cerebral infarction, cerebrovascular accident + facial paresis, myocardial infarction, cardiac failure + pulmonary hypertension, deep vein thrombosis, squamous cell carcinoma of the skin, different malignancies. Only the infections and the hypersensitivity reactions (except DRESS) were possibly treatment related. The remaining cases, including the 2 cases of DRESS and one case of DILI, were confounded by other risk factors or alternative explanations.

Across studies, the treatment discontinuation rate due to AEs varied between approximately 2-25%. Many AEs leading to discontinuation of study treatment could be regarded as treatment failure or worsening of underlying condition. In most other cases, the patient discontinued treatment due to a SAE or severe AE that was considered unrelated to spesolimab. AEs considered related to study treatment and leading to discontinuation were reported within the UDAEC hypersensitivity and were reported in placebo-treated as well as spesolimab-treated subjects.

3.5. Uncertainties and limitations about unfavourable effects

Due to the small, single pivotal study, the safety assessment is largely dependent on data from other GPP studies, with other dose regimens, and from studies in other indications. Across studies, the number of patients treated with placebo was small, and the treatment duration for placebo shorter. In GPP studies, the number of patients concomitantly treated with other immunosuppressants is small, although data of such treatment is available from AD, PPP and UC studies.

Safety data from re-treatment with spesolimab at a new flare is very limited. Although no trend for an increased risk of hypersensitivity reactions could be seen in patients with spesolimab antibodies, the relatively small database might preclude conclusions in this respect. In order to provide comprehensive data on safety of the re-treatments of flares the applicant committed to conduct the post-authorisation study 1368-0120 as a SOB.

A subgroup analysis was only presented for the pivotal study, trial no. 0013. The number of subjects in each subgroup is therefore small and the data should be interpreted with caution.

Based on the immunomodulating properties of spesolimab, an increased risk of severe, serious or opportunistic infections and of malignancies could possibly be expected. The currently available data, including non-clinical data, gives no strong indications of such risks, but as the database is still relatively small and the total treatment period short, no firm conclusions can be drawn. These items are therefore listed as important potential risks in the RMP and will be followed in the planned PASS.

Administration of spesolimab, being an antibody, may be expected to cause serious systemic hypersensitivity reactions, such as anaphylaxis or DRESS. One case of anaphylaxis and two cases of DRESS have been reported across spesolimab studies. However, the case of anaphylaxis was observed in a patient treated with placebo. The DRESS cases were unverified and/or confounded. The potential risks for systemic hypersensitivity reactions therefore needs further characterisation post-marketing. The potential risk is addressed in the SmPC, section 4.4 and listed in the RMP. It will be followed in the planned PASS.

One case of Guillain-Barre syndrome (GBS) was reported within the spesolimab clinical programme at time of submission of the current application. The applicant suggests that the event was due to a Covid-19 infection. Since the submission, one additional case of GBS and one case of demyelinating polyneuropathy have been reported. The applicant has clarified that based on expert consultation, a diagnosis of GBS was not considered likely in the two latter cases, and was uncertain in the first case. The symptoms were suggested to be more in line with peripheral neuropathy. A causal relationship between the events and spesolimab could not be assessed. Peripheral neuropathy is added as an important potential risk in the RMP and will be followed in the planned PASS.

Data on concomitant immunosuppressive therapy for treatment of GPP flares is limited. Supportive data are available from AD, PPP and UC trials. The lack of such data in GPP patients, however, preclude firm conclusions on the safety of concomitant immunosuppressive therapy for the treatment of GPP flares. The indication is therefore limited to spesolimab as monotherapy.

3.6. Effects Table

Effects Table for spesolimab in the treatment of flares in adult patients with GPP as monotherapy (05 Jan 2021).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
GPPGA pust subscore of 0 Wk1	Proportion of patients with a GPPGA pustulation subscore of 0 at Week 1	%	54.3	5.6	p=0.0004	Study 1368-0013

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
GPPGA 0 or 1 Wk 1	Proportion of patients with a GPPGA total score of 0 or 1 at Week 1	%	42.9	11.1	p=0.0118	Study 1368-0013
GPPASI75 Wk4	Proportion of patients with a GPPASI 75 at Week 4 (EN-NRI)	%	45.7	N/A	Large uncertainty due to high numbers receiving open-label spesolimab at W1.	Study 1368-0013

GPPGA: Generalized Pustular Psoriasis Physician Global Assessment

GPPASI: Psoriasis Area and Severity Index for Generalized Pustular Psoriasis

Effect (SOC)	PTs (n=1 unless otherwise specified)	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
Skin and subcutaneous disorders	PTs *Speso:* Pustular psoriasis (see below), DRESS *Placebo*: Pustular psoriasis (see below)	N (%)	18 (51.4)	9 (50.0)	The frequencies represent AEs during the first week after one IV dose of spesolimab 900 mg. After week 1, patients were censored if they received open-label spesolimab on Day 8. Only 3 patients in the placebo group did not receive open-label spesolimab on Day 8, therefore no reliable comparison of treatment groups can be made after week 1.	Study 0013
	Pustular psoriasis	N (%)	13 (37.1)	7 (38.9)		
General disorders and administration site condition	PTs *Speso:* Pyrexia (see below), Oedema peripheral (n=2), Fatigue (n=2), Asthenia (n=2), Chills, Infusion site haematoma, Injection site bruising, Non−cardiac chest pain *Placebo*: Pyrexia (see below), Oedema peripheral, Asthenia, Chills,	N (%)	9 (25.7)	5 (27.8)		
	Pyrexia	N (%)	2 (5.7)	4 (22.2)		
Infections and infestations	PTs *Speso*: Urinary tract infection (n=2), Bacteraemia, Bacteriuria, Cellulitis, Herpes dermatitis, Oral herpes, Pustule, Upper respiratory tract infection *Placebo*: Streptococcal infection	N (%)	6 (17.1)	1 (5.6)		
Nervous system disorders	PTs *Speso:* Headache (n=3), Presyncope *Placebo*: Dizziness (n=2), Headache	N (%)	4 (11.4)	3 (16.7)		

Effect (SOC)	PTs (n=1 unless otherwise specified)	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Investigations	PTs *Speso:* C−reactive protein increased (n=2), Blood creatinine increased, Blood pressure increased *Placebo*: Alanine aminotransferase increased, Eosinophil count increased, Eosinophil percentage increased, Haematocrit decreased, Haemoglobin decreased, High density lipoprotein decreased, Protein total decreased	N (%)	4 (11.4)	2 (11.1)		
Musculoskeletal and connective tissue disorders	PTs *Speso:* Pain in extremity (n=2), Arthralgia *Placebo*: Pain in extremity, Myalgia	N (%)	4 (11.4)	2 (11.1)		
Metabolism and nutrition disorders	PTs *Speso:* Dehydration, Hypercholesterolaemia, Hyperlipidaemia *Placebo*: Decreased appetite, Hyperuricaemia	N (%)	3 (8.6)	2 (11.1)		
Blood and lymphatic system disorders	PTs *Speso:* Anaemia *Placebo*: Anaemia, erythropenia	N (%)	1 (2.9)	2 (11.1)		

Abbreviations: PT= Preferred term, SOC = System organ class

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The pivotal study 1368-0013 has shown a statistically and clinically relevant effect of spesolimab in comparison with placebo for the treatment of an acute GPP flare. A considerably larger proportion of patients in the spesolimab arm achieved pustular clearance at Week 1 as well as a relevant response (GPPGA score of 0 or 1) in the GPPGA total score, evaluating also erythema and scaling/crusting. A GPPGA pustulation subscore of 0 reflects complete clearance of the GPP pustules, which is a relevant outcome.

The study population includes primarily patients with a moderate GPP flare, while less than 20% of the study population had a severe GPP flare. Although the number of patients with a severe flare is low, the subgroup results give no indication of a poorer effect. The CHMP therefore agreed that mild to severe GPP flare can be treated with spesolimab.

There are currently very limited (n=5 in the pivotal study) data on treatment of subsequent GPP flares. The recurrence of GPP flares is a very likely scenario since GPP patients are expected to experience new flares at some point in time. This limitation of re-treatment data has been reflected in SmPC sections 4.2 and 4.4.

In study 1368-0013, a large proportion of subjects (46%, 23/50) developed ADA by Week 12-17 with median onset time of 2.3 weeks and maximum titre at a median time of 11.7 weeks. With an ADA onset time of 2.3 weeks, the incidence of ADAs has no impact on the decision to administer a second dose at day 8. It may however have an impact in case of recurrent flares treated by spesolimab.

Comprehensive data is planned to be obtained to support efficacy and safety of treatment of subsequent flares (in the context of a CMA; see below) and on the impact of ADA formation from interventional post-authorisation trial 1368-0120 in approximately 40 patients treated with spesolimab i.v.

The limited number of patients exposed to the recommended dose and the duration of treatment or number of treatment cycles are major limitations of the safety database. However, across studies, including studies with maintenance treatment and studies in other indications, the AE profile of spesolimab appeared overall manageable. The most commonly reported AEs across studies, infections and hypersensitivity reactions, were generally mild to moderate in severity. There were few discontinuations due to treatment-related AEs. Thus, despite the limited data available for the currently proposed dose regimen and indication, no major safety concerns have been raised. Safety data for re-treatment of additional flares is, however, essentially missing in GPP patients without maintenance treatment with spesolimab. The planned SOB study 1368-0120 is expected to provide further safety data on re-treatment of flares.

Although spesolimab, as an immunomodulating agent, could theoretically increase the risk for malignancy, the available non-clinical data does not give raise to concern in this respect for administration of one or two doses of spesolimab for the treatment of GPP flare.

A PASS (category 3) as an additional PV activity to assess the rates of all important potential risks (serious or opportunistic infections, systemic hypersensitivity reaction, malignancy, and peripheral neuropathy) in adult patients experiencing a GPP flare who are treated with spesolimab or other treatments in the clinical care setting, using data from both existing psoriasis registries and claims/electronic medical record databases is proposed.

3.7.2. Balance of benefits and risks

A clinically relevant effect of spesolimab in the treatment of a single GPP flare has been demonstrated vs. placebo. There are limitations pertaining to the small data package and a short placebo-controlled study period, leading to uncertainties for the clinically relevant secondary efficacy endpoints assessed after week 1. Data on re-treatment for a potential subsequent flare is also very limited. These uncertainties are planned to be addressed in the SOB study 1368-0120 (see below).

The CMHP agreed not to specify the severity of a flare in section 4.1 but, considering that the design of the pivotal study required withdrawal of other GPP treatments, the indication has been restricted to use as monotherapy.

The safety database for spesolimab treatment of GPP flares is very small, however, the observed safety profile across studies, also in other indications and with maintenance treatment, appeared overall manageable. The observed effect of anti-spesolimab antibodies on the plasma concentrations of spesolimab constitute an important limitation in the knowledge about re-treatment at new flares.

In order to address the uncertainties concerning the re-treatment both with respect to efficacy and safety the applicant plans to conduct an interventional post-authorisation trial 1368-0120 in approximately 40 patients treated with spesolimab i.v. to evaluate the efficacy and safety as well as the impact of immunogenicity on efficacy, safety, and PK of spesolimab i.v. for the treatment of recurrent, new flares after initial flare treatment with spesolimab i.v., as an SOB. Furthermore, a PASS

(category 3) as an additional PV activity in the RMP is planned to be conducted to further characterise the safety of spesolimab for flare treatment in patients with GPP.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

The applicant has applied for a standard, full marketing authorisation for the proposed indication (treatment of flares in adult patients with generalised pustular psoriasis), which would imply that the data can be considered as comprehensive. For the treatment of one flare, this is agreed; the quality of evidence, precision of effect size, clinical relevance of the primary endpoint the duration of response, and the documented safety profile support that the data is comprehensive. In addition, the pharmacological rationale is reasonable, and the natural course of the disease is known.

However, considering the limited data available for the re-treatment of a subsequent flare (a use that is covered by the proposed indication), it is not considered that the data is comprehensive. As comprehensive data on the product are not available for the re-treatment of subsequent flares, a conditional marketing authorisation was proposed by the CHMP during the assessment, after having consulted the applicant. At Day 181 of the procedure, the applicant applied for a conditional marketing authorisation.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating and life-threatening disease.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive in the target population of adult patients with GPP flares, as discussed in section 3.7.2. The available data demonstrates a clear benefit, as a significantly larger proportion of patients in the spesolimab arm achieved pustular clearance at week 1 as well as relevant response in the GPPGA total score, evaluating also erythema and scaling /crusting. It is acknowledged by CHMP that long-term efficacy data is scarce and more information on safety is required. However, the demonstrated risk to patients is manageable. Therefore, the benefits of treatment of adult patients with GPP flares with spesolimab outweigh the risk inherent in the absence of comprehensive data on flares re-treatment.

- It is likely that the applicant will be able to provide comprehensive data.

  - Data from the planned additional interventional post-authorisation trial 1368-0120 in approximately 40 patients treated with spesolimab i.v. will evaluate the efficacy and safety as well as the impact of immunogenicity on efficacy, safety, and PK of spesolimab i.v. for the treatment of recurrent, new flares after initial flare treatment with spesolimab i.v. The primary endpoint of trial 1368-0120, the achievement of a GPPGA pustulation subscore of 0 one week after treatment of the first recurrent flare with spesolimab i.v., is in line with the primary endpoint of the pivotal trial 1368-0013. The trial aims to confirm the positive benefit-risk balance of the approved indication "Treatment of flares in adult patients with generalised pustular psoriasis as monotherapy" and to provide comprehensive data on efficacy, safety, immunogenicity, and PK data on the treatment of subsequent GPP flares. A feasibility assessment of the study 1368-0120 was provided. Based on the current feasibility, the final clinical trial report is planned by January 2028. Study 1368-0120 is considered to be feasible within the proposed timeframe.

- Unmet medical needs will be addressed, as this is the first targeted therapy for GPP flare/s. Most of the systemic non-targeted immunomodulatory therapies used in GPP (e.g. methotrexate, ciclosporin, retinoids, systemic corticosteroids) are associated with toxicities and have only limited evidence of efficacy. Some biologics, including TNF-, IL-17, and IL-23 inhibitors, are approved for treatment of GPP in Japan based on small, open-label, single-arm trials that did not specifically evaluate response to flares. Thus, even though some products are used for the treatment of GPP (including off-label use), none is specifically indicated and documented for (re-)treatment of GPP flares, and their effectiveness is considered suboptimal by dermatologists and patients. In pivotal trial 1368-0013, spesolimab was shown to improve GPP pustulation in comparison to placebo and to have beneficial effects on other (systemic) symptoms and efficacy endpoints (including patient-reported outcomes) associated with GPP flares, while showing an acceptable safety profile. Hence, spesolimab addresses the unmet medical need for the treatment of GPP flare. The planned clinical trial 1368-0120 will focus on treatment of subsequent flares to provide comprehensive data to address the unmet need for subsequent flare treatment.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.
  - While the severity of GPP flares can vary, any individual GPP flare can lead to failure in multiple organ systems, e.g. lung (acute respiratory distress syndrome), liver/kidney, cardiovascular/shock, and possibly to sepsis. All GPP flares have the potential to progress to a life-threatening status, requiring hospitalisation and potentially intensive care unit treatment. GPP flares have a substantial mortality; the all-cause mortality for patients hospitalised with a GPP flare was estimated to be 2.5% within 4 weeks after the flare. Aside from the potential risk of hospitalisation and mortality, GPP flares are also associated with significant burden on patients' lives. Based on patient experience data, patients living with GPP ranked pustules, pain, and itch as the most burdensome symptoms. In addition to skin symptoms, patients reported fever, poor sleep, general malaise, exhaustion, anxiety, and depression. They described being socially isolated and having negative impacts on their professional life, relationships, and daily activities.

  - Spesolimab improves GPP pustulation while having beneficial effects on other (systemic) symptoms and patient-reported outcomes relevant for GPP flares, with manageable risks. Considering that spesolimab is effective and based on assessment of available data no serious safety issues have been identified in the treatment of GPP flares, which are associated with significant impairment of the quality of life of patients and their families, hospitalisation with/without intensive care, disability, and potential mortality, the benefits to public health of the immediate availability of spesolimab outweigh the risks inherent in the fact that more comprehensive efficacy and safety data are still required.

3.8. Conclusions

The overall benefit/risk balance of Spevigo is positive, subject to the conditions stated in the section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus

that the benefit-risk balance of Spevigo is favourable in the following indication:

Spevigo is indicated for the treatment of flares in adult patients with generalised pustular psoriasis (GPP) as monotherapy.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

NA

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
In order to confirm the efficacy and safety of spesolimab in the treatment of flares in adult patients with generalised pustular psoriasis (GPP), the MAH should conduct and	January 2028

Description	Due date
submit the final results of study 1368-0120, an open-label trial in the treatment of recurrent flares in adult patients with generalised pustular psoriasis, conducted according to an agreed protocol.	

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that spesolimab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

5. Appendices

5.1. CHMP AR on New Active Substance (NAS) dated 13 October 2022