25 July 2024
EMA/372955/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Spevigo

International non-proprietary name: Spesolimab

Procedure No. EMEA/H/C/005874/X/0006/G

Note

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

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Administrative information

Name of the medicinal product:	Spevigo
MAH:	Boehringer Ingelheim International GmbH Binger Strasse 173 55216 Ingelheim am Rhein GERMANY
Active substance:	Spesolimab
International Non-proprietary Name/Common Name:	Spesolimab
Pharmaco-therapeutic group (ATC Code):	Immunosuppressants, interleukin inhibitors (L04AC22)
Therapeutic indication(s):	Spevigo is indicated for the treatment of generalised pustular psoriasis (GPP) flares in adults and adolescents from 12 years of age as monotherapy. Spevigo is indicated for the prevention of generalised pustular psoriasis (GPP) flares in adults and adolescents from 12 years of age.
Pharmaceutical form(s):	Concentrate for solution for infusion; Solution for injection
Strength(s):	450 mg and 150 mg
Route(s) of administration:	Intravenous use and Subcutaneous use
Packaging:	Vial (glass) and pre-filled syringe (glass)
Package size(s):	2 vials and 2 pre-filled syringes

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List of abbreviations

ACH	Acrodermatitis continua of Hallopeau
AD	Atopic dermatitis
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criterion
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BI	Boehringer Ingelheim
BIcMQs	Boehringer Ingelheim customized-MedDRA Query
BMI	Body mass index
BSA	Body surface area
CD	Crohn's disease
CHMP	Committee for Medicinal Products for Human Use (of the EMA)
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMC	Chemistry, manufacturing, and control
CMH	Cochran-Mantel Haenszel
CO	Clinical overview
CRF	Case report form
CRP	C-reactive protein
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Cardiovascular
CYP	Cytochrome P450
DBL	Database lock
DDCP	Drug device combination product
DDDP	Division of Dermatology and Dental Products
DILI	Drug-induced liver injury
DLQI	Dermatology Quality of Life Index
DP	Drug product
DRESS	Drug reaction with eosinophilia and systemic symptoms
eGFR	Estimated glomerular filtration rate (GFR)
EM	Primary estimand for the randomised maintenance treatment period in 1368-0027, with use of investigator prescribed SoC for GPP or use of OL spesolimab i.v. for GPP flare treatment regarded as event/treatment failure
EMA	European Medicines Agency
EoS	End of study
ERASPEN	European Rare And Severe Psoriasis Expert Network
EU	European Union
FDA	US Food and Drug Administration
GBS	Guillain-Barré syndrome
GCP	Good Clinical Practice
GPP	Generalised Pustular Psoriasis
GPPASI	Generalised Pustular Psoriasis Area and Severity Index
GPPGA	Generalised Pustular Psoriasis Physician Global Assessment

HCP	Healthcare professional
HFE	Human factors engineering
HR	Hazard ratio
HS	Hidradenitis suppurativa
iFF	Intended final formulation
IFU	Instruction for use
i.v	intravenous
IBD	Inflammatory bowel disease
ICH	International Council on Harmonisation
IL	Interleukin
IL36RN	Interleukin 36 receptor antagonist
IMP	Investigational medicinal product
IND	Investigational new drug
ISI	Integrated Summary of Immunogenicity
ISS	Integrated Summary of Safety
ITT	Intent to treat
JDA	Japanese Dermatological Association
KM	Kaplan-Meier
LD	Loading dose
MAA	Marketing Authorization Application
MACE	Major adverse cardiovascular event
MCP-Mod	Multiple comparison procedure with modelling techniques
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency of the UK
MI	Multiple imputation
NAb	Neutralizing antibody
NMPA	National Medical Products Administration of China
NRI	Non-response imputation
OC	Observed cases
OL	Open-label
OLE	Open-label extension
PBRER	Periodic benefit-risk evaluation report
PD	Pharmacodynamic(s)
PDCO	Paediatric Committee of the EMA
PFS-NSD-1	1 mL pre-filled syringe with needle safety device
PGI-C	Patient global impression of change
PGI-S	Patient global impression of severity
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
PM	Primary method for handling missing data for time-to-event endpoints
PMDA	Pharmaceuticals and Medical Device Agency of Japan
PoC	Proof of concept
PPP	Palmoplantar psoriasis
PSS	Psoriasis Symptom Scale
PT	Preferred Term of MedDRA
Pt-yrs, py	Patient-years
qxw	Once every x weeks
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual effects period
RS	Randomised set

RWE	Real-word evidence
s.c.	subcutaneous
SAE	Serious adverse event
SAF	Safety analysis set
sBLA	Supplemental Biologics License Application
SCE	Summary of clinical efficacy
SCS	Summary of clinical safety
SD	Single dose / standard deviation
SM	Sensitivity method for handling missing data for time-to-event endpoints
SOC	System Organ Class of MedDRA
SoC	Standard of Care
TEAE	Treatment-emergent adverse event
TF	Trial formulation
TFL	Tables, figures, listings
TNF	Tumor necrosis factor
TPSS	Target plaque severity score
TS	Treated set
TSAP	Trial statistical analysis plan
UC	Ulcerative colitis
UDAEC	User-defined adverse event category
UE	Usability engineering
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cell

1. Background information on the procedure

1.1. Submission of the dossier

Boehringer Ingelheim International GmbH submitted on 23 June 2023 a group of variation(s) consisting of extensions of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to introduce a new pharmaceutical form (solution for injection) associated with a new strength (150 mg) and new route of administration (subcutaneous use), for the prevention of generalised pustular psoriasis (GPP) flares in adults and adolescents from 12 years of age.

This line extension is grouped with a type II variation (C.I.6.a) indication for Spevigo 450 mg concentrate for solution for infusion to include treatment of generalised pustular psoriasis (GPP) flares in adolescents (from 12 years of age), based on final results from study 1368-0027 (Effisayil 2) and extrapolation; this is a multi-center, randomised, parallel group, double blind, placebo controlled, phase IIb dose-finding study to evaluate efficacy and safety of BI 655130 (spesolimab) compared to placebo in preventing GPP flares in patients with history of GPP. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The Annex II and Package Leaflet are updated in accordance. Version 2.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce editorial changes to the PI and update the list of local representatives in the Package Leaflet.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7(2) of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0049/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the P/0049/2022 was completed.

The PDCO issued an opinion on compliance for the P/0049/2022.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH 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.

1.5. Scientific advice

The MAH received Scientific advice from the CHMP on the development for the indication from the CHMP on 22 February 2018 (EMEA/H/SA/3721/1/2017/III) and 28 March 2019 (EMEA/H/SA/3721/1/FU/1/2019/III). The Scientific advice pertained to quality, non-clinical, and clinical aspects.

- agreement that the proposed pre-filled syringe (PFS) is not considered to be a needle-based injection system (NIS), acceptability of the design verification for the PFS-NSD, acceptability of the analytical comparability approach to support the use of Phase III clinical trial supplies and commercial supplies, the clinical trial supply strategy, the combination product development program based on use risk assessment, acceptability of design control, risk management and human factors engineering activities for registration of the combination product, the concept to usability data generated with PPP patients as surrogates for GPP patients,

-appropriateness of the overall non-clinical safety program together with the emerging clinical safety information

- overall acceptability of the clinical investigation approach in particular that GPP is a seriously debilitating or life-threatening disease, choice of endpoints, the dosing regimen, immunogenicity and PK assessment, the study population in particular the inclusion of patients of ages 16 and older in the proposed pivotal studies, the strategy to generate safety data, the trial designs of studies 1368.13 and 1368.27, in particular the endpoints, the approach for assessing therapeutic protein-drug interaction, and statistical analysis plan.

1.6. 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

CHMP Peer reviewer(s): <N/A>

The application was received by the EMA on	23 June 2023
The procedure started on	13 July 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	2 October 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	10 October 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	26 October 2023
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	9 November 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	18 January 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all	20 February 2024

CHMP and PRAC members on	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	07 March 2024
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	21 March 2024
The MAH submitted the responses to the CHMP List of Outstanding Issues on	29 April 2024
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	15 May 2024
The CHMP agreed on a 2nd list of outstanding issues to be sent to the MAH on	30 May 2024
The MAH submitted the responses to the CHMP List of Outstanding Issues on	24 June 2024
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	05 July 2024
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	25 July 2024

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 and risk factors

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

GPP flares may be idiopathic or triggered by external stimuli (e.g. infection, corticosteroid use or withdrawal, stress, or pregnancy).

2.1.3. Clinical presentation, diagnosis and prognosis

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).

The diagnosis of GPP is defined by European Rare And Severe Psoriasis Expert Network (ERASPEN) and the Japanese Dermatological Association (JDA).

GPP flares may cause significant morbidity and mortality. All flares have the potential to progress to a life-threatening status, requiring hospitalization for inpatient medical management and monitoring; however, there is no specific marker to predict the evolution of the disease, i.e. it is impossible to predict the clinical progression of flares at patient level. As such, 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 hospitalised 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%.

2.1.4. Management

To date, there are no approved therapies specifically indicated for the prevention of GPP flares, despite the morbidity and mortality associated with GPP flares. For the use of non-targeted immunomodulatory therapies (e.g. methotrexate, cyclosporine, retinoids, systemic corticosteroids), there is limited evidence on efficacy. There had been no randomised, controlled clinical trials for the prevention of GPP flares (including with biologics). 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, etc.), and IL-23 inhibitors (risankizumab and guselkumab). Although spesolimab i.v. was the first treatment demonstrated to be effective for acute flares and has been approved for it, considering the unpredictable onset of flares, the burden to the patients, and the potentially life-threatening nature of any flare, it remains important to have a treatment option to prevent flares in the first place.

Additionally, the needs to further control the symptoms of the disease between flares and to improve the quality of life are high from patients' perspective.

2.2. About the product

Spesolimab (BI 655130) is a humanised, 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.

The IL-36 pathway is central to GPP pathogenesis. In patients with GPP, blockade of IL-36R signalling is a targeted therapeutic approach. Biomarker data from serum and skin samples in trials 1368-0013 and 1368-0011 strongly support the therapeutic targeting of IL-36 for the treatment of GPP. IL-36R inhibition with spesolimab led to normalization 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.

Spesolimab was granted marketing authorisation for the treatment of GPP flares in several countries, including the US, EU, Japan, and China. For the prevention of GPP flares, spesolimab has the potential to address the high unmet medical need for an effective and well-tolerated targeted therapy by blocking IL-36R.

The new 150 mg solution for injections is intended for subcutaneous administration. It is proposed to be suitable for patient self-administration.

The active substance for manufacture of spesolimab solution for injection 150 mg/PFS (150 mg/mL) remains unchanged as previously approved.

2.3. Type of Application and aspects on development

The clinical development program with spesolimab in GPP comprises 4 trials that are completed or ongoing and was designed to evaluate spesolimab for the:

- Treatment of GPP flares: the completed trials **1368-0011** (proof of concept trial) and **1368-0013** (Effisayil 1, pivotal trial) showed efficacy and safety of spesolimab i.v. for flare treatment.
- Prevention of GPP flares:
  - Trial **1368-0027** (Effisayil 2): this pivotal trial investigated efficacy and safety of spesolimab s.c. for flare prevention in patients with a history of GPP. This trial forms the basis for the current MAA and is assessed below.
  - Trial **1368-0025** (Effisayil-ON): The objective of this ongoing open-label extension (OLE) trial is to evaluate long-term safety and efficacy of spesolimab s.c. (with the option of spesolimab i.v. for recurring flare treatment) in eligible patients who completed trials 1368-0013 and 1368-0027. Interim data are included in the current MAA.

In May 2020, a Paediatric Investigation Plan (PIP) waiver for children <12 years of age was accepted by the PDCO, and enrolment of adolescent patients in trial 1368-0027 was requested by the PDCO.

CHMP Scientific Advice (SA) took place in February 2018 and a Follow-up SA in March 2019 (please see section 1.5.).

On 13 October 2022, CHMP adopted a positive opinion for the conditional marketing authorisation of Spevigo in the treatment of flares in adult patients with generalised pustular psoriasis (GPP) as monotherapy.

In this procedure, the MAH applies for a new pharmaceutical form (solution for injection) associated with a new strength (150 mg) and new route of administration (subcutaneous use), for the prevention of GPP flares in adults and adolescents from 12 years of age. In addition, the authorised indication in the treatment of GPP flares is proposed to be extended to include adolescents (from 12 years of age).

2.4. Quality aspects

2.4.1. Introduction

This line extension concerns a new strength and dosage form, Spevigo 150 mg solution for injection in pre-filled syringe equipped with a needle safety device (NSD) which is administered subcutaneously (SC).

The finished product is presented as injection in pre-filled syringe containing 150 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 pre-filled glass syringe assembled with an automatic needle guard, extended finger flange, plunger rod, and plunger stopper (coated butyl rubber, siliconised).

2.4.2. Active Substance

The active substance is the same as for the already approved Spevigo 450 mg, concentrate for solution for infusion. Therefore, no new documents in section 3.2.S were provided with this submission.

However, section 3.2.S.4.4 Batch Analyses has been updated with additional active substance batches to support the registration of the spesolimab solution for injection in pre-filled syringe 150 mg.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Spevigo (spesolimab), is currently approved as a 60 mg/mL formulation, concentrate for solution for infusion, including 450 mg/vial for intravenous (IV) administration.

This line extension includes a new Spevigo 150 mg formulation, also referred to as spesolimab 150 mg/ml in this report and is presented as a solution for injection in a pre-filled syringe assembled within a needle safety device (PFS-NSD-1), 150 mg/syringe, for SC administration.

The nominal fill volume is 1.0 mL and an overfill has been introduced and has been sufficiently justified.

All excipients in the formulation are identical to the already approved product and comply with Ph. Eur. grade.

The pre-filled glass syringe, plunger stopper and needle shield are compliant with appropriate Ph. Eur. monographs for primary containers and closures.

During the development, different formulations have been developed and used for clinical studies of spesolimab, covering finished products for IV as well as SC administration.

A formulation robustness study has been performed based on a design of experiments (DOE) where different formulations were included. These different formulations were stored at 2-8 °C and 25 °C and tested for relevant quality attributes. The formulation robustness study showed that the commercial formulation of Spevigo 150 mg is robust at the proposed storage condition.

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

Information 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.

There are no formula overages in the manufacturing of Spevigo 150 mg and the information provided on overages and physicochemical and biological properties is found sufficient.

Manufacturing process development has been sufficiently described and justifies the commercial manufacturing process.

The manufacturing process includes thawing, pooling/splitting and sterile filtration of the active substance batches, filling into syringes and stoppering. Eventually, the syringes are visually inspected and assembled with an extended finger flange, plunger rod and needle safety device with subsequent packaging and labelling. The commercial manufacturing process has been characterized through process characterization studies of each process step and details for these studies have been provided in the dossier.

The product-contact surface materials used during manufacture of the finished product has been evaluated with respect to the potential leachables under consideration of the safety concern threshold. Extractable data from the respective vendors of disposables or by extractable studies conducted by the applicant were utilized for the evaluation. A toxicological assessment was conducted for potential leachables with the conclusion that the materials used in the manufacturing of the finished product pose no risk to patients treated.

The comparability of spesolimab concentrate for solution for infusion and solution for injection in vials was demonstrated in the initial submission for the already approved 60 mg/mL finished product, 450 mg/vial. The comparability studies provided in this line extension, focus on the comparability of spesolimab 150 mg/mL in pre-filled syringes, 150 mg/syringe, to the already approved spesolimab 60 mg/mL finished product in the vial presentation, 450 mg/vial.

Comparability has been evaluated in accordance to ICH Q5D, based upon a combination of evaluation of historical batch release data, side-by-side testing of release data, extended characterization data and stability studies from long-term storage (2-8 °C), accelerated (25 °C) and stressed (40 °C) storage conditions.

All results provided, batch analysis data and extended characterization data, met the comparability assessment criteria. In addition, all the batch analysis results were also within the specification acceptance criteria and the historical range.

Comparability has been sufficiently demonstrated for the comparisons described above, for the 150 mg/mL finished product in pre-filled syringes (150 mg/syringe) to the already approved 60 mg/mL finished product in the vial presentation (450 mg/vial) with a high degree of similarity and few and minor differences noted for all the quality attributes studied. The few and minor differences noted have all been satisfactorily justified to have no effect on efficacy and safety. For instance, the level of HMWs by HPSEC was determined to be slightly higher for the PFS-presentation compared to the vial-presentation but still highly comparable and well within the proposed limit in the finished product specification.

The 150 mg/syringe (150 mg/mL) finished product (PFS-NSD-1) is a sterile, isotonic, solution for injection in a pre-filled syringe (PFS) assembled within a needle safety device. Furthermore, the PFS-NSD-1 device is a pre-assembled, single-use injection device intended to subcutaneously inject a single fixed dose of the finished product solution i.e., the entire content of the pre-filled syringe. The PFS-

NSD-1 device forms a combination product and integral device between the spesolimab finished product solution and the NSD and the corresponding Notified Body Opinion (NBOp) has been provided in section 3.2.R of the dossier.

The primary packaging components of spesolimab solution for injection in pre-filled syringe 150 mg/syringe consist of a 1 mL glass syringe with a 27G ½" staked needle and rigid needle shield. The syringe is closed with a plunger stopper. The rigid needle shield is composed of an inner needle shield and an outer rigid shield. The needle safety device covers the needle post-injection and prevents user and patients from accidental needle stick injuries.

The glass syringe barrel and the rubber plunger stopper are compliant with appropriate Ph. Eur. monographs for primary glass container and rubber stoppers (Ph. Eur. monographs 3.2.1 (Glass containers for Pharmaceutical use) and 3.2.9 (Rubber closures)).

The platform is already commercially available and used in some other approved medicinal products.

Each pre-filled syringe contains 1.0 mL of finished product solution, and the PFS-NSD-1 has no graduation marks.

It can also be noted that the finished product solution does not come in contact with any component of the NSD-PFS-1 components (needle safety device, extended flinger flange and plunger rod).

Compliance to the requirements in the Ph. Eur. monographs 3.2.1 (Glass containers for Pharmaceutical use) and 3.2.9 (Rubber closures…) has been demonstrated.

It has been concluded in the NBOp report of the PFS-NSD-1 device that the design validations and usability studies as well as design verifications have been demonstrated to be acceptable and all relevant ISO standards and other requirements met. Furthermore, it is also concluded that the device fully conforms with the General Safety and Performance Requirements (GSPRs) and no nonconformities were found. For all applicable GSPRs, compliance has been demonstrated by sufficient supporting evidence like test reports, summaries and evaluations.

In conclusion, it has been demonstrated and concluded in the NBOp report that the PFS-NSD-1 device meet all the relevant requirements of Annex I of regulation (EU) 2017/745. Furthermore, it has also been demonstrated that the intended user population can safely and effectively operate the PFS-NSD-1 device to deliver a complete dose, using the Instructions for use, per its intended uses and use environment.

A 1.0 ml pre-filled syringe (PFS-1) was used for the administration spesolimab subcutaneously during the phase II and III clinical trials. For the commercial presentation (PFS-NSD-1), the applicant has incorporated a needle safety device into the finished product. The primary packaging components (syringe incl. needle, RNS and plunger stopper) remain unchanged. The applicant has performed a technical and performance comparison of the PFS-1 and PFS-NSD-1 and concluded that the introduction of a needle safety device to the spesolimab PFS-1 for the commercial product, does not have an impact on the representativeness of the clinical data that was generated with PFS-1. This conclusion is agreed to.

Functionality and performance have been studied for the PFS-NSD-1 device including spesolimab 150 mg/mL finished product solution. The applicant has classified dose accuracy, exposed needle length and break loose, glide and actuation forces as CQAs and essential performance requirements (EPRs) and control strategies have been introduced accordingly. These EPRs (dose accuracy, exposed needle length and break loose, glide and actuation forces) have been included in the spesolimab finished product specifications document for the PFS-NSD-1 device in the dossier and have also been included in the process validation studies.

Human factors/usability validation has been conducted for the spesolimab PFS-NSD-1 according to IEC 62366 and these provided data are assessed in the clinical section of this line extension for Spevigo. However, it has been assessed and concluded that the provided data of functionality and performance tests, including human factors engineering/design validation studies, has been sufficiently shown. Furthermore, it has also been sufficiently demonstrated that the intended user population can safely and effectively operate the spesolimab PFS-NSD-1 device to deliver a complete dose, using the IFU, per its intended uses and use environment. See the clinical report for further assessors comments on the human factors/usability validation.

Compatibility of the finished product has been studied and satisfactorily discussed in relation to siliconization of the inner glass surface of the barrel and the plunger stopper, tungsten compatibility as well as to the use of ethylene oxide for sterilization of the PFS.

2.4.3.2. Manufacture of the product and process controls

The manufacturers of the finished product are appropriately authorised and GMP compliant. The finished product manufacturers and testing sites are identical for the commercial 150 mg/mL finished product in pre-filled syringes (150 mg/syringe) and the already approved commercial 60 mg/mL finished product vial presentation (450 mg/vial).

The manufacturing process for the 150 mg/mL finished product consist of thaw of active substance (AS) (150 mg/mL), splitting/pooling of AS batches, sterile filtration, and aseptic filling. The filled syringes are thereafter stoppered, visually inspected and eventually assembled into the PFS-NSD-1 device. The assembled PFS-NSD-1 are labelled, packaged in boxes and stored at 2-8 °C.

The AS 150 mg/mL may be stored refrigerated at 2 – 8°C, frozen, thawed, split or pooled. Different batches of the AS may be pooled or split to yield to an adequate amount for aseptic filling.

The commercial manufacturing process of the 150 mg/mL finished product is at large based upon the same commercial manufacturing process as for the already approved 60 mg/mL finished product with the main differences related to the filling into the syringe and the assembly process into the PFS-NDS-1 device.

Acceptable ranges are provided for the process parameters, and IPCs are defined with acceptable limits.

Hold times for the 150 mg/mL drug product at both room temperature and refrigerated (2-8 °C) temperatures have been defined and found acceptable. These hold times are very similar/identical to the ones for the already approved 60 mg/mL finished product and have been established and confirmed via small-scale studies provided in the dossier.

Three commercial scale consecutive PPQ batches of spesolimab 150 mg/mL finished product in pre-filled syringe (150 mg/syringe) as well as in assembled needle safety device, PFS-NSD-1, have been manufactured at full commercial scale. The validation covers the minimum and maximum batch size using a bracketing approach. Three separate PPQ-batches were manufactured of each of the 150 mg/mL finished product in pre-filled syringe and on the assembled PFS-NSD-1, respectively.

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 stoppering has been successfully demonstrated for the pre-filled syringe within a single batch as well as between the validation/PPQ batches.

The process validation for the PFS-NSD-1 included functionality testings. Further, it has been shown that the assembly process of the syringes into the PFS-NSD-1 device do not impact the product quality. In addition, container closure integrity was successfully demonstrated for both the pre-filled syringe and the PFS-NSD-1.

In conclusion, the process validation approach of the 150 mg/mL finished product manufacturing is found acceptable. All manufacturing process steps included in the process validation of both the pre-filled syringe and the PFS-NSD-1 were performed successfully. Furthermore, the provided process validation data demonstrate that the process is robust and performs as intended when run within the defined operating ranges, giving the 150 mg/mL drug product which meets the quality requirements.

2.4.3.3. Product specification

The specifications for release and stability of spesolimab solution for injection in pre-filled syringe 150 mg/syringe (150 mg/mL) are provided in the dossier.

A comprehensive set of relevant tests is included in the specifications document for the 150 mg/mL finished product covering limits for both release and end-of-shelf life of the various attributes. Some attributes are tested at the level of the pre-filled syringe or at the level of the assembled PFS-NSD-1.

The specifications setting approach for the purity tests heterogeneity and potency is based on clinical experience and clinical justification and statistically derived ranges. The proposed acceptance criteria are all found acceptably justified. It can also be noted that the proposed acceptance criteria for the 150 mg/mL finished product are identical to the ones for the already approved 60 mg/mL finished product for almost all attributes except for the functionality testing of the assembled PFS-NSD-1. Additionally, the 150 mg/mL finished product for SC administration can be considered as a worst-case compared to the 60 mg/mL finished product for IV administration with respect to tendency for aggregation (i.e. level of HMWs by HPSEC). In addition, it can also be noted that the clinical PK-studies performed have shown a comparable level of immunogenicity (i.e. level of antibodies formed) for the 150 mg/mL finished product for SC administration to the already approved 60 mg/mL finished product for IV administration. This is found acceptable.

There are no new impurities introduced during manufacture of the 150 mg/mL finished product in pre-filled syringe or in PFS-NSD-1 compared to the already approved 60 mg/mL finished product.

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. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed 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.

Analytical methods

Many tests used for release and stability testing of the 150 mg/mL finished product are also used for testing of active substance. These methods and validation results are presented in the dossier. It can also be noted that almost all methods included in the specifications of the 150 mg/mL finished product (150 mg/syringe) are identical to the tests used for the already approved 60 mg/mL finished product (450 mg/vial). The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

Batch analysis

Batch analysis data on a large number of batches of the finished were provided. The results are within the specifications and confirm consistency of the manufacturing process. Batch analysis data has been provided for 150 mg/mL finished product batches used for clinical studies, stability studies and/or for process validation/PPQ batches manufactured at full commercial scale. Information with respect to splitting and pooling of active substance batches is also included. The commercial process of active substance is used for all batches manufactured of the 150 mg/mL finished product.

Reference materials

Information on reference standard is provided in the active substance section and these are valid for the finished product.

2.4.3.4. Stability of the product

For the pre-filled syringe and the PFS-NSD-1, the applicant has provided stability results at 2-8 °C for up to 36 months for three primary stability batches and up to 18 months data for three PPQ batches. In addition, up to 12 months data are provided for accelerated storage conditions of 25 ± 2°C / 60 ± 5 % relative humidity (RH) as well as data from photostability testing.

The stability studies are performed in-line with ICH Q5C and testing has been performed on both the pre-filled syringe and the assembled PFS-NSD-1.

All stability results available for the primary stability batches and the PPQ batches stored at 2-8 °C for both the pre-filled syringe and the PFS-NSD-1 comply with the proposed end-of-shelf-life/stability specification for up to 36 months for the primary stability batches and up to 18 months for the PPQ batches. No significant/very minor changes or trends are seen in any of the attributes tested. Also, the attributes included in the functionality testing for the PFS-NSD-1 are found almost unchanged over the course of the stability studies. Furthermore, as expected some changes/trends are seen during the stability testing at 25 °C. However, no indication was seen for change in functional testing for the PFS-NSD-1 at 25 °C-storage.

Photostability testing has been performed according to ICH Q1B and showed that the spesolimab 150 mg/mL pre-filled syringe and PFS-NSD-1 is sensitive to light exposure and should be kept in the outer carton to protect from light induced degradation, in line with the wording in section 6.4 in the SmPC.

Based on stability data obtained, the recommended shelf-life for spesolimab pre-filled syringe, 150 mg/syringe (150 mg/mL), is 36 months at refrigerated conditions, 2-8°C. Considering design verification data as provided in section P.2 (the sequential preconditioning study) and real time stability data, the shelf-life for the PFS-NSD-1, 150 mg/syringe (150 mg/mL), is limited to 24 months. In addition, the spesolimab PFS-NSD-1 can be stored at room temperature for up to 14 days prior to use. The 14 days are included in the 24 months.

Based on available stability data, the shelf-life of 2 years for the PFS-NSD-1 at refrigerated conditions, 2-8°C as stated in the SmPC is acceptable.

2.4.3.5. Adventitious agents

Adventitious agents risk assessment performed for 60 mg/ml finished product is applicable to 150 mg/ml finished product.

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.

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

No new non-clinical data have been submitted by the Applicant.

2.5.2. Ecotoxicity/environmental risk assessment

The Applicant has submitted a justification for not submitting ERA studies. The absence of specific environmental risk study data is justified as spesolimab is a humanized monoclonal antibody (a protein), which is in accordance with relevant guidelines.

2.5.3. Discussion on non-clinical aspects

No new non-clinical data have been submitted by the Applicant in this procedure. The existing non-clinical data did not identify findings which would warrant additional toxicity studies (i.e., JAS studies) to support the extension to include pediatric patients from the age of 12 and no JAS has been requested in the accepted PIP; this is acceptable.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, spesolimab is not expected to pose a risk to the environment.

2.5.4. Conclusion on the non-clinical aspects

No new-clinical data have been submitted and this is acceptable in the context of this application.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

The MAH 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.

- **Tabular overview of clinical studies**

Table 2. Completed or ongoing clinical trials with spesolimab in patients with GPP

Trial	Treatment duration (follow-up period)	Design / objectives	Doses studied	N Treated	Status / report
GPP flare treatment (previous MAA)					
1368-0013 Effisayil 1 Phase II, pivotal trial	Phase II Single dose (up to 16 weeks)	Multi-center, randomised, double blind, parallel group, placebo controlled / efficacy and safety in GPP flare treatment	Placebo Spesolimab 900 mg i.v.	18 35	Completed / Final CTR
1368-0011 Proof of Concept	Phase I Single dose (20 weeks)	Multi center, open label, single arm / efficacy and safety in GPP flare treatment	Spesolimab 10 mg/kg body weight i.v.	7	Completed / Final CTR
GPP flare prevention (current MAA)					
1368-0027 Effisayil 2 Phase IIb, pivotal trial	Phase IIb 48 weeks (up to 16 weeks)	Multi-center, randomised, double-blind, parallel-group, placebo-controlled / efficacy and safety in GPP flare prevention	Placebo Spesolimab s.c. total LD 600 mg, then 300 mg q4w LD 600 mg, then 300 mg q12w LD 300 mg, then 150 mg q12w Spesolimab 900 mg i.v. as OL flare treatment	31 92 30 31 31 32	Completed / Final CTR
1368-0025 Effisayil-ON	Phase II 252 weeks (16 weeks)	OL extension of trials 1368-0013 and 1368-0027 / long-term safety and efficacy of spesolimab in patients with GPP	Spesolimab s.c. total 300 mg q4w 300 mg s.c. q12w Spesolimab 900 mg i.v. as flare treatment	128 23 105 12	Ongoing[1] / interim data used in TFL

i.v. = intravenous, LD = loading dose, MAA = Marketing Authorisation Application, OL = open label, q4w = once every 4 weeks, q6w = once every 6 weeks, q12w = once every 12 weeks, s.c. = subcutaneous, TFL = tables, figures, and listings

1 First patient screened in May 2019 and planned final DBL in Q1 2028; interim data up to a cut-off date of 01 Dec 2022 combined with 1368-0013 and 1368-0027 are included as tables, figures, and listings (TFL).

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The clinical pharmacology of spesolimab has been investigated in six Phase I trials in healthy volunteers (HV) and four studies in patients with GPP. Trial 1368-0027 was the first trial in the clinical program in GPP to include adolescent patients (planned age range: 12 to <18 years), which fulfilled the requirement in the Paediatric Investigation Plan. Eight adolescent patients with an age range of 14 to 17 years were randomised in 1368-0027. PK and immunogenicity data from studies in patients with other indications than GPP that are complete or have a relevant amount of data available (e.g., completed primary analysis period) are included in the pop-PK analysis.

Analytical methods

Assay methodology used to monitor the pharmacokinetic (PK), anti-drug antibodies (ADA), and neutralising anti-drug antibody (NAb) of spesolimab in the clinical trials has not changed from what was described in the initial flare treatment MAA where the validation of the methods were presented and assessed. Partial validation of newly included patient populations has since been performed.

Pharmacokinetic data analysis

Pharmacokinetic data in the target population was sampled with sparse sampling designs and analysed using a population PK (PopPK) approach as described below. In some of the earlier clinical studies, non-compartmental analysis was performed.

Evaluation and Qualification of Models

PopPK analysis

The objectives of the PopPK analysis were to characterise the plasma pharmacokinetics of spesolimab following i.v. and s.c. administration, evaluate the influence of pre-specified covariates on pharmacokinetic parameters and to derive individual exposures for ER analyses. An additional objective was to evaluate the benefit-risk profiles of spesolimab subcutaneous (SC) dosing regimens by simulating PK.

The PopPK model included 8920 samples from 760 subjects. Data from 18 studies were pooled for the PopPK model development including a mix of HV and patients with GPP, atopic dermatitis, hidradentitis suppurativa, palmoplantar pustulosis and ulcerative colitis patients. The PK sampling designs varied (rich vs sparse) across these studies. Compared to the model submitted in the initial application procedure for Spevigo (EMEA/H/C/005874/0000), additional PK and ADA data from several emerging studies were included in the population PK analysis (1368-0043, 1368-0016, 1368-0027, 1368-0025, 1368-0052, 1368-0067). Studies 1368-0027 and 1368-0025 are considered the most important studies for the current procedure where trough values were sampled using sparse plasma PK sampling schemes.

Available PK and ADA data from 8 adolescent GPP subjects who were included in study 1368-0027 was considered in this analysis.

The continuous baseline covariates that were considered and their correlations are shown in **Figure 1**. The distribution of body weight including calculation of the 5^{th} to 95^{th} percentiles of the distribution is shown in **Figure 2**. The time-constant categorical covariates are summarised in **Table 3.** Injection site

was a categorical time-varying covariate where, for SC-treated subjects, 78.5% of the data were for periumbilical injections, 1.1% were for arm injection, 18.2% were thigh injections and 2.1% were categorised as "both/other". Anti-drug antibody (ADA) was a continuous time-varying covariate and are summarised further below.

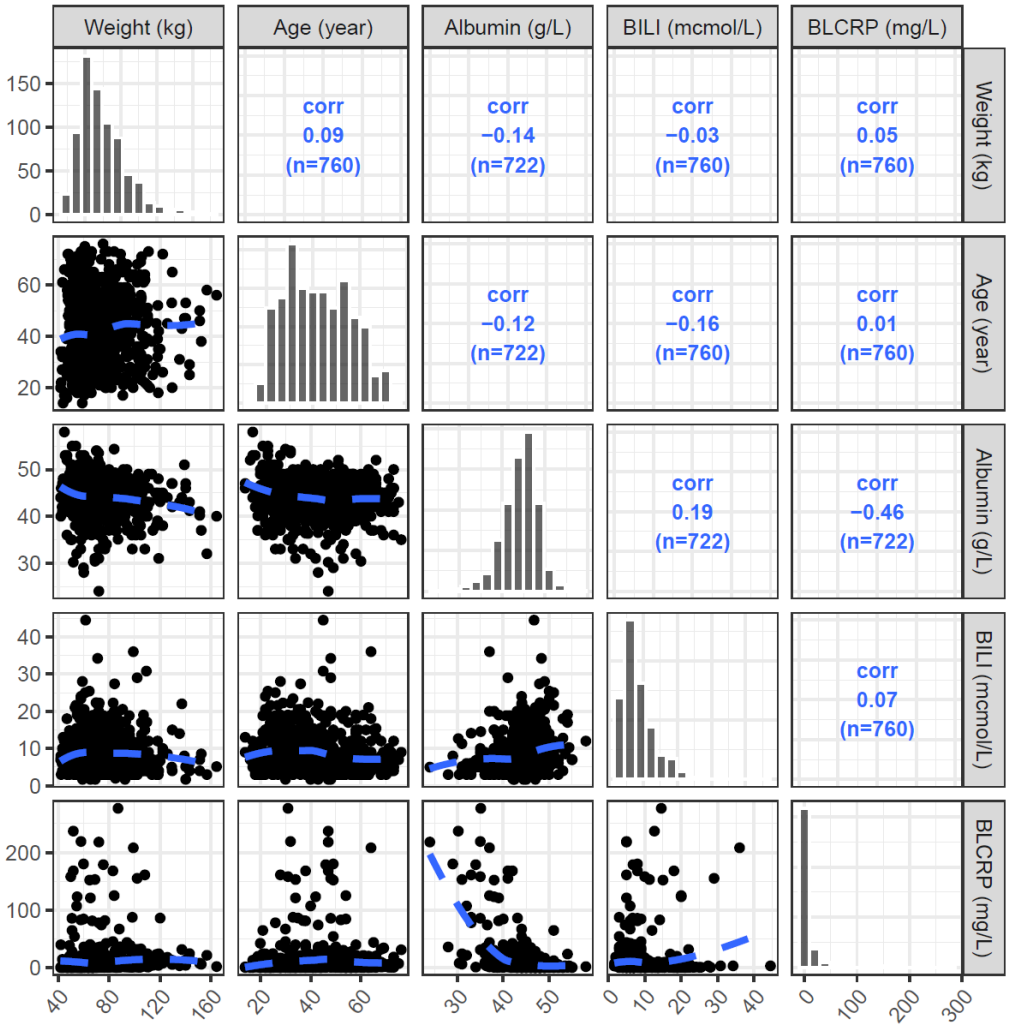


Figure 1. PK model: Correlation and distribution of baseline continuous covariates. The lower off-diagonal shows a bivariate scatter plot with values indicated by black circles and a dashed blue LOESS smooth trend line through the data. The diagonal shows density frequency (count) plots of the data, and the correlation coefficient is reported in the upper off-diagonal. Abbreviations: BILI = baseline bilirubin, CRP = baseline serum C-reactive protein.

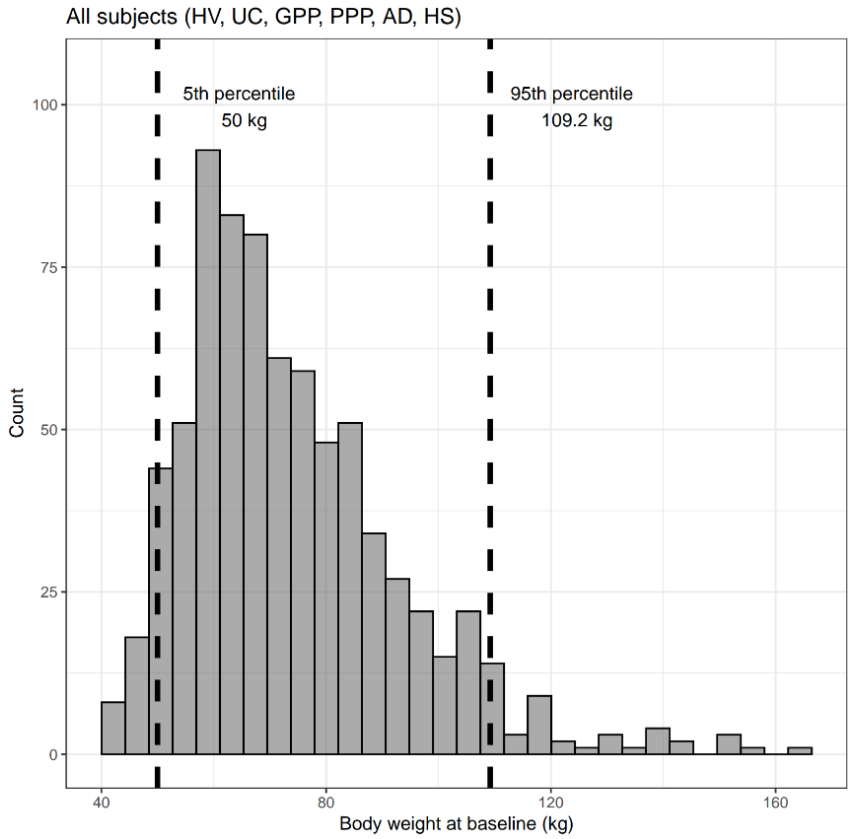


Figure 2. Body weight histogram including all patients in the PopPK dataset including IV+SC treated subjects in the same panel. AD = atopic dermatitis, GPP = generalised pustular psoriasis, HS = hidradenitis suppurativa, HV = healthy volunteer, IV = intravenous, PPP = palmoplantar pustulosis, SC = subcutaneous, UC = ulcerative colitis.

Table 3 PK Model: Summary of time-constant categorical covariates

Covariate	Category	N (%)
Patient type	HV	226 (29.7)
	GPP	171 (22.5)
	UC	96 (12.6)
	PPP	183 (24.1)
	AD	36 (4.7)
	HS	48 (6.3)
Sex	Male	344 (45.3)
	Female	416 (54.7)
Race	White	458 (60.3)
	Asian	266 (35.0)
	Black	16 (2.1)
	American Indian or Alaska Native	1 (0.1)
	Missing	18 (2.4)

	Native Hawaiian or other Pacific Islander	1 (0.1)
Country	Non Asian	495 (65.1)
	Korea	10 (1.3)
	Japan	99 (13)
	China	83 (10.9)
	Other/Unknown	73 (9.6)

The analysis was carried out in NONMEM, version 7.5. The stochastic approximation expectation maximisation (SAEM) estimation method was used. A two-compartment model with parallel linear and nonlinear clearance and a sequential zero-order and first-order absorption after subcutaneous dosing was used. Body weight (WT) was used to scale clearance and volume terms according to fixed allometric exponents (0.85 for clearance and 1 for volume terms). Evaluation of other covariates was guided by biological plausibility, visual predictive checks (VPCs) and statistical significance. ADA titer was included as a time-varying continuous covariate on the total clearance implemented as:

$$CL_{ADA} = CL_{ADA-Slope} \times ADA_{titer} \; if \; ADA_{titer} > threshold$$

The final model parameter estimates are shown in Table 4 and Table 5 where the Vmax and Km parameters were fixed to the values estimated in the previous PK model. All parameters were well estimated and similar to those estimated in the full model. The covariates of potential clinical importance included subject type (AUCss was approximately 30 to 40% higher in subjects with PPP and healthy volunteers, respectively, compared to the reference subject), injection site (AUCss was approximately 12% lower following periumbilical injection), weight (AUCss changed approximately 30% at the extreme body weights, 48 kg and 94 kg, compared to the reference subject), and ADA titer (AUCss was approximately 24% lower at high titer values of 57600).

Table 4 PPK Final model: summary of fixed effect parameter estimates

			Estimate	95% CI
Structural model parameters				
CL (L/d)	$\exp(\theta_1)$	Clearance	0.179	0.165, 0.193
V2 (L)	$\exp(\theta_2)$	Central volume	3.65	3.45, 3.85
k_a (1/d)	$\exp(\theta_3)$	First order absorption rate	0.232	0.147, 0.367
F1	$\exp(\theta_4)/(1+\exp(\theta_4))$	Bioavailability	0.947	0.902, 0.972
Q (L/d)	$\exp(\theta_5)$	Intercompartmental clearance	0.516	0.481, 0.553
V3 (L)	$\exp(\theta_6)$	Peripheral volume	2.64	2.53, 2.76
D1 (d)	$\exp(\theta_7)$	Duration of zero-order absorption	0.124	0.122, 0.127
Vmax (ug/d)	$\exp(\theta_8)$	Maximum elimination rate TMDD	50.7	FIXED
KM (ug/L)	$\exp(\theta_9)$	Concentration at half-max elimination rate TMDD	8.87	FIXED
Covariate effect parameters				
ADA_{thresh} (titer)	$\exp(\theta_{10})$	Threshold for ADA effect	340	275, 420
CLADA (L/d/titer)	$\exp(\theta_{11})$	ADA clearance slope	1.25e-06	6.19e-07, 2.53e-06
CL_{HV}	$\exp(\theta_{12})$	Covariate effect for HV	0.709	0.659, 0.762

CL_{UC}	$\exp(\theta_{13})$	Covariate effect for UC Patients	1.10	1.02, 1.18
CL_{PPP}	$\exp(\theta_{14})$	Covariate effect for PPP Patients	0.781	0.725, 0.842
CL_{Black}	$\exp(\theta_{15})$	Covariate effect for Black race	1.08	0.902, 1.29
CL_{Asian}	$\exp(\theta_{16})$	Covariate effect for Asian race	1.06	1.01, 1.11
CL_{alb}	θ_{17}	Covariate effect for baseline albumin	-0.588	-0.823, -0.354
CL_{crp}	θ_{18}	Covariate effect for baseline CRP	0.0487	0.0321, 0.0654
$F1_{sc,peri}$	$\exp(\theta_4 + \theta_{23})/(1+\exp((\theta_4 +\theta_{23}))$	Bioavailability for SC injection site (periumbilicum)	0.824	0.546, 0.948
$k_{a,sc,peri}$	$\exp(\theta_{24})$	Covariate effect for SC injection site (periumbilicum, on k_a)	1.10	0.645, 1.87
CL_{flare1}	$\exp(\theta_{25})$	Covariate effect for flare status 1*	1.24	1.13, 1.35
CL_{flare2}	$\exp(\theta_{26})$	Covariate effect for flare status 2*	1.08	0.980, 1.19
CL_{flare3}	$\exp(\theta_{27})$	Covariate effect for flare status 3*	1.14	1.01, 1.30

Parameters estimated in the log-domain were back-transformed for clarity. Fixed allometric scaling terms for body weight of 0.85 and 1 were applied to clearance and volume parameters, respectively (ref 70 kg). Reference subject was GPP/HS/AD, post-flare in 1368.13, CRP = 3 mg/L, Albumin = 44 g/L, age = 40 y, and bilirubin = 7 umol/L. *The flare status effect was estimated for (i) subjects in studies other than GPP (CLflare 1), (ii) subjects that are pre-flare in study 1368.27 or 1368.25 (prior to IV treatment for flare in study 1368.27 or if subject received first active dose in 1368.2; CLflare 2), and (iii) subjects post-flare in study 1368.27 (following any IV treatment for flare in study 1368.27; CLflare3). Abbreviations: ADA = anti-drug antibody; AD = atopic dermatitis; CI = confidence intervals; CRP = baseline serum C-reactive protein; HS = hidradenitis suppurativa; HV = healthy volunteers; PPP = palmoplantar pustulosis; SC = subcutaneous; SE = standard error; TMDD = target-mediated drug disposition; UC = ulcerative colitis.Confidence intervals = estimate ± 1.96 · SE

Table 5 PPK Final model: summary of random effect parameter estimates

		Estimate	95% CI	Shrinkage (%)
Interindividual variance parameters				
IIV-CL [CV%=29.3]	$\Omega_{(1,1)}$	0.0826	0.0754, 0.0897	12.5
IIV-V2 [CV%=36.9]	$\Omega_{(2,2)}$	0.127	0.110, 0.145	28.7
IIV-k_a [CV%=144]	$\Omega_{(3,3)}$	1.13	0.890, 1.36	49.5
IIV-F1 [SD=0.0729]	$\Omega_{(4,4)}$	0.976	0.653, 1.30	55.4
IIV-CLADA	$\Omega_{(11,11)}$	6.24 [CV%=2260]	3.70, 8.77	62.3
Interindividual covariance parameters				
V2-CL	$\Omega_{(2,1)}$	0.0662 [Corr=0.646]	0.0596, 0.0728	-
F1-k_a	$\Omega_{(4,3)}$	-0.328 [Corr=-0.312]	-0.541, -0.114	-
Residual variance				
Proportional	$\Sigma_{(1,1)}$	0.0713 [CV%=26.7]	0.0710, 0.0717	7.19

Abbreviations: CI = confidence intervals; Corr = Correlation coefficient; CV = coefficient of variation; SD = standard deviation; SE = standard error. CV% of log-normal omegas = sqrt(exp(estimate) - 1) · 100. CV% of sigma = sqrt(estimate) · 100

A prediction-corrected VPC (pcVPC) for the overall data vs time since the most recent dose, stratified by route of administration are shown in **Figure 3**. A VPC for dose-normalised spesolisumab concentration vs time since first dose in GPP patients, stratified by route of administration and subject type is shown in **Figure 4**. A pcVPC stratified by body weight is shown in **Figure 5**.

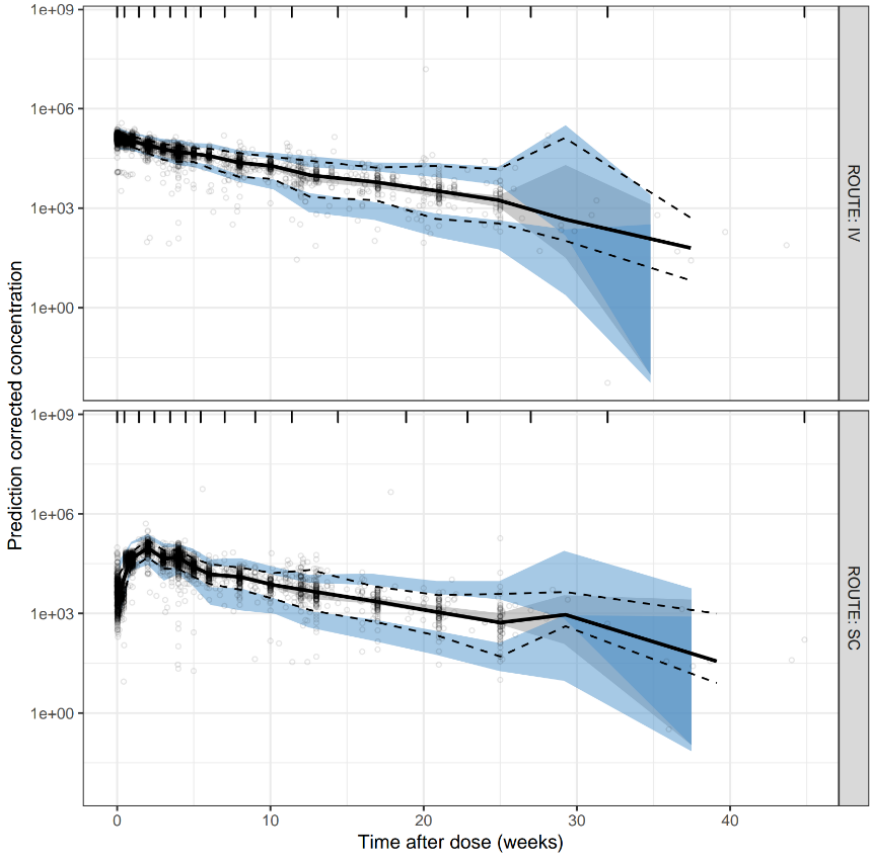


Figure 3. PPK Final Model: Prediction-corrected visual predictive check (pcVPC) of the spesolimab concentration versus time after dose, by route. Black lines represent the median (solid), 5th and 95th percentiles (dashed) of the observed data. Blue and grey shaded regions represent the 95% prediction interval of the corresponding (i.e. 5th, 50th and 95th) percentiles. IV: intravenous; SC: subcutaneous

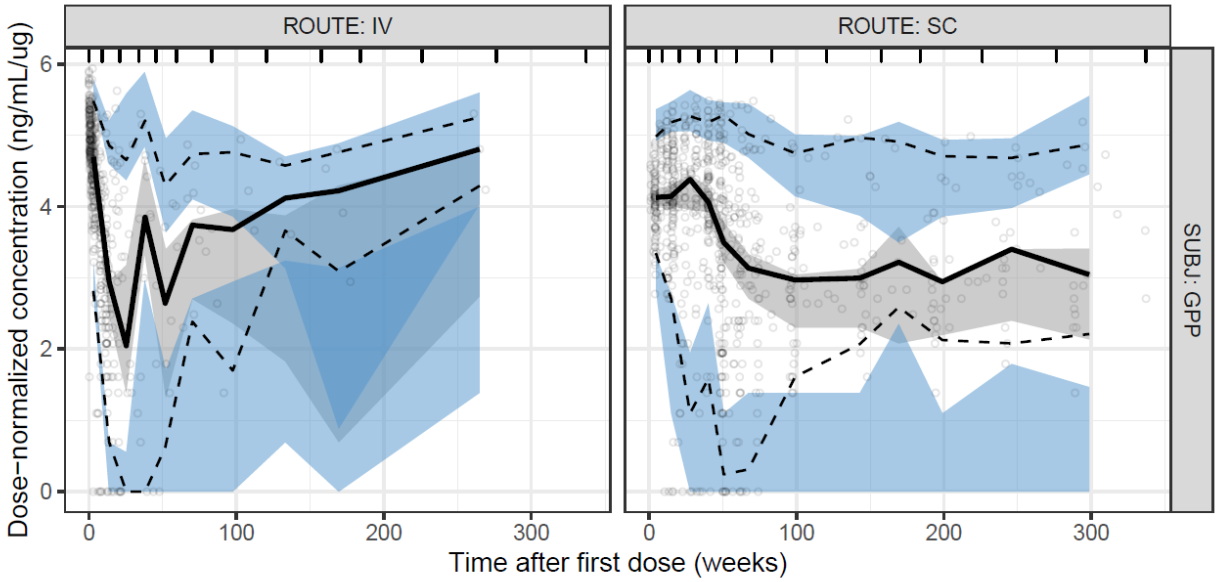


Figure 4. PPK Final Model: Visual predictive check (VPC) of the dose-normalised spesolimab concentration versus time after first dose, by route and subject type. Black lines represent the median (solid), 5th and 95th percentiles (dashed) of the observed data. Blue and grey shaded regions represent the 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; GPP: generalised pustular psoriasis

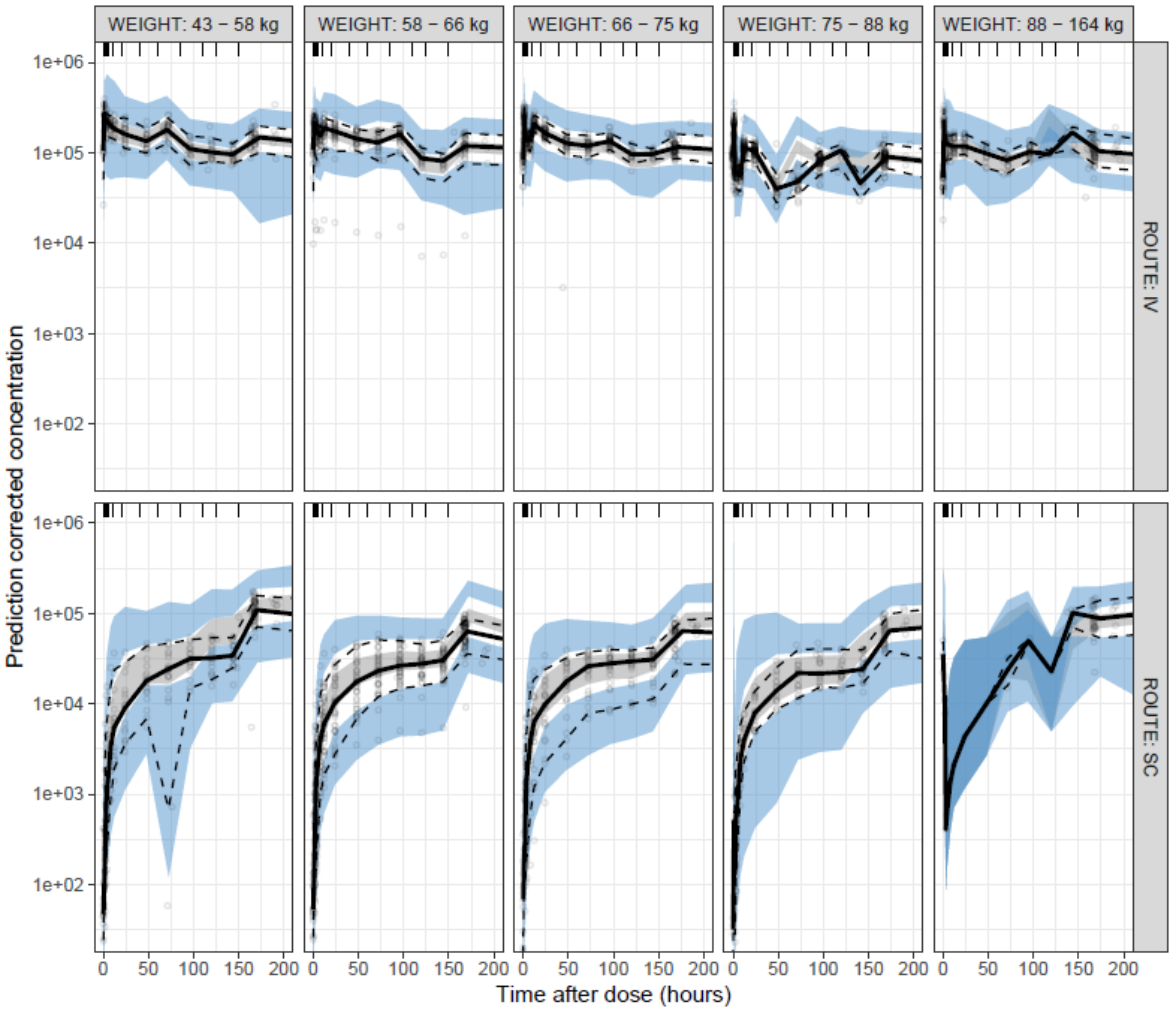
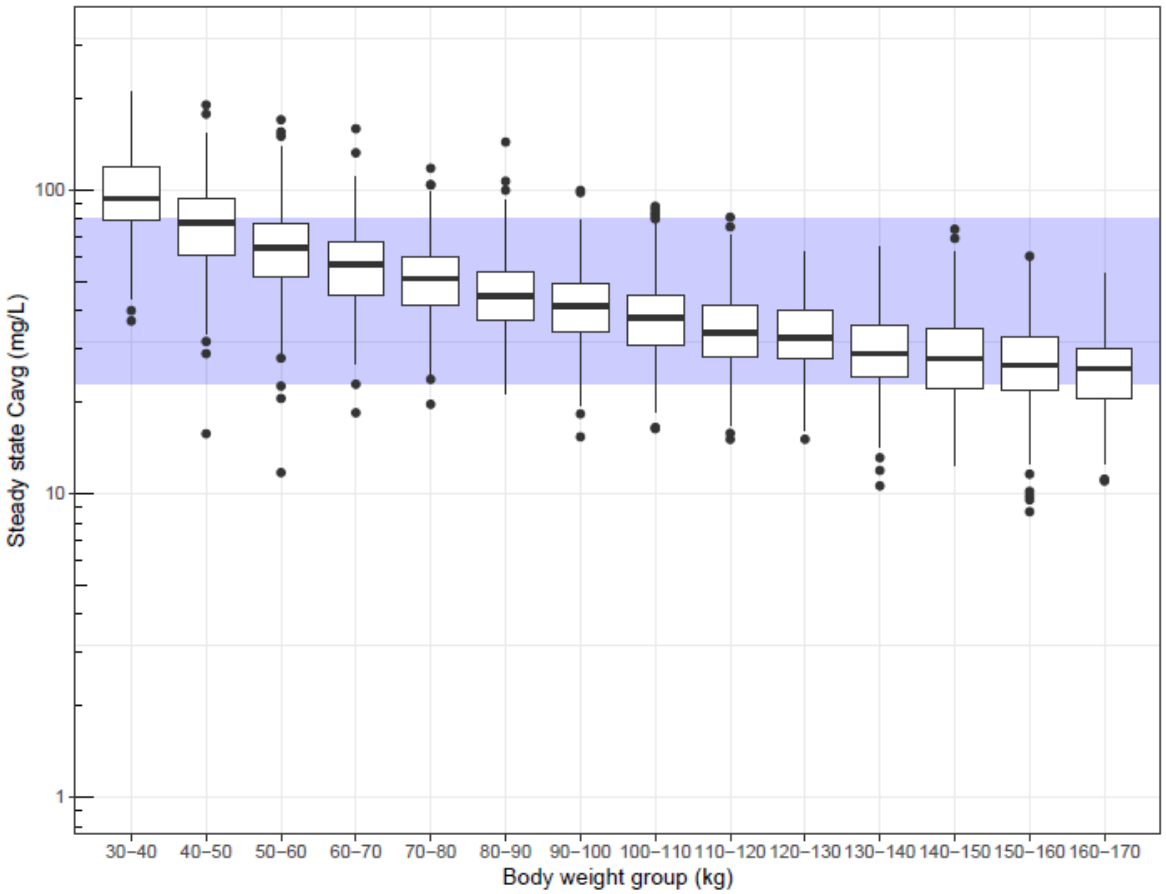


Figure 5. Prediction correction visual predictive check (pcVPC) of spesolimab plasma concentration versus time after dose, stratified by route of administration and body weight. Black lines represent the median (solid), 5th and 95th (percentiles) of the observed data. Blue and grey shaded regions represent the 95% prediction interval of the corresponding (i.e., 5th, 50th and 95th) percentiles.

Population simulations were performed using the final PopPK model stratified by body weight. Body weights were sampled from a uniform distribution ranging from 30 kg to 170 kg. The 5th to 95th percentile of expected exposures from the high s.c. dose in study 1368-0027 and i.v. doses in 1368-0013 were generated using the population PK model derived empirical Bayes estimates and covariate distributions for individuals in those study cohorts. The individual exposures were simulated using an intention to treat approach in which all individuals were assumed to receive the protocol dosing in the respective cohorts as intended and assuming ADA negative status. The reference ranges shown in the results below leverage this approach rather than considering individuals actual dosing history since many patients did not follow protocol dosing as intended, dropped out early, received i.v. rescue doses etc.

Steady state exposure metrics were simulated from the population pharmacokinetic model for the proposed s.c. dose regimen in GPP prevention (600 mg s.c. loading dose, then 300 mg q4w starting week 4) and stratified by body weight. Body weights in the simulation ranged from 30 kg – 170 kg, divided into weight groups in 10 kg increments. Cavg at steady state was simulated from the PK model by randomly sampling from the respective weight group, considering interindividual variability in

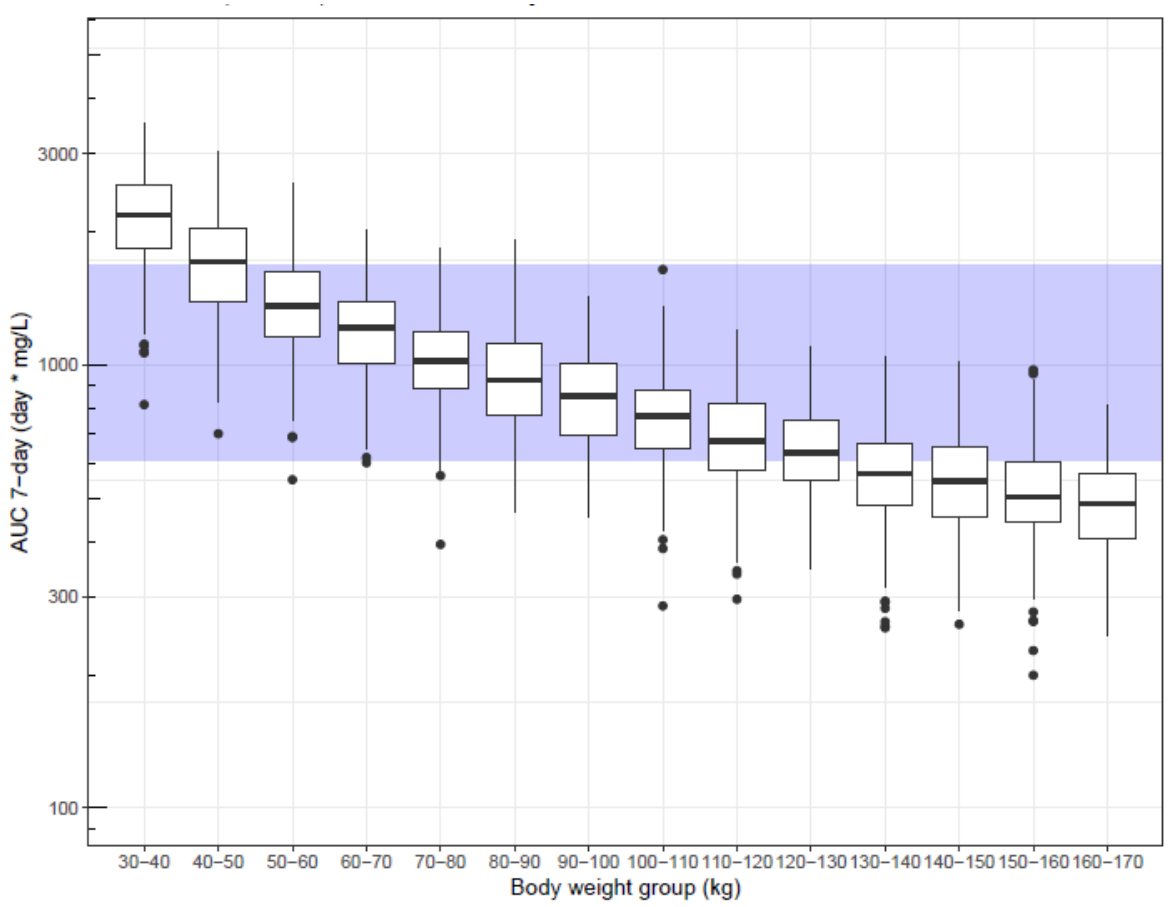
pharmacokinetic parameters, and assuming ADA negative status. There were 250 simulated GPP patients in each weight group and results are presented in **Figure 6**. The exposure metrics C_{min} and C_{max} at steady state were also simulated.



Source code: question5-pk-by-bodyweight-sc.R
Source graphic: question5-SC-CAVGSS-by-weight-NOADA.pdf page: 1

Figure 6. Population PK model simulations of Cavg at steady state without ADA, for the proposed s.c. dose, stratified by body weight group. Median values are designated by a solid line in the center of the box. Boxes indicate the inter-quartile range (IQR) with whiskers extending to 1.5*IQR. The blue shaded region is a reference range, representing the 5th and 95th percentile of model derived exposure from 30 subjects in the high-dose arm of 1368-0027.

Exposure following a single 900 mg IV dose in terms of AUC_{0-1} was simulated from the PK model by randomly sampling from the respective weight group, considering interindividual variability in pharmacokinetic parameters, and assuming ADA negative status. Body weights in the simulation ranged from 30 kg - 170 kg, divided into weight groups in 10 kg increments. There were 250 simulated GPP patients in each weight group and results are presented in **Figure 7** below. Exposure metrics AUC_{0-12} weeks and C_{max} were also simulated.



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Source graphic: question5−IV−1dose−AUC7−by−weight−NOADA.pdf page: 1

Figure 7 Population PK model simulations of AUC0-7days after one IV dose without ADA, stratified by body weight group. Median values are designated by a solid line in the center of the box. Boxes indicate the inter-quartile range (IQR) with whiskers extending to 1.5*IQR. The blue shaded region is a reference range, representing the 5th and 95th percentile of model derived exposure from 50 individuals in 1368-0013.

Reduced dosing regimens were simulated in patients 30-40 kg. For s.c., 300 mg loading dose followed by 150 mg Q4W were compared with 600 mg loading dose followed by 300 mg Q4W (**Figure 8**). A target exposure range was also considered based on the observed PK exposure in the GPP patients in study 1368-0027 allocated to the s.c. high dose regimen (n=30). For i.v., 450 mg was compared with 900 mg (**Figure 9**). A target exposure range was also considered based on the observed PK in the GPP patients in study 1368-0013 who received at least one spesolimab 900 mg i.v. dose (n=50).

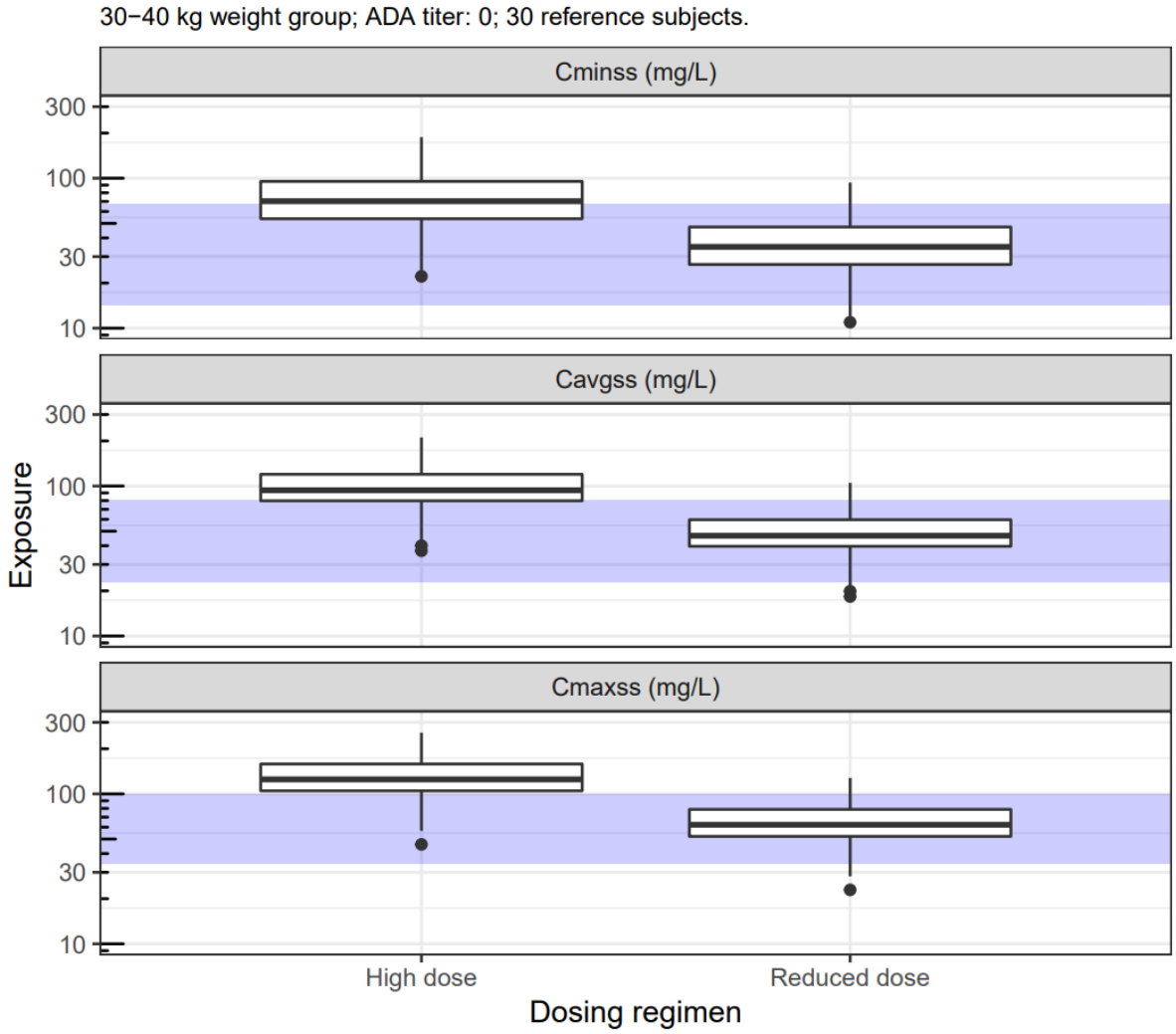


Figure 8 Subcutaneous dosing regimen: population PK model simulations of steady state exposures in the 30 – 40 kg weight group, following a recommended dose regimen (High dose - 600 mg s.c. loading dose followed by 300 mg s.c. q4w for 48 weeks) vs alternative reduced dose regimen (Reduced dose - 300 mg s.c. loading dose followed by 150 mg s.c. q4w for 48 weeks). Median values are designated by a solid line in the center of the box. Boxes indicate the inter-quartile range (IQR) with whiskers extending to 1.5*IQR. The blue shaded region is a reference range, representing the 5th and 95th percentile of model derived exposure from 30 subjects in the high-dose arm of 1368-0027.

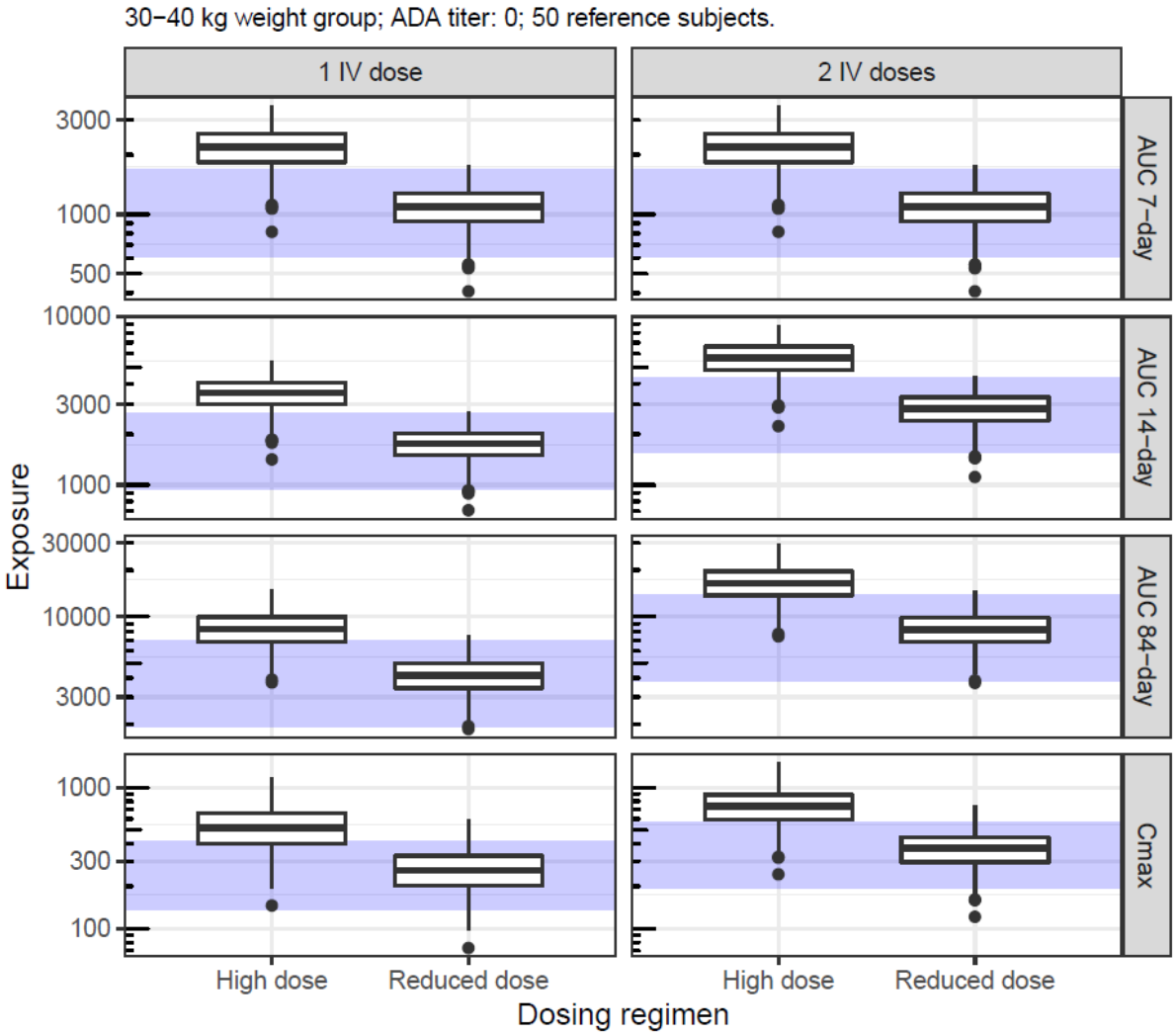


Figure 9 Intravenous dosing regimen: population PK model simulations of exposures in the 30 – 40 kg weight group, following a recommended dose regimen (High dose - 900 mg i.v.) vs alternative reduced dose regimen (Reduced dose - 450 mg i.v.) (1 dose or 2 doses,7 days apart). AUC (mg*day/L) and Cmax (mg/L) in 30–40 kg weight group. Median values are designated by a solid line in the center of the box. Boxes indicate the inter-quartile range (IQR) with whiskers extending to 1.5*IQR. The blue shaded region is a reference range, representing the 5th and 95th percentile of model derived exposure from 50 subjects receiving i.v. treatment in study 1368-0013.

Absorption

Following periumbilical injection, the bioavailability of s.c. spesolimab trended higher with increasing dose: the bioavailability (90% CI) was approximately 58% (51%, 66%), 65% (60%, 69%), and 72% (65%, 79%) at 150 mg, 300 mg, and 600 mg, respectively. The bioavailability following injection at the thigh was approximately 85% at 300 mg, which was higher compared with periumbilical injection at the same dose.

Three investigational subcutaneous (s.c.) spesolimab drug products /drug substances have been used. Analytical comparability studies have been carried out, see quality assessment. No dedicated clinical PK comparability study was conducted between the three s.c. spesolimab drug products/ drug substances.

The bioavailability of s.c. spesolimab was also estimated using a population PK model developed based on i.v. and s.c. data from HV, patients with GPP and patients in other indications. In the model, spesolimab absorption was described by sequential zero-order and first-order absorption (**Table 4**),

with site-dependent rate of absorption and bioavailability. Subcutaneous bioavailability was estimated to be ~ 82% (55 – 95 %, 95% CI) when administered into the perimbilicum while this was increased to ~95% (90 – 97 %, 95% CI) when administered into the thigh or other sites (e.g. combination of thigh and periumbilicum). Note that the bioavailability estimated from the model used a larger and more heterogeneous data source considering healthy volunteer studies and patient studies, a wider dose range, disparate information content (e.g. rich and sparse sampling), mixes of injection sites, and potential confounding with disease state. Therefore this estimate is not directly comparable to the estimate derived from non-compartmental analyses considering data from richly sampled, healthy volunteer studies.

Distribution

Due to the size of spesolimab (~150 kDa), spesolimab administered via the i.v. and s.c. route of administration 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. Individual studies to define the protein binding and tissue distribution of spesolimab were not conducted. The volume of distribution was estimated to 6.3 L according to the PopPK analysis, which is similar to the previous estimate of 6.4 L.

Elimination

The spesolimab elimination was characterised in the PopPK analysis. The linear plasma CL was estimated to 0.179 L/day in a typical patient with a corresponding terminal t½ of 26 days. This is similar to the previous estimate of 0.184 L/h. There was also a non-linear, concentration-dependent elimination pathway which may be due to target mediated drug disposition (TMDD) which was described using the Michaelis-Menten equation (Vmax=50.7 ug/day and Km=8.87 ug/L). The PopPK model also included an ADA-driven elimination pathway.

Dose proportionality and time dependencies

The population PK model predicted time-varying PK differences in certain subjects due to changes in time-varying covariates which includes ADA titer, GPP flare status and injection site. For ADA positive subjects, CL increased along with ADA titer (above a threshold titer value of 340) with 1.26e-6 L/day/titer. CL increased with by ~12-20% in connection to a GPP flare event. When the SC injection site was the periumbilicum, the bioavailability decreased from ~95% to ~82% and the absorption rate increased by ~10%.

Target population

Pharmacokinetic observations in the target population were mainly measured using a sparse PK sampling design. The PK observations in the target population were described using model-based methods (PopPK approach). PK and immunogenicity data in GPP patients is currently available from 4 studies:

- 1368-0011: Proof of concept, spesolimab i.v. 10 mg/kg
- 1368-0013 (Effisayil 1): pivotal trial, spesolimab 900 mg i.v.
- 1368-0027 (Effisayil 2): dose-finding study, spesolimab high, medium and low dos s.c. with 900 mg i.v. (up to two doses) as flare rescue treatment
- 1368-0025 (Effisayil-ON): open-label extension (OLE), spesolimab s.c. 300 mg Q12w / Q6w (with the option of spesolimab i.v. for recurring flare treatment) in patients who completed trials 1368-0013 and 1368-0027. Currently available interim analyses are for patients who rolled over from trials 1368-0013 and 1368-0027.

Summary of observed PK data

Spesolimab trough concentrations after s.c. injection were collected in patients with GPP in the pivotal study 1368-0027 and the OLE study 1368-0025.

In study 1368-0027, following the proposed recommended dose/regimen 600 mg loading dose followed by 300 mg s.c. q4w, the mean steady-state trough concentration ranged 33.4 to 42.3 µg/mL.

Population PK analysis

The spesolimab PK profile was found to be different between the included patient populations according to the covariate analysis. The final PK model parameters listed in **Table 4** are reported for GPP patients. CL in a typical ADA negative subject in the target population was 0.184 L/day. The spesolimab CL was found to be different between GPP patients and healthy volunteers (~30% lower CL in healthy volunteers), UC patients (10% higher CL in UC patients) and PPP patients (~20% lower CL in PPP patients).

Immunogenicity

In ADA-positive patients, ADA developed with a median onset time of 8.0 weeks for patients in the high dose s.c. spesolimab treatment group (which is the dose applied for in this submission) 41% of the patients developed ADAs and 24% of patients had a maximum ADA titer greater than 4 000 and were NAb-positive.

Special populations

The effect of intrinsic factors is evaluated via population PK analysis.

The size of spesolimab is ~150 kDa, hence no renal elimination is expected. No hepatic degradation is expected. Bilirubin was tested as a covariate when developing the PopPK model but was statistically significant. Sex was also tested as a covariate and was not a statistically significant covariate. The PopPK analysis explored race as a covariate; Black and Asian patients were included as categorical covariates in the final model and were predicted to have 8 and 6% higher CL compared to white subjects, respectively (**Table 4**).

A total of 8 adolescent patients were included in Study 1368.27 where six of these patients were randomised to receive spesolimab. Among these six patients, two were randomised to the highest (proposed) dose. The youngest patient was 14 years old. Age was explored as a covariate in the covariate analysis during the PopPK model development. Age was not identified as a statistically significant covariate in the final model. PK simulations were also performed, comparing the expected PK exposure in 1000 adolescents vs adults (see **Table 4**) which showed that the PK exposure is predicted to be higher in adolescents than adults.

Weight was identified as both a statistically and clinically significant covariate for the PK of spesolimab and was included on CL- and V terms with fixed allometric exponents of 0.85 and 1, respectively.

Pharmacokinetic interaction studies

No formal drug interaction studies with spesolimab have been performed.

2.6.2.2. Pharmacodynamics

Mechanism of action

In the initial application for Spevigo for GPP flare treatment, the following information was available to support the mechanism of action of spesolimab in GPP:

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 humanised, 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.

In the initial MAA, it was concluded that 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

No new data have been submitted in this extension application.

Relationship between plasma concentration and effect

Exposure-response (ER) analyses were performed for efficacy- and safety endpoints. The objectives were to:

- Characterise the ER relationship between spesolimab exposure and efficacy (time to first GPP flare) in adult GPP patients in Study 1368.27, and assess covariate effects
- Characterise the ER relationship between spesolimab exposure and safety (time to first infection prior to a GPP flare) in GPP patients from Study 1368.27, and assess covariate effects
- Assess the similarity in spesolimab efficacy between adults and adolescents with GPP by predicting the adolescent outcomes based on the ER (population PK/pharmacodynamic (PD)) model built from adult patients in Study 1368.27, and comparing predictions to observed adolescent outcomes
- Evaluate the benefit-risk profiles of spesolimab subcutaneous (SC) dosing regimens by simulating efficacy and safety responses

ER analyses were conducted using R and Stan through the Rstan interface (cmdstanr v.0.5.3, CmdStan v.2.31.0). Bayesian methods were used with weakly informative priors for developing discrete time-to-event models. Individual time-varying Cavg,7d, Cmax,7d, and Cmin,7d predicted by the PPK model were evaluated as appropriate exposure metrics. The effect of spesolimab exposure on baseline hazard was included by evaluating linear, log-linear and sigmoidal Emax functional forms.

Covariates were explored using a full model approach. Linear, log-linear and sigmoidal Emax functional forms were evaluated. A reduced full model was potentially fitted by including only covariate effects that were considered statistically significant.

Efficacy

Only adult patients from study 1368-0027 intent-to-treat population were included. A sensitivity analysis was performed with the pooled adult and adolescent data. In total, 122 patients were included in the analysis. Covariates included weight, CRP, age, BMI, sex, race, background medication, presence of plaque psoriasis and nAb.

Exposure was a statistically significant covariate in the exposure-response model for efficacy. Exposure, as the time-varying Cavg,7d was included as a predictor for the hazard using a linear function. The base hazard model was described by a piece-wise linear model with a fixed transition at day 30, where the hazard decreased with time. The only significant covariate was prior GPP medication, which was included as separate coefficients on the base hazard before and after day 30, respectively. The final parameter estimates for the efficacy exposure-response model are shown in **Table 6.** A final model VPC stratified by dose level is shown in **Figure 10**.

A sensitivity analysis was conducted by re-estimating the final model with both adult and adolescent data from Study 1368.27. The estimates (not shown) were similar to the final model, with largely overlapping CrIs.

Table 6 ER Efficacy Model: Final model parameter estimates.

Parameter	Description	Posterior median	95% CrI	Bulk-ESS	Tail-ESS	$\hat{R}$
λ_1	Baseline hazard for day <= 30 (1/day)	0.004205	(0.0009139, 0.01297)	6019	5586	1.00
λ_2	Baseline hazard for day > 30 (1/day)	0.001374	(0.0005270, 0.002844)	6576	5859	1.00
δ_1	GPP medication=yes for day <= 30	3.604	(1.121, 16.15)	6484	6202	1.00
δ_2	GPP medication=yes for day > 30	0.4058	(0.1385, 1.246)	6921	5801	1.00
$\exp(\theta)$	Cmin,7d (21.1 mg/L)	0.4606	(0.2702, 0.7218)	8422	7364	1.00

All covariate effect estimates are expressed as a hazard ratio: per 1 SD increase in continuous variables (listed in parentheses), and comparator to reference group for categorical variables. Reference subject defined in the placebo cohort (Cmin,7d = 0) with no prior GPP medication. Abbreviations: SD = standard deviation; CrI = credible interval; ESS = effective sample size; Cmin,7d = 7 day Cmin; $\hat{R}$ = Gelman-Rubin diagnostic; GPP = generalised pustular psoriasis

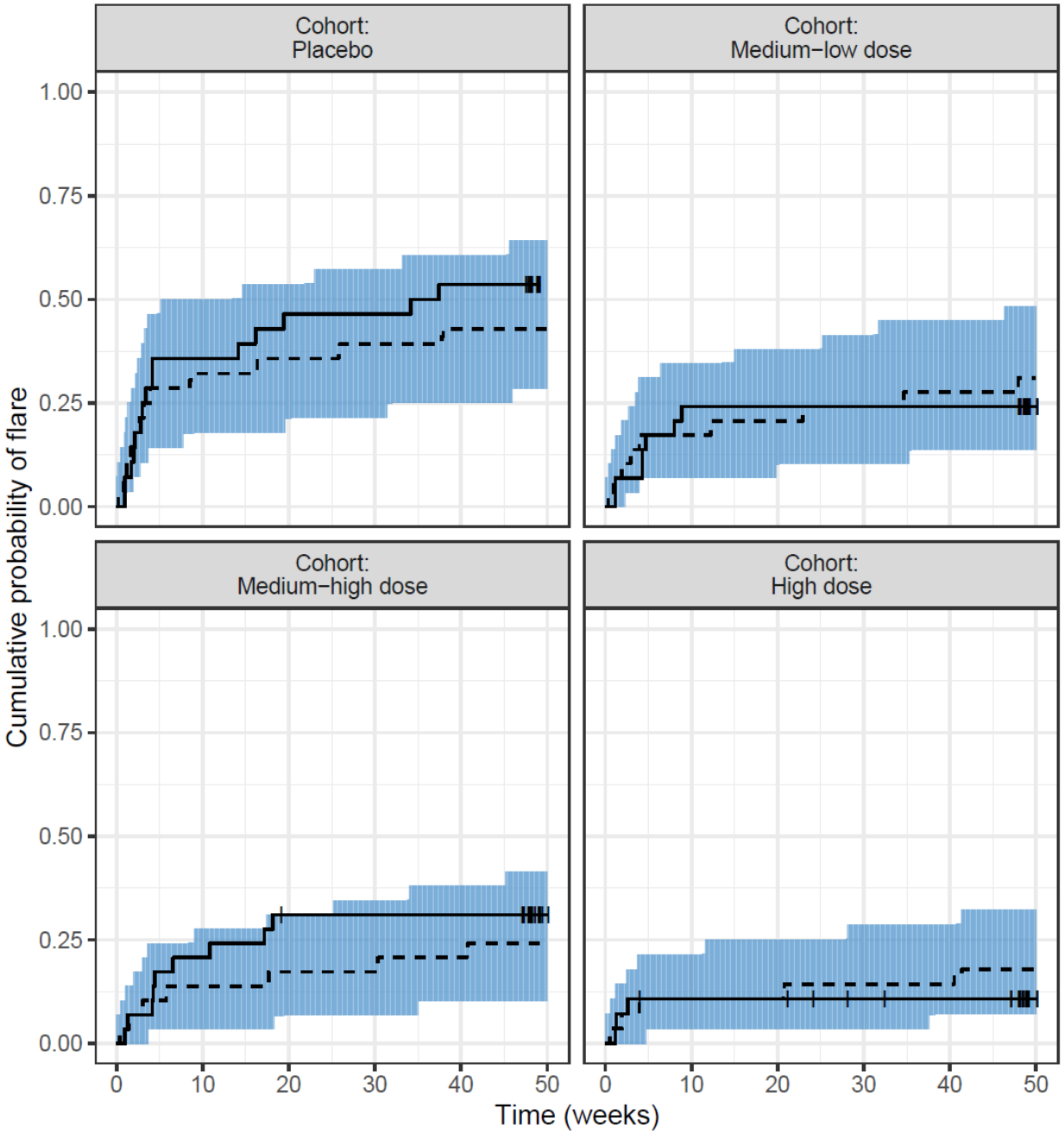


Figure 10 ER Efficacy Model: Visual predictive check of cumulative probability of flare by dose cohort for final model. Solid lines indicate the observed probability. Dashed lines indicate the median of simulated probability. Blue shaded regions represent the 90% confidence interval of the simulated probability. Vertical tick marks indicate censored events.

Safety

The base hazard model in the exposure-response model for safety was described using an exponential function. The base model estimated a non-significant exposure effect on the hazard of infection.

The final model included the covariates age and immunosuppressant use on the baseline constant hazard. Increasing age was associated with a reduced risk of developing an infection. Immunosuppressant use was associated with lower risk of infection. The final parameter estimates for the safety exposure-response model are shown in **Table 7**.

Table 7 ER Safety Model: Final model parameter estimates.

Parameter	Description	Posterior median	95% CrI	Bulk-ESS	Tail-ESS	$\hat{R}$
λ	Baseline hazard (1/day)	0.00167	(0.00116, 0.00233)	9939.6	8002.0	1.00
exp(θ)	Log(Cmax,7d) (mg/L)	0.958	(0.920, 1.00)	10388	7955.8	1.00
exp(β_1)	Age (15.9 y)	0.627	(0.448, 0.868)	9309.5	7897.0	1.00
exp(β_2)	Immunosuppressant use prior to infection = Yes	0.390	(0.147, 0.893)	10756	7755.4	1.00

All covariate effect estimates are expressed as hazard ratio: per 1 SD increase in continuous covariates (listed in parentheses), and comparator to reference group for categorical covariates. Reference subject defined as having Cmax,7d = 1 mg/L (log(Cmax,7d) = 0), age of 41.5 y, with no immunosuppressant use prior to infection.
Abbreviations: CrI = credible interval; ESS = effective sample size; Cmax,7d = 7 day Cmax; $\hat{R}$: Gelman-Rubin diagnostic; CRP = C reactive protein; y = years; SD = standard deviation

Simulations

The ER efficacy final model developed from adult GPP patients was used to predict the flare events of the 8 adolescent subjects in Study 1368-0027. The observed and predicted time to first flare generally overlapped, however, the prediction interval was wide given the small sample size.

At week 4, approximately a 20% reduction in flare was predicted for medium and high dose adult cohorts compared to the adult placebo cohort. The predicted probability of flare in adult patients within 48 weeks of treatment decreased from 0.463 at placebo to 0.166 at high dose. Similar magnitude of flare probability decrease was predicted in adolescent patients (**Table 8**).

Table 8 ER EfficacyModel: Population simulation of cumulative probability of flare

Week	Cohort	Adult	Adolescent
4	Placebo	0.297 (0.198,0.410)	0.201 (0.125,0.314)
4	Med-low dose	0.169 (0.116,0.232)	0.103 (0.0656,0.159)
4	Med-high dose	0.106 (0.0680,0.158)	0.0616 (0.0353,0.102)
4	High dose	0.106 (0.0680,0.159)	0.0605 (0.0363,0.102)
24	Placebo	0.388 (0.279,0.503)	0.333 (0.230,0.452)
24	Med-low dose	0.245 (0.184,0.314)	0.201 (0.140,0.275)
24	Med-high dose	0.168 (0.119,0.229)	0.134 (0.0868,0.200)
24	High dose	0.138 (0.0910,0.202)	0.0898 (0.0535,0.149)
48	Placebo	0.463 (0.345,0.582)	0.448 (0.315,0.587)
48	Med-low dose	0.318 (0.243,0.399)	0.301 (0.208,0.409)
48	Med-high dose	0.232 (0.168,0.308)	0.216 (0.140,0.316)
48	High dose	0.167 (0.111,0.244)	0.118 (0.0686,0.203)

PI = prediction interval. value is median (90% PI)

2.6.3. Discussion on clinical pharmacology

Pharmacokinectics

Analytical methods

The bioanalytical method is considered validated in line with current guidelines and adequate for its purpose. The full validation has been described and assessed in the original MAA application, partial validations new to this submission are acceptable.

Method performance in the clinical studies was acceptable (including studies in other indications).

The ADA-assay for the GPP population was assessed in the original application and concluded adequately validated. During analysis of samples from clinical studies the assay performed acceptably.

Drug tolerance is an issue for the NAb-assay. Drug tolerance in GPP matrix was determined to be 100 µg/mL at the LPC (507 ng/ml) and 400µg/mL at the MPC (900 ng/ml) where drug tolerance for C_{trough} levels at ADA-levels of 100 ng/ml is desirable. This was discussed already in the original application for GPP flares. It was accepted that there were limited possibilities of developing a more adequate assay. From the clinical studies in the GPP population only five samples had inconclusive NAb status due to spesilomab concentrations higher than the established drug tolerance for the assay. As no influence on efficacy by ADAs is noted in the clinical studies the development of NAbs appears not to be a relevant clinical issue for treatment or prevention of flares in GPP.

Absorption

Overall, the bioavailability of s.c. spesolimab was characterised over the dose range of 150 to 600 mg and at the two injections sites (periumbilical or at the thigh). The bioavailability following injection at the thigh was approximately 85% at 300 mg, which was higher compared with periumbilical injection at the same dose. The absorption data is adequately reflected in the SmPC.

The absorption characteristics of spesolimab was also quantified in a PopPK analysis where the conclusions overall agree with the non-compartmental analysis which is reassuring.

Distribution

No plasma protein binding or tissue distribution study was performed. This is acceptable. The distribution of spesolimab is consistent with reported PK parameters for other IgG1s in human. In the initial MAA, the volume of distribution was estimated to 6.4 L. This is similar to the estimate of 6.3 in the current procedure.

Elimination

The metabolic pathways of spesolimab have not been investigated. This is acceptable for an IgG antibody. Commonly the $t_{1/2}$ reported for human IgG is around 20 days which is in line with the t½ for spesolimab of 25.5 days, though there is a wide range in the reported value.

In the current extension of application, a subcutaneous route of administration is introduced in addition to IV spesolimab which was the subject of the initial MAA. A change in route of administration is not expected to alter the elimination characteristics of spesolimab which was confirmed by the population PK analysis.

Dose proportionality and time dependencies

The PopPK model includes a concentration-dependent CL function which, in theory, indicates that there is a dose-dependency in spesolimab exposure. However, in practical terms, the concentration-

dependent non-linear CL will be negligible at the observed concentration range at the proposed dosing regimen.

The spesolimab PK profile may change over time due to time-varying covariates including ADA titer, GPP flare status and injection site. Of these, only ADA titer is considered to be of clinical importance.

Target population

Describing the PK exposure in the target population using a PopPK approach is considered reasonable given that a sparse PK sampling design was used in GPP patients. The final PK model was shown to give acceptable description of the PK vs time data for GPP patients. The PopPK model can thus be considered a reasonable source of information, e.g. for the SmPC. In addition, the PopPK model can be used to better understand the expected PK exposure in adolescents which is considered important information for determining the benefit/risk in adolescents where there are very limited efficacy, safety and PK data.

The PopPK model was developed on a dataset including 8920 samples from 760 subjects, including data from Studies 1368-0027 (562 observations from 106 subjects) and Study 1368-0025 (402 observations from 107 subjects). Overall, it is considered a solid dataset for development of a robust and fit-for-purpose PopPK model. Relevant covariates were explored and their distributions are considered adequate for the purpose of identifying covariates. Body weight is considered a covariate of particular importance given that this procedure concerns a monoclonal antibody in adolescents.

The Applicant presented parameter estimates and various goodness-of-fit plots for the final model. The parameter estimates were overall reasonable and with reasonable precision, however, the variability in the ADA-driven CL is noted to be very large.

The presented VPCs indicate that the final model gave acceptable description of the observed data including data vs time in GPP patients and stratified by body weight.

The Applicant considered subject type, injection site, weight, and ADA titer to be covariates of potential clinical importance. This is agreed. All of these covariates are relevant to be aware of.

ADA was estimated to have a large impact on the PK profile of spesolimab, to a larger extent than what is seen for most monoclonal antibody therapeutics. ADA was implemented in the model using an overall reasonable strategy in that the time-varying continuous ADA titer value was used to describe the increase in CL (using a linear equation). This implementation is considered overall acceptable for describing this effect in the target population (including adult and adolescent GPP patients). As a sensitivity analyses, the Applicant estimated separate ADA parameters (slope- and threshold parameter) for GPP patients and although there were numerical differences, they were not considered clinically significant (data not shown).

There were only data available from few adolescents treated with Spevigo and there were an uncertainty regarding if the ADA development could be different between adults and adolescents which could not be answered using the current dataset. The Applicant provided a theoretical/biological discussion to describe if the ADA development against spesolimab could be different between adolescents and adults with reference to available scientific literature. The provided discussion is however not considered comprehensive and there is still remaining uncertainty whether the ADA development for Spevigo could be different between adults and adolescents. It should be acknowledged that the scientific literature concerning immune system development and ADA development between adults and adolescents is scarce and hence, this issue is not pursued further.

The inter-individual variability in CL of ~30% is reasonable and is in line with estimates from the previous PopPK model in the initial MAA. Other sources of variability as predicted from the PopPK

model are IIV in the ADA-dependent CL (CV% of 2260) and IIV in bioavailability (standard deviation of 0.0729 on the logit-scale). The variability in observed Ctrough was also reasonable (~40%).

Immunogenicity

With the current amount of immunogenicity data, it is considered appropriate to include overall incidence of ADA (i.e., not only ADAs above a specific titer) and mention that a majority of ADA-positive subjects also developed NAbs. The immunogenicity data presented in the SmPC has been amended accordingly.

Special populations

Body weight was identified as a clinically significant covariate for the PK of spesolimab. This finding agrees with other monoclonal antibodies. Using fixed allometric exponents of 0.85 and 1 is considered acceptable.

An important aspect in the current procedure is the lower body weight expected in adolescents, which necessitates a lower dose in very light subjects to prevent overexposure to spesolimab. Given the few included adolescents in the dataset, adequate understanding of the PK exposure across different body weights among adolescents is gained from the simulations stratified by body weight compared with adult exposure (the reference range). The settings and simulation workflow are considered acceptable.

The simulations for the s.c. dosing (prevention setting) and i.v. dosing (treatment of flare setting) were assessed mainly from a safety perspective, with focus on exposure in adolescents with low body weight. The PK exposure in all weight groups down to 50 kg displays reasonable overlap with the reference range both for s.c. and i.v. treatment. This, together with the fact that Spevigo displays an overall favourable safety profile in adults at the recommended doses suggests that the proposed doses (s.c. and i.v.) are reasonable in subjects down to 50 kg.

Below 50 kg, the exposure is overall higher than the reference range which could imply a safety concern. For the 40-50 kg weight group, there is only partly overlap with the reference range. The proposed i.v. and s.c. dose is, however, considered acceptable in patients 40-50 kg since there are observed PK, efficacy and safety data from patients in this weight group following 900 mg i.v. and 300 mg Q4W s.c. In addition, Spevigo displays an overall favourable safety profile in adults at the proposed doses (s.c. and i.v.) and higher doses in studies in other indications have not been apparently associated with a more serious safety profile.

Patients weighing between 30-40 kg have clearly higher exposure than the reference range when administered the corresponding adult dose regimen.

The Applicant provided simulations to support reduced dose regimens in patients weighing 30-40 kg. Based on pharmacokinetic modelling and simulation, the recommended dose for adolescents from 12 years of age weighing 30 - 40 kg is a single dose of 450 mg (one vial of 450 mg) administered as an intravenous infusion (see section 4.2 and 5.2 of the SmPC). If flare symptoms persist, an additional 450 mg dose (one vial of 450 mg) may be administered 1 week after the initial dose. A 300 mg loading dose followed by 150 mg Q4W is recommended for s.c. dosing in patients 30-40 kg.

A PopPK analysis was used to assess the relevance of the other special populations (impaired renal function, impaired hepatic function, gender, race and elderly) which is acceptable and no concerns are raised. Age, gender and race do not have a clinically relevant effect on the PK of spesolimab.

Pharmacokinetic interaction studies

No formal drug interaction studies with spesolimab have been performed. The potential of spesolimab to cause clinically significant DDI as a perpetrator is low for both the prevention of GPP flares when

patients are not experiencing flares and for the treatment of GPP flares when patients are experiencing flares. The applicant's justification for the low risk of cytokine mediated CYP interactions is agreed.

Pharmacodynamics

No new, dedicated pharmacodynamic studies have been submitted in support for this extension application for Spevigo. In the initial MAA for the GPP flare treatment indication, it was concluded that based on published data, there is a plausible mechanism of action for spesolimab in GPP, as a blocker of human IL-36R activation. This hypothesis seems relevant also for a GPP flare prevention indication and no additional pharmacodynamic studies are considered necessary.

With respect to pharmacodynamic interactions, similar to the pivotal study in the initial Spevigo MAA (1368-0013), spesolimab was not to be combined with products commonly used to treat GPP, and there were restrictions in concomitant medications also in the GPP flare prevention study 1368-0027. For instance, the use of methotrexate, retinoids and ciclosporin had to be stopped at randomisation. Hence, there is no vast experience from the use of spesolimab concomitantly with other immunomodulating drugs. This is further discussed in other parts of this report.

Spesolimab is directed against IL36 receptor 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 not been available for all patients across the GPP clinical studies and this was not among the inclusion criteria. Sub-group analyses for efficacy were performed based on the mutation status; these are evaluated below. Having an IL-36RN mutation was not a requirement for inclusion the GPP flare prevention pivotal study (1368-0027), nor in the flare treatment or POC study (1368-0013 and 1368-0011) and this is not included as a requirement in the indication either. This is endorsed and aspects related to this are further discussed in other sections of this report.

Pharmacokinetics-pharmacodynamics

Overall, reasonable objectives were established for the exposure-response analyses. The performed exposure-response analyses are considered supportive to the standard efficacy and safety analyses when it comes to assess the benefit-risk.

The data used to develop the efficacy and safety model seems reasonable. The selected covariates and their distributions (not shown) seem reasonable for identifying significant covariates. A similar time-to-first event model development workflow was used for developing exposure-response models for both efficacy and safety endpoints. This is considered appropriate. Exposure was evaluated as the time-varying exposure which is considered a strength.

A significant relationship was identified where increasing spesolimab exposure was shown to reduce the probability of a GPP flare event. A linear functional form was identified for this relationship. The fact that a linear function is used is considered a limitation. As for most drug, the actual underlying exposure-response relationship may follow a sigmoidal Emax model but this was not identifiable. The consequence of this linear model is that the model cannot be used to extrapolate efficacy outside of the observed exposure range.

A time-varying base hazard function was used. There seems to be a considerable time-dependency in the hazard based on the development of the cumulative probability in the placebo arm. However, a piece-wise linear model with a fixed inflection point at day 30 is considered a limitation since this represent an empirical time-varying hazard model. Most likely this hazard function is specific for the setting of study 1368.27 and the model should be used with caution e.g. when simulating outside the setting of the observed study.

Background GPP medication was identified as a significant covariate on the base hazard. Interestingly, subjects with background GPP medication had a considerable increase in the base hazard prior to day

30 whereas after day 30, the base hazard was lower in subjects with background GPP medication. This is considered another empirical element in the final model which is a limitation.

In summary, the exposure-response analysis for efficacy identified an exposure-response relationship which supports the selection of the highest dose level. Several limitations have been identified related to empirical elements in the model which means that model simulations outside the setting of the observed data should be interpreted with caution. As the exposure-response analysis of efficacy has low impact, these issues are not further pursued.

The Applicant performed simulation of efficacy. The predicted and observed probability of flare in adolescents overlapped. Thus, the model can be used for predicting the effects in adults, however, the prediction intervals are wide since there were only 8 adolescents included, where 6 received spesolimab.

Simulations of a larger number of GPP patients was also performed to compare efficacy and safety between adults and adolescents. The simulations did not show any substantial difference between adults and adolescents where the confidence intervals were generally overlapping. The way the simulations were conducted is not optimal (see assessment above for the PopPK model). However, the impact of the efficacy simulations is considered to be lower than the corresponding PK simulations. Hence, these issues will not be further pursued.

The exposure-response analysis for safety did not identify an exposure-response relationship between spesolimab exposure and risk of infection.

2.6.4. Conclusions on clinical pharmacology

The PK of spesolimab following subcutaneous administration is adequately described.

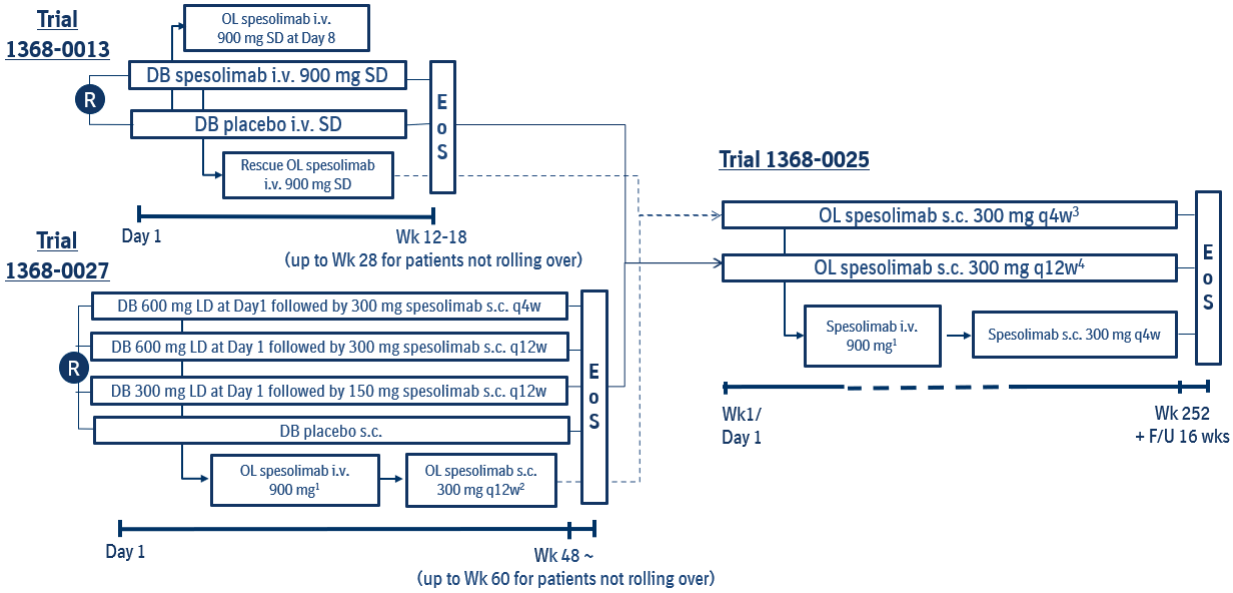
No new, dedicated pharmacodynamic studies have been submitted in support for this extension application for Spevigo, which is accepted.

Exposure-response analyses for efficacy and safety were provided but were considered to have low impact and no questions are raised.

2.6.5. Clinical efficacy

The clinical development program with spesolimab in GPP comprises 4 trials that are completed or ongoing (see **Figure 11**) and was designed to evaluate spesolimab for the:

- Treatment of GPP flares: the completed trials **1368-0011** (proof of concept trial) and **1368-0013** (Effisayil 1, pivotal trial) showed efficacy and safety of spesolimab i.v. for flare treatment.
- Prevention of GPP flares:
  - Trial **1368-0027** (Effisayil 2): this pivotal trial investigated efficacy and safety of spesolimab s.c. for flare prevention in patients with a history of GPP. This trial forms the basis for the current MAA and is assessed below.
  - Trial **1368-0025** (Effisayil-ON): The objective of this ongoing open-label extension (OLE) trial is to evaluate long-term safety and efficacy of spesolimab s.c. (with the option of spesolimab i.v. for recurring flare treatment) in eligible patients who completed trials 1368-0013 and 1368-0027. Interim data are included in the current MAA.



DB = double-blind, LD = loading dose, OL = open label, q4w = once every 4 weeks, q12w = once every 12 weeks, SD = single dose

1 Option of a second 900 mg i.v. dose of spesolimab 7 days after the first dose if flare symptoms persist

2 If the patient's GPPGA total score or pustulation subscore increases by ≥1 from any previous OL maintenance visit, dosing frequency may be increased to 300 mg q4w (intensified maintenance treatment)

3 If patients fulfill the criteria of dose de-escalation, they may be switched to 300 mg q12w. The dosing frequency of q6w was implemented before CTP amendment 2

4 If patients fulfill the criteria of dose escalation, they may be switched to 300 mg q4w

Figure 11. Overview of completed or ongoing Phase II clinical trials with spesolimab in patients with GPP

2.6.5.1. Dose response study(ies)

For the GPP prevention indication, the Phase IIb study 1368-0027 included three dose arms of spesolimab. Since this study is also the pivotal study to support the prevention indication (and not only serves as a dose finding study), it will be described below, *Main study*.

2.6.5.2. Main study

This application for an extension of the indication for Spevigo is supported by study 1368-0027 (or sometimes referred to only as study 0027). This was a global, multi-center, double-blind, randomised, placebo-controlled Phase IIb dose-finding trial that evaluated efficacy and safety of 3 s.c. dosing regimens of spesolimab compared with placebo in preventing GPP flares in patients with a history of GPP.

Supportive information on spesolimab s.c. for the maintenance treatment of patients with GPP (and on spesolimab i.v. for GPP flare treatment) is also derived from the ongoing Phase II trial 1368-0025. Interim data from this trial up to a cut-off date of 01 Dec 2022 is included in the current MAA.

Study 1368-0027 (Effisayil 2)

Methods

- **Study Participants**

Inclusion criteria

1. Patients with a known and documented history of GPP per ERASPEN criteria regardless of IL36RN mutation status (see below), with at least 2 presentations of moderate to severe GPP flares with fresh pustulation (new appearance or worsening) in the past. The ERASPEN criteria are as follows:

Primary, sterile, macroscopically visible pustules on non-acral skin (excluding cases where pustulation was restricted to psoriatic plaques)

- With or without systemic inflammation
- With or without plaque-type psoriasis
- Either relapsing (>1 episode) or persistent (>3 months)

2. Patients with a GPPGA score of 0 or 1 at screening and randomisation.
3. Patients who were not on concomitant GPP treatment at time of randomisation (V2) must have had at least two presentations of moderate to severe GPP flare in the past year, at least one of which had evidence of either fever and/or elevated CRP and/or elevated WBC, and/or asthenia and/or myalgia.
4. Patients who were not on concomitant GPP treatment at time of randomisation (V2) but who were on concomitant GPP treatment until shortly before randomisation (V2) (≤12 weeks before randomisation), these patients must have a history of flaring while on concomitant treatment for GPP or in case of dose reduction or discontinuation of their concomitant medication.
5. Patients who were on concomitant treatment regimen with retinoids and/or methotrexate and/or cyclosporine must stop at the day of randomisation (V2). These patients must have had a history of flaring while on concomitant treatment for GPP or in case of dose reduction or discontinuation of these concomitant medications.
6. Male or female patients aged 12 to 75 years at screening. For all patients, a minimum weight of 40 kg was required.
7. Signed and dated written informed consent and assent in accordance with ICH-GCP and local legislation prior to admission in the trial.
8. Women of childbearing potential (WOCBP), as specified in the protocol, were ready and able to use highly effective methods of birth control per ICH M3 (R2) that result 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 clinical trial protocol (CTP) as well as in the patient, parent(s) (or patient's legal guardian) information.

Patients with a history of GPP were included regardless of their IL36RN mutation status based on the following reasons:

- Efficacy has been seen in patients with GPP both with and without the IL36RN mutation (early response to flare treatment with spesolimab in 1368.11).

- In addition to the described IL36RN mutation, other mutations in the same gene and other genes linked to the IL36 pathway have been described, which points to a general role of the IL36 pathway as disease trigger/driver.
- Mutation status was only available for a subset of GPP patients.

Exclusion criteria

1. Patients with SAPHO (Synovitis acne–pustulosis–hyperostosis–osteitis) syndrome.
2. Patients with primary erythrodermic psoriasis vulgaris.
3. 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.
4. Treatment with:

    a. Any restricted medication as specified in the CTP, or any drug considered likely to interfere with the safe conduct of the study, as assessed by the investigator.

    b. Any prior exposure to spesolimab or another IL36R inhibitor biologic.
5. Increased risk of infectious complications (e.g. recent pyogenic infection, any congenital or acquired immunodeficiency (e.g. HIV), past organ or stem cell transplantation), as assessed by the investigator.
6. Relevant chronic or acute infections including active tuberculosis, human immunodeficiency virus (HIV) infection or viral hepatitis at the time of randomisation.

    Patients may have been re-screened if the patient was treated and was cured from the acute infection.
7. Active or Latent TB:
    - Patients with active tuberculosis were excluded
        - Patients with a positive QuantiFERON (or if applicable, T-Spot) TB test during screening were excluded, unless the patient had previous diagnosis of active or latent TB and had completed appropriate treatment per the discretion of the local investigator within the last 3 years and at the latest at the time of screening (i.e. 2 to 4 weeks before study drug administration); patients may have been re-screened once to meet this criterion)
        - Patients with suspected false positive or indeterminate QuantiFERON (or if applicable, T-Spot) TB result may have been re-tested once
        - If QuantiFERON (or if applicable, T-Spot) TB testing was not available or provides indeterminate results after repeat testing, a tuberculin skin test (TST) or any alternative test/procedure (as per local standards) to rule out TB can be performed: A TST reaction of ≥10mm (≥5mm if receiving ≥15mg/d prednisone or its equivalent) was considered positive.
8. History of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients.
9. Exclusion criteria removed in global amendment 1. Numbering of subsequent criteria was not changed.

10. 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.
11. Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s) or receiving other investigational treatment(s). Exception: Patients in the 1368-0013 study who are in the screening period and who were not randomised in the 1368-0013 trial due to the study meeting target number of randomised patients or who did not qualify to be randomised into the 1368-0013 study may have been enrolled in the 1368-0027 study if they meet all inclusion/exclusion criteria.
12. Women who are pregnant, nursing, or who plan to become pregnant while in the trial. Women who stop nursing before the study drug administration do not need to be excluded from participating; they should refrain from breastfeeding for 16 weeks after the last study drug administration.
13. 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, e.g. hip replacement, aneurysm removal, stomach ligation, as assessed by the investigator.
14. Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse or congestive heart disease 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 make the study participant unreliable to adhere to the protocol, comply with all study visits/procedures or to complete the trial, compromise the safety of the patient or compromise the quality of the data.

- **Treatments**

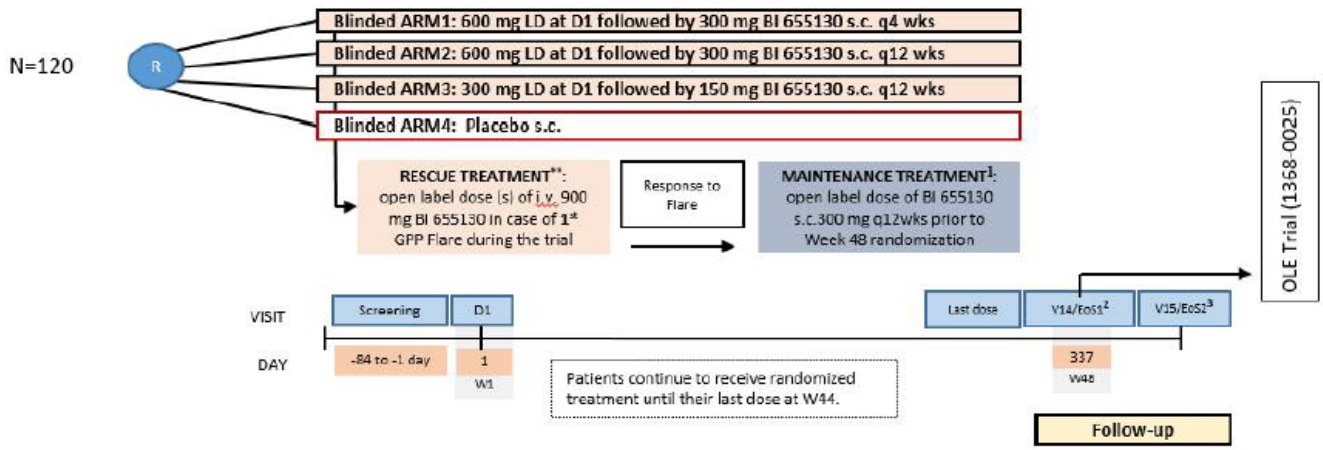
Eligible patients with GPP were randomised in a 1:1:1:1 ratio to placebo, low, medium, or high treatment arms. The active treatment arms consisted of active loading dose and active maintenance treatment:

Arm 1: Spesolimab 600 mg s.c. loading dose on Day 1, followed by 300 mg s.c. q4w maintenance treatment (high dose)

Arm 2: Spesolimab 600 mg s.c. loading dose on Day 1, followed by 300 mg s.c. q12w maintenance treatment (medium dose)

Arm 3: Spesolimab 300 mg s.c. loading dose on Day 1, followed by 150 mg s.c. q12w maintenance treatment (low dose)

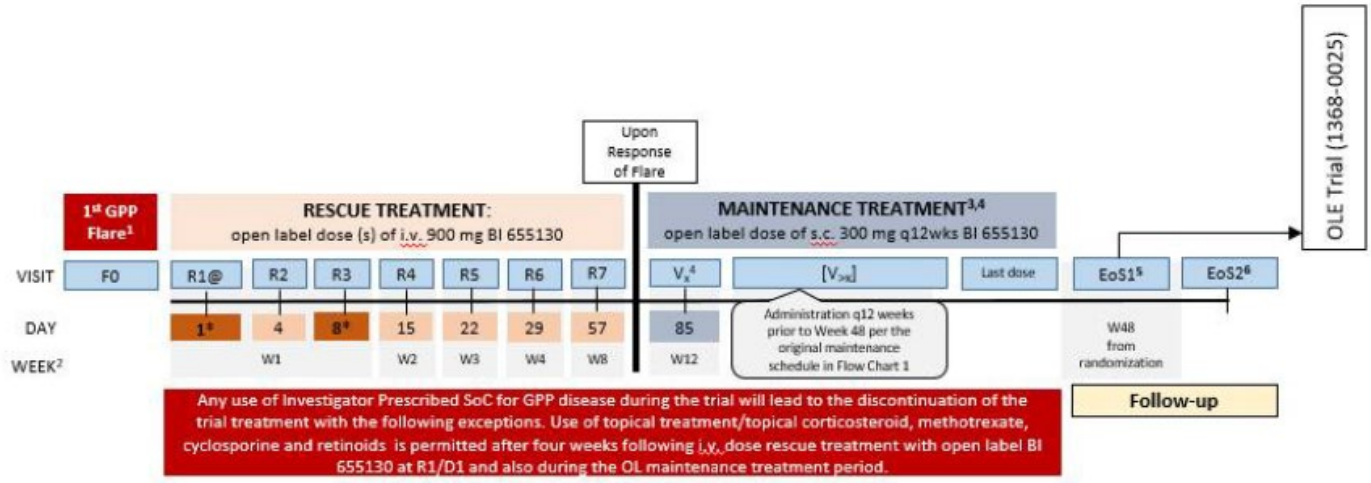
Arm 4: Placebo loading dose on Day 1, followed by placebo maintenance treatment



** In an event a patient experienced 1st GPP flare, please refer to the figure below for further details.

1 If the patient's GPPGA total score increased by ≥1 (with or without the presence or new appearance of pustules), or if there was an increase in the pustular component of GPPGA ≥ 1, the investigator may have treated the patient with intensified maintenance therapy of OL spesolimab s.c. 300 mg q4weeks.
LD = Loading Dose; EoS = End of Study
2 EoS 1: V14 was recorded as the End of Study visit (i.e. EoS1) for patients who qualified and agreed to enter the OLE trial (1368-0025). V14 was also recorded as End of Study visit for patients who prematurely discontinued with the last dose of treatment up to and including Day 232 and who agreed to complete all remaining study visits up to Week 48 from randomisation. Since these patients prematurely discontinued, they would not qualify to enter OLE trial.
3 EoS 2: It was applicable to patients who did not qualify or did not agree to enter the OLE Trial (1368-0025) at Week 48.
EoS2 was also applicable for patients who prematurely discontinued with the last dose of treatment after Day 232. Since these patients prematurely discontinued, they would not qualify to enter OLE trial. EoS2 was their End of Study visit for the trial.

Figure 12. Overall trial design



[1] increased in GPPGA score by ≥2 from baseline and the pustular component of GPPGA ≥2

[2] Week represented the end of each week (e.g. End of Week1 = D8, End of Week2 = D15, End of Week3 = D22, End of Week4 = D29, etc.). w* represents * weeks after the rescue treatment.

[3] Investigator may have treated the patient with intensified maintenance therapy of OL spesolimab s.c. 300 mg q4 weeks if the patient met protocol specified criteria. Please refer to Section 9.1.

[4] Patients who received rescue treatment with spesolimab up to Week 34 (Day 239) of randomization started the OL s.c. maintenance treatment 12 weeks later following the response of the GPP flare. If the first dose of OL s.c. maintenance treatment was outside of any scheduled visit window by ±7 days per Table 9: 7, it needed to be assigned to one of the scheduled visits following the rules in Table 3.1: 1 in CTP (see Appendix 16.1.1); Patients who received rescue treatment with spesolimab after Week 34 (Day 239) of randomization were to attend visits as described in Table 3.1: 2 in CTP (Appendix 16.1.1).

@The day of administration of rescue treatment = Day 1. All subsequent study Days were counted from this Day 1 except for 'Last dose' for the maintenance treatment, EoS1 and EoS2.

***Dosing days**.

[5] **EoS1**, V14 was recorded as the End of Study visit (i.e. EoS1) for patients who qualified and agreed to enter the OLE trial (1368-0025). V14 was also recorded as End of Study visit for patients who prematurely discontinued with the last dose of treatment up to and including Day 232 and who agreed to complete all remaining study visits up to Week 48 from randomization. Since these patients prematurely discontinued, they did not qualify to enter OLE trial.

[6] **EoS2 was** applicable for patients who did not qualify or who did not agree to enter OLE trial (1368-0025) at Week 48. EoS2 was also applicable for patients who prematurely discontinue with the last dose of treatment after Day 232. Since these patients prematurely discontinued, they did not qualify to enter OLE trial.

Figure 13. Trial design in the event a patient experiences 1st GPP flare

Randomisation was stratified by use of systemic GPP medications at randomisation (yes vs. no), region (Japan vs. non-Japan, to ensure that sufficient Japanese patients per treatment group were recruited), and age (adult vs. adolescents). If the investigator treated a patient during the randomised maintenance treatment period with Standard of Care (SoC) for GPP disease worsening, the patient had to discontinue from trial drug administration.

Patients who experienced their first flare in this trial, defined as an increase in the GPPGA total score by ≥2 from baseline and the GPPGA pustulation subscore ≥2, during the randomised maintenance treatment period, were eligible to receive treatment with an open-label dose of i.v. spesolimab 900 mg. Patients might have qualified for another dose of spesolimab 900 mg i.v. treatment after 1 week if their symptoms persisted according to the prespecified criteria.

If the patient responded to the spesolimab flare treatment, the patient could continue to receive open label spesolimab s.c. for maintenance. They received OL s.c. doses of 300 mg spesolimab q12w, which could be escalated to q4w. If the patient's GPPGA total score increased by ≥1 (with or without the presence or new appearance of pustules), or if there was an increase in the pustular component of GPPGA ≥1 from any of the previous OL maintenance visit(s), then the investigator could treat the patient with intensified maintenance therapy with open label s.c. dose of 300 mg spesolimab q4 weeks.

Patients who completed the randomised period of 48 weeks as planned and met the eligibility criteria of trial 1368-0025 were offered to enter the OLE trial.

Concomitant treatments

All concomitant medications were carefully evaluated by the investigator and the Clinical Trial Manager was contacted when there were questions regarding concomitant medications.

The use of Investigator Prescribed SoC led to the discontinuation of the trial treatment except for the use of topical treatment/topical corticosteroids, methotrexate, cyclosporine, and retinoids during OL flare treatment period (4 weeks following i.v. dose rescue treatment with OL spesolimab at R1/D1) and OL maintenance treatment period.

The medications (or classes of medications) listed in the table below were not to be taken for the time periods as specified for washout:

Table 9. Restricted medications

Medication or class of medications	Restriction duration
Biologic Treatments, e.g.: secukinumab (Cosentyx®), tildrakizumab (Ilumya™), rituximab, ustekinumab (Stelara®), risankizumab (Skyrizi™), natalizumab, alemtuzumab, guselkumab (Tremfya®), ixekizumab (Taltz®), adalimumab (Humira®), brodalumab, efalizumab, visilizumab, briakinumab. infliximab (Remicade®), certolizumab (Cimzia®)	12 weeks or 5 half-lives, whichever is shorter, prior to Visit 2 (randomization)
Investigational products for psoriasis	12 weeks or 5 half-lives, whichever is shorter, prior to Visit 2 (randomization)
IL36R inhibitors	Not allowed
Etanercept (Enbrel®) live virus vaccinations[2]	6 weeks prior to Visit 2
Any investigational device or product (excludes psoriasis products) Other systemic immunomodulating treatments (e.g. corticosteroids[1], cyclophosphamide), tofacitinib (Xeljanz®), apremilast (Otezla®) Other systemic psoriasis treatments (e.g. fumarates, any other drug known to possibly benefit psoriasis) photochemotherapy (e.g. PUVA).	4 weeks prior to Visit 2
GMA (Granulocytes and monocytes adsorptive apheresis)[2]	4 weeks prior to Visit 2
Topical corticosteroids	Must be stopped at the day of randomization.
Anakinra (Kineret®)	7 days prior to Visit 2
Methotrexate, cyclosporine, retinoids	Must be stopped at the day of randomization. Patients can be on these background medications at screening visit (V1); however they can only be randomized (V2) into this trial on the day of their next scheduled dose for the background treatment (where the patient should not take the dose) but instead be randomized on the trial.

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

[2] Live virus vaccination and use of GMA should be restricted until the end of the trial.

Restrictions regarding concomitant treatment

The following listed medications were not permitted throughout the study participation unless they were prescribed by investigators to treat disease worsening of GPP. However, it was strongly recommended not to prescribe SoC even for GPP disease especially when patients were on the randomised treatment. The use of Investigator Prescribed SoC for GPP will lead to the discontinuation of the trial treatment with some exceptions as described below.

Biologic treatments

Treatment with biologics was not allowed throughout the study.

Topical treatments

Topical treatment and any other therapies (e.g. Phototherapy) for GPP were not allowed throughout the study with some exceptions, e.g. use for other conditions (e.g. fungal infections, plaque psoriasis etc.), for treatment of GPP after 4 weeks following i.v. dose rescue treatment with OL spesolimab at R1/D1 and during the OL maintenance treatment period.

Topical corticosteroids

Topical corticosteroids for the treatment of GPP were not allowed throughout the study with the following exceptions:

- Topical corticosteroid for other conditions (e.g. fungal infections, plaque psoriasis etc.) may have been initiated post visit 2 if needed.
- Topical corticosteroid was permitted for treatment of GPP after 4 weeks following i.v. dose rescue treatment with OL spesolimab at R1/D1.
- Topical corticosteroid was permitted for treatment of GPP during the OL maintenance treatment period.

Systemic immunomodulating treatments

Systemic immunomodulating treatments (e.g. corticosteroids, cyclophosphamide), tofacitinib (Xeljanz), apremilast (Otezla) and other systemic psoriasis treatments (e.g. fumarates, any other drug known to possibly benefit psoriasis) photochemotherapy (e.g. PUVA) for the treatment of GPP were not allowed.

Methotrexate, Cyclosporine, Retinoids

- Randomised treatment period: Treatment with Methotrexate, Cyclosporine, Retinoids was not allowed.
- Rescue treatment period and open-label maintenance treatment period: Methotrexate, Cyclosporine, or Retinoids were allowed for the treatment of GPP only for those who had received a flare rescue treatment with i.v. dose of spesolimab and had a partial response to the rescue treatment as following.

After at least 4 weeks from the rescue treatment at R1/D1, it was recommended to first initiate treatment with topical corticosteroids to manage skin symptoms, and then if further adjunctive treatment was required, then methotrexate, cyclosporine and/or retinoids were initiated and continued with stable dosing until the patient achieves GPPGA score 0 or 1 or as per the investigator's judgement.

Other medications/products:

Treatment with a list of other medications/products were also not allowed throughout the study, e.g. investigational products for psoriasis, IL36R inhibitors, etanercept, live virus vaccinations, any investigational device or product (excludes psoriasis products), anakinra (Kineret) and GMA (Granulocytes and monocytes adsorptive apheresis).

- **Objectives**

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

The secondary objective was 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 was to evaluate safety and tolerability of multiple s.c. doses of spesolimab in patients with history of GPP.

The use of intravenous (i.v.) dose of spesolimab for treating patients with onset of acute GPP flare was evaluated for safety and efficacy as an additional objective.

- **Outcomes/endpoints**

The primary, key secondary, and secondary endpoints of trial 1368-0027 are summarised in **Table 10.**

Table 10. Primary and secondary efficacy endpoints in trial 1368-0027

Efficacy endpoints	Definition	In testing strategy
Primary: time to first GPP flare	Increase in GPPGA score by ≥2 and GPPGA pustulation subscore ≥2 from baseline up to Week 48	Yes
Key secondary: occurrence of at least 1 GPP flare		Yes
Secondary: time to first worsening of PSS	4-point increase in total score from baseline up to Week 48	Yes
Secondary: time to first worsening of DLQI	4-point increase in total score from baseline up to Week 48	Yes
Secondary: sustained remission	GPPGA score of 0 or 1 at all visits up to Week 48	No

The use of spesolimab i.v. treatment or investigator-prescribed standard of care (SoC) to treat GPP worsening were considered events or treatment failures for all endpoints

GPPGA-related endpoints

The **GPPGA** score is the mean of the subscores for the three components erythema, pustules, and scaling/crusting of all GPP lesions, with each component to be scored from 0 (clear) to 4 (severe). A GPPGA score of 0 requires all 3 subscores to be 0.

The GPPGA relies on clinical assessment of the GPP patient's skin presentation. It is a modified PGA, a physician's assessment of psoriatic lesions, which has been adapted to the evaluation of GPP patients. The investigator (or qualified site personnel) scores the erythema, pustules, and scaling of all GPP lesions from 0 to 4. Each component was graded separately, the average was calculated, and the final GPPGA was determined from this composite score. A lower score indicates a lesser severity, with 0 being clear and 1 being almost clear.

Patient-reported outcome measures

The **PSS** score is a 4-item instrument that includes the symptoms pain, redness, itching, and burning, with scores of current symptom severity ranging from 0 (none) to 4 (very severe); these scores are added to an unweighted total score ranging from 0 to 16. Validation of this patient-reported outcome had been detailed in the dossier of the GPP flare treatment MAA.

The **DLQI** is a 10-question quality of life questionnaire that covers 6 domains, including symptoms and feelings, daily activity, leisure, work and school, personal relationships, and treatment (with a 1-week recall period). The DLQI total score is calculated by summing the scores of each question resulting in a

range of 0 to 30, with higher scores representing greater impairment of the patient's quality of life. A 4-point change from baseline is considered a clinically important difference.

In addition to the primary and secondary endpoints described in the table above, a large number of further endpoints were evaluated, based on e.g. Pain VAS score, GPPASI, EQ-5D-5L, SF-36, WPAI, etc. These were not included in the hierarchical testing strategy and will therefore not be described in this report.

- **Sample size**

Based on an application of the defined testing strategy, a power calculation was performed for sample size assessment on the dose finding analysis (primary objective) and on the formal analysis (secondary objective) of the trial.

Assumptions were made on the effect of each dose on preventing a GPP flare on variables: patient with history of GPP; overall GPP flare rate; overall hazard ratio under the base scenario; as well as the distribution for the time to first GPP flare in each arm of this trial. Based on these assumptions, the success probability was approximately 99.5% for the base Scenario.

Success probability estimates (defined as the probability to obtain a significant test for non-flat dose-response curve) for the dose finding analysis for the primary endpoint when the primary analysis was to be performed the last time the last patient had completed the study, or early discontinued 48-week treatment were calculated for a sample size of 120 patient and a 1-sided type I error of 0.05.

In the case that there was no treatment benefit, the false positive probability was limited by the α-level for the significance testing of the non-flat dose-response curve of 5% (one-sided).

Power estimates for the formal analysis (primary and key secondary endpoint) was based on the last time the last patient had completed or early discontinued 48-week treatment and on the display of the non-flat dose-response curve in the dose finding analysis. The calculations were done for a sample size of 120 subjects and a 1-sided type I error of 0.025.

- **Randomisation and Blinding (masking)**

An Interactive Response Technology (IRT) was used to screen eligible patients, perform drug assignment, manage initial/re-supply ordering of drug supplies and handle emergency un-blinding. The investigator received all necessary instructions to access the IRT from the Sponsor. Detailed IRT functions and procedures were documented in the user requirement specifications mutually agreed to by the sponsor and the IRT vendor.

If applicable, BI was to arrange for the randomisation and the packaging and labelling of trial Medication. The randomisation list was to be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment would be both reproducible and non-predictable. Access to the codes were to be controlled and documented.

During Visit 2 and after the patient's eligibility was confirmed, patients were randomised to blinded treatment arms according to a randomisation plan in a 1:1:1:1 ratio to one of the following treatment arms:

- Arm 1: BI 655130 600 mg total loading dose at Week 1/Day1 followed by maintenance treatment 300 mg s.c. q4 weeks
- Arm 2: BI 655130 600 mg total loading dose at Week 1/Day1 followed by maintenance treatment 300 mg s.c. q12 weeks
- Arm 3: BI 655130 300 mg total loading dose at Week 1/Day1 followed by maintenance treatment 150 mg s.c. q12 weeks

- Arm 4: Placebo Loading dose Placebo

Stratification for the concomitant use of systemic GPP medications at randomisation (yes or no) was done. If a patient received any GPP medication within 4 weeks prior to or at randomisation, then this patient would be categorised as "yes" and otherwise, "no". Primary and key secondary efficacy analyses would be performed including an adjustment for this stratum.

Blocking for region (Japan versus Rest of World) was done in order to ensure that sufficient patients per treatment group would be recruited specifically to support individual country submission in Japan; this factor was treated as operational factor and was not included into the analyses of efficacy endpoints.

Blocking for population (Adults versus Adolescents) was done to ensure that there would be adolescent patients randomised in each treatment group for paediatric investigational plan; this factor was treated as operational factor and was not included into the analyses of efficacy endpoints. The first twelve adolescent patients would be randomised in a 1:1:1:1 ratio to the four arms regardless of concomitant use of systemic GPP medications at randomisation (yes vs. no) and blocking factor region (Japan vs. Rest of world). This was to ensure that within each randomised arm, there would be at least 2 randomised adolescent patients. Any additional adolescent patients within each stratum (concomitant use of systemic GPP medications at randomisation (yes vs. no) and each blocking factor region (Japan vs. Rest of world), was randomised in a 1:1:1:1 ratio to the four arms.

The adult patients within each stratum (concomitant use of systemic GPP medications at randomisation (yes vs. no) and each blocking factor region (Japan vs. Rest of world), were randomised in a 1:1:1:1 ratio to the four arms.

The block size of the randomisation was to be documented in the CTR. The assignment occurred in a blinded fashion via Interactive Response Technology (IRT).

- **Statistical methods**

Analysis of the Primary endpoint: Dose finding

The primary analysis for the primary objective consisted of a MCPMod-based testing (with respect to a non-flat dose response curve). MCPMod (multiple comparison and modelling techniques) was used to evaluate several possible dose response models (patterns), and to identify the best-fitting model or subset of models (while keeping full control of the type I error at 0.05, one-sided). The generalised MCPMod procedure for time to event endpoints was based on the log hazard ratio of the active doses vs. placebo obtained via a Cox regression model on the time to first GPP flare, based on the estimated log hazard rates as well as the estimated variance-covariance matrix. The hazard function for patient in stratum (systemic concomitant use of GPP medications at randomisation (yes or no)) is described in section 7.2.2 of the protocol.

For the PoC testing and for the sample size calculation, the contrasts of each of the models to be tested i.e Linear; Emax; Emax2 and Exponential was pre-defined. The HRs were derived based on models using planned total doses (i.e. the sum of all doses before Week 48):

- Linear; Emax1: assumed 70% of the maximum effect would be achieved at low dose;
- Emax2: assumed 95% of the maximum effect would be achieved at low dose;
- Exponential: assumed 35% of the maximum effect would be achieved at medium dose.

Candidate case scenarios covering both the plausible and a diverse range of potential dose response patterns are presented in Table 7.2.2:1 of the protocol. The primary analysis would be considered robust and provide sufficient power if HR were different but similar to the trends presented table 7.2.2:1 of the protocol.

A non-flat dose response was established if at least one contrast test (after adjusting for multiplicity using MCP step in MCP-Mod approach) was statistically significant, thereby rejecting the null hypothesis of a flat dose-response curve and indicating a benefit of spesolimab over placebo. If a non-flat dose response was established, the statistically significant model(s) were refitted to the data to generate new estimates for all model parameters.

A table, presenting the contrast coefficients per dose group as well as candidate model, together with the MCP-Mod test statistics and p-values for each model and the critical values were presented in the dossier. For averaging model, figure of the dose-response curve was also presented. For all significant model shapes, figures of the dose-response curve as well as 95% confidence band (of the predicted shape) and 95% CI per dose (estimated from stratified Cox model) were presented.

Analysis of the Primary endpoint: Formal Statistical analysis

The primary analysis for the secondary objective on the time to first GPP flare up to week 48 for each dose of BI 655130 versus placebo was tested using the stratified log-rank test, stratified by the systemic concomitant use of GPP medications at randomisation (yes or no) and based on the randomised set (RS).

The estimated hazard ratios based on the same stratified Cox regression model as for the primary objective was displayed for active spesolimab treatment arm versus placebo. In the case of zero event in one/some of the arms by stratum, the stratified Cox regression model was conducted using Firth's penalisation. A hazard ratio of less than one would favor spesolimab. The treatment comparison was made regardless of the treatment adherence or early discontinuation up to Week 48.

Kaplan-Meier (KM) estimates of the survival/failure probabilities at 4-week intervals, as well as the median time-to-event, was presented by treatment arm. Confidence intervals was based on two-sided $\alpha = 0.05$. A Kaplan-Meier graph was also produced. KM estimates of the event probability did not take the stratification factor, use of systemic GPP medication at baseline, into account.

Analysis of the Key secondary endpoint

For the dose finding analysis of the study, there were no key secondary endpoints defined.

For the formal analysis of the study, the treatment effect on the key secondary endpoint, the occurrence of at least one GPP flare up to Week 48 (defined by increase in GPPGA score by ≥2 from baseline and the pustular component of GPPGA ≥2), was tested using the stratified Cochran-Mantel-Haenszel (CMH) test, performed for each dose of BI 655130 versus placebo, stratified by the concomitant use of systemic GPP medications at randomisation (yes or no) and based on the RS.

The difference in proportion of subjects who had at least one GPP flare up to week 48, was presented for each active group versus placebo group using the Mantel-Haenszel type weighted average of risk differences. The averaged risk difference used weights as proposed by Greenland & Robins. The associated confidence intervals of the averaged risk difference used Sato's method.

Analysis sets

The following analysis sets were defined for the randomised maintenance treatment period of this trial:

- Enrolled Set (ES): all subjects who signed informed consent. It was used to display the subject disposition.

- Randomised Set (RS): all randomised subjects. Treatment assignment was used as randomised. It was used for analyses of subject for baseline demographics and disease characteristics and was the main set for the analyses of efficacy endpoints during the randomised maintenance treatment period.
- Safety Analysis Set (SAF): all subjects who were randomised and received at least one dose of study drug. This was the main analysis set for safety. Subjects were analysed according to the actual treatment received.
- Per-Protocol Set (PPS): all subjects in the randomised set who adhered to the CTP without any iPDs (potentially affecting the study outcome) which were flagged for exclusion from the PPS. The PPS was used for sensitivity analysis on the primary and key secondary endpoints.

For the flare treatment period, the following set was defined as below:

- Safety Analysis set for flare treatment period (SAF-FT): This patient set included all patients who took at least one flare treatment with OL i.v. dose of spesolimab. This was the main analysis set for efficacy and safety during the flare treatment period.

For the OL maintenance treatment period, the following set was defined as below:

- Safety Analysis set for OL maintenance treatment period (SAF-MT): This patient set included all patients who received at least one dose of OL s.c. maintenance treatment. This was the main analysis set for efficacy and safety during OL maintenance treatment period.

Sensitivity analyses

Secondary analysis of the primary endpoint included:

- A sensitivity analysis utilising the PPS to evaluate the impact on treatment outcomes of patients who may have relevant deviations from the conduct described in the CTP.
- Analysis of an additional estimand for patients who used rescue medication or investigator prescribed SoC prior to the first onset of a GPP flare. This was considered to indicate the onset of such a flare. For patients who used restricted medication for other disease and not for the onset of a GPP flare, data was censored for further analysis following the use and imputed using the methods described in the CTR.
- Sensitivity analyses which utilise alternative methods for the handling of missing data.
- Descriptive comparisons between the levels of each stratification (use of systemic GPP medications at randomisation (yes or no)) and blocking factors (region (Japan or Rest of world) and population (adults versus adolescents)) was performed.

Secondary analyses of the key secondary endpoint were the same as those defined for the primary endpoint. In addition, a sensitivity analysis using a landmark analysis was performed to evaluate treatment effects. This test compared Kaplan Meier estimates at Week 48 between each dose of spesolimab and placebo whereby the variance of each KM estimate was calculated by the Greenwood's formula. Further details for the landmark test were described in the TSAP.

Multiplicity

Formal testing of all trial endpoints in the testing hierarchy (primary, key secondary, and secondary endpoints) was performed at a one-sided alpha level of 0.025. Overall, the testing strategy followed a closed testing principle defining five families of endpoints/comparisons.

To control the overall type I error rate for the comparison of both high and medium doses of spesolimab vs. placebo on the primary endpoint, the truncated Hochberg method was applied. The weight of the truncated Hochberg method was chosen as 0.5. If both primary endpoint p-values were ≤0.01875 (one-sided), then both comparisons involving the two Spesolimab dose regimens were declared to be statistically significant. If the maximum of the p-values for the two dose comparisons was >0.01875 (1- sided), then the remaining p-value was to be tested at the 0.0125 (one-sided level) and declared to be statistically significant if the p-value was ≤0.0125 (1-sided). The remaining alpha to be used in the second family was to be 0.025 (one-sided) if both high and medium doses of Spesolimab were statistically significant and superior to placebo on the primary endpoint. If only one comparison was successful, then alpha was to be 0.025/4 = 0.00625 according to the truncated Hochberg procedure with a weight of 0.5. If neither dose was declared to be statistically significantly superior to placebo for the primary endpoint, then no further formal testing in the hierarchical sequence was conducted. Testing of subsequent families followed a similar procedure.

Censoring rules

For the formal statistical analysis of the primary endpoint: the primary analysis included patients on- and off-treatment data up to Week 48. If a patient had no GPP flare event through 48 weeks of study or was lost to follow up or withdrawn from the trial prior to achieving such an event, then the primary endpoint was censored at the day of the last visit upon which it was confirmed that no GPP flare had yet been observed. Only observed GPP flare events were included in the primary analysis. No further imputation was implemented on the missing values of GPPGA score and/or missing GPPGA pustule sub score.

For the key secondary endpoint: any use of rescue medication or investigator prescribed SoC prior to the onset of the first GPP flare was considered to represent a failure, i.e. the onset of a GPP flare event. Furthermore, as described for the primary endpoint analysis, the key secondary endpoint analysis also included both on- and off-treatment data of all patients up to Week 48.

Table 11. Primary Method (PM) - Description of censoring rules for primary endpoint, and two secondary endpoints in hierarchical testing procedure

Situation	Outcome (event or censored)	Date of outcome
Without post randomisation assessment		
No use of rescue medication or investigator prescribed SoC	Censored	Date of randomisation.
The first use of rescue medication or investigator prescribed SoC	Event	Date of first use of rescue medication or investigator prescribed SoC, whichever come earlier.
With post randomisation assessment		
No event and no use of rescue medication or investigator prescribed SoC	Censored	Date of last assessment with no event confirmed.

Situation	Outcome (event or censored)	Date of outcome
The first event, or first used of rescue medication or investigator prescribed SoC	Event	Date of the first event, or the date of first use of rescue medication or investigator prescribed SoC whichever came first.

Table 12. Sensitivity Method: Description of censoring rules for primary endpoint and two secondary endpoints in hierarchical testing procedure

Situation	Outcome (event or censored)	Date of outcome
Without post randomisation assessment		
No use of rescue medication or investigator prescribed SoC	Censored	Date of randomisation
The first use of rescue medication or investigator prescribed SoC prior to the second scheduled assessment	Event	Date of the first use of rescue medication or investigator prescribed SoC, whichever comes earlier
The first use of rescue medication or investigator prescribed SoC post the second scheduled assessment	Censored	Date of randomisation
With post randomisation assessment		
No event, and no use of rescue medication or investigator prescribed SoC, no more than one consecutively missed assessment	Censored	Date of last assessment with no event confirmed
No event, and no use of rescue medication or investigator prescribed SoC, two or more consecutively missed assessments	Censored	Date of last assessment prior to missed assessments
The first event or the first use of rescue medication or investigator prescribed SoC, none or one missed assessment prior to the listed scenarios.	Event	Date of assessment of the first event, or the first use of rescue medication or investigator prescribed SoC, whichever came first
The first event or the first use of rescue medication or investigator prescribed SoC, but two or more consecutively missed assessments prior to the listed scenarios.	Censored	Date of last assessment prior to missed assessments

Intercurrent events

Any use of rescue medication with OL i.v. spesolimab, or investigator-prescribed Standard of Care (SoC) to treat GPP worsening was considered part of the composite primary endpoint in addition to the increase in Generalised Pustular Psoriasis Physician Global Assessment (GPPGA) score by ≥2 from baseline and the pustular component of GPPGA ≥2 up to Week 48 (Primary estimand - **EM**).

Use of restricted medication other than as defined in the primary estimand was handled using the hypothetical approach under the scenario that the restricted medication had not been administrated i.e data after use of restricted medication was censored (secondary estimand - **EMR**).

Treatment policy strategy that excluded use of rescue medication with OL i.v. spesolimab for GPP worsening was planned as the secondary estimand (abbreviated as **ET**). All intercurrent events except for the rescue medication use of i.v. spesolimab was to be handled using the treatment policy approach.

Primary estimands was applied for the key secondary endpoint. Occurrence of first GPP flare was considered treatment failure while the use of rescue treatment of i.v. spesolimab or use of investigator prescribed SoC was also attributed as treatment failure. The estimands specified for primary endpoint was applied to the secondary time-to event endpoints.

Missing data and outliers

Multiple imputation method (MI) was applied for the primary analysis of the key secondary endpoint and the secondary binary endpoint. Missing GPPGA or GPPGA pustulation subscores were not imputed and only observed values were utilised. The imputation of the binary endpoint was only done at a binary level, i.e. success or failure. It was taken into consideration that the endpoint emphasised either the positive side (sustained remission) or negative side (occurrence of GPP flare) of the disease outcome. The imputation method focused on the imputation on the failure to avoid confusion.

Before the occurrence of failure, if for any reason, 1 or more patients had a missing visit, e.g. due to loss of follow-up or early discontinuation from the study before reaching the time-point of Week 48, a sequential logistic regression multiple imputation method was implemented to impute the missing outcome by each visit at a binary level ('Yes' as failure vs 'No' as success). Before the imputation procedure, any non-monotone missing outcome (binary level) was imputed by the next observed value. The achieved monotone missing data were then imputed per the following steps:

1. Multiple Imputation of Missing data: A sequential logistic regression method was used to impute missing values of the binary event (Yes vs No) at each visit.
2. Analysis of Completed Datasets: The imputed complete dataset was used to perform the corresponding statistical analysis per permutation.
3. Combine Results: Approaches were applied to pool the estimates of the response rate for each arm and the risk difference between active arms and placebo from each imputed dataset.

The multiple imputation above was also applicable for further binary endpoints for the randomised maintenance treatment period. For the binary endpoint that was not monotonically increasing, the subsequent visits after an observed failed visit were not imputed as a failure automatically.

For continuous efficacy endpoints during the randomised maintenance treatment period, after applying hypothetical strategy in **EC** estimand, the restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach was utilised, if applicable. Missing data handling through MMRM ensured that the missing data was handled implicitly by assuming missing at random.

Interim analyses

To support a spesolimab GPP flare treatment submission, interim analyses of the open-label rescue treatment and subsequent maintenance treatment periods was performed using all open-label data up to a cut-off date, which was pre-specified in the data cleaning plan for the interim analysis.

Randomised maintenance s.c. treatments remained blinded and data from the randomised treatment period was not analysed in the interim analysis.

Subgroup analyses

For randomised maintenance treatment period, each subgroup was investigated based on RS for efficacy analysis, when the actual sizes of at least two levels of the subgroup were no less than 8. The subgroup analysis of adult v.s. adolescent was done regardless of the actual sizes of each subgroup.

Table 13. Categories of subgroups for display of trial endpoints

Subgroup performed	Endpoints for which subgroup analyses are to be conducted
- Baseline GPPGA score (0 vs 1) - Mutation status in IL36RN from genotyping (Yes vs No) - Concurrent baseline plaque psoriasis (Yes vs No) - Concomitant use of systemic GPP medication at randomisation (Yes or No) - Sex (Male vs Female) - Age (≥65 years vs. <65 years) - Adult vs adolescent (Age ≥18 or Age>=12 to <18) - Race (Asian vs White vs Other) - BMI category (< 25 kg/m2, 25 to < 30 kg/m2, ≧ 30 kg/m2) - Weight (< 53.8 kg, 53.8 to < 91 kg, ≧ 91 kg)*	- Primary endpoint - Key secondary endpoint - Secondary efficacy endpoints

*The cut-off values of weight was based on the body weight values corresponding to the range of 80% to 125% of steady-state AUC0-τ (any dosing regimen) using 70 kg as a reference, according to the population PK model.

Additional subgroup analyses for regional submission were done. See Section 10.4 in the TSAP for more information.

Results

- **Participant flow**

A total of 157 patients were enrolled (screened) across 71 centres in 23 countries (Argentina, Belgium, Chile, China, France, Germany, Greece, Italy, Japan, Korea, Netherlands, Philippines, Republic of Malaysia, Mexico, Russian Federation, South Africa, Spain, Taiwan, Thailand, Tunisia, Turkey, USA, Vietnam). Countries that contributed most randomised patients were Malaysia, China, and Russian Federation.

Table 14. Number of patients by region and country – ES

Geographical region	Countries	Number of sites	Patients screened, N (%)	Patients randomized, N (%)	Patients treated, N (%)
Total	23 countries	71	157 (100.0)	123 (100.0)	123 (100.0)
Asia (except Japan)	China, Korea, Republic of Malaysia, Philippines, Taiwan, Thailand, Vietnam	27	87 (55.4)	72 (58.5)	72 (58.5)
Europe	Belgium, France, Germany, Greece, Italy, Netherlands, Russian Federation, Spain, Turkey	25	44 (28.0)	32 (26.0)	32 (26.0)
Africa	South Africa, Tunisia	6	9 (5.7)	5 (4.1)	5 (4.1)
Japan	Japan	6	6 (3.8)	6 (4.9)	6 (4.9)
South America	Argentina, Chile	3	7 (4.5)	6 (4.9)	6 (4.9)
North America (excluding USA)	Mexico	2	2 (1.3)	1 (0.8)	1 (0.8)
USA	USA	2	2 (1.3)	1 (0.8)	1 (0.8)

Of the 157 screened patients, 123 patients were randomised in a 1:1:1:1 ratio to spesolimab low dose (31 patients), medium dose (31 patients), high dose (30 patients), and placebo (31 patients).

All 123 patients were treated and 78 patients (63.4%) completed 48 weeks of randomised treatment period without flare. There were no deaths. A total of 32 patients (26.0%) received OL spesolimab 900 mg i.v. treatment for GPP flares, of whom 20 patients further received OL spesolimab 300 mg s.c. for maintenance. A total of 13 patients (10.6%) prematurely discontinued randomised treatment for reasons other than flare treatment with spesolimab i.v. Of the randomised patients, 111 (90.2%) completed the trial as planned, of whom 93 (75.6%) continued in the extension trial 1368-0025.

Table 15. Disposition of patients – ES

	Placebo	Spesolimab low dose (LD 300 mg, 150 mg q12w)	Spesolimab medium dose (LD 600 mg, 300 mg q12w)	Spesolimab high dose (LD 600 mg, 300 mg q4w)	Overall Total
	N (%)	N (%)	N (%)	N (%)	N (%)
Enrolled					157
Randomized	31 (100.0)	31 (100.0)	31 (100.0)	30 (100.0)	123 (100.0)
Treated	31 (100.0)	31 (100.0)	31 (100.0)	30 (100.0)	123 (100.0)
Completed 48-week randomized period without flare	14 (45.2)	23 (74.2)	20 (64.5)	21 (70.0)	78 (63.4)
Switched to OL spesolimab i.v. for flare	15 (48.4)	7 (22.6)	8 (25.8)	2 (6.7)	32 (26.0)
Completed flare treatment period (12 weeks)	14 (45.2)	6 (19.4)	8 (25.8)	2 (6.7)	30 (24.4)
Started OL s.c. for maintenance	12 (38.7)	2 (6.5)	5 (16.1)	1 (3.3)	20 (16.3)
Discontinued from flare treatment period	1 (3.2)	1 (3.2)	0 (0.0)	0 (0.0)	2 (1.6)
Discontinued randomized period for reasons other than OL spesolimab i.v. for flare	2 (6.5)	1 (3.2)	3 (9.7)	7 (23.3)	13 (10.6)
Adverse event	0 (0.0)	0 (0.0)	1 (3.2)	3 (10.0)	4 (3.3)
Lack off efficacy	0 (0.0)	0 (0.0)	1 (3.2)	0 (0.0)	1 (0.8)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by subject	0 (0.0)	0 (0.0)	1 (3.2)	1 (3.3)	2 (1.6)
Other	2 (6.5)	1 (3.2)	0 (0.0)	3 (10.0)	6 (4.9)
Completed trial	30 (96.8)	27 (87.1)	28 (90.3)	26 (86.7)	111 (90.2)
Continued in the extension trial	26 (83.9)	24 (77.4)	23 (74.2)	20 (66.7)	93 (75.6)
Prematurely discontinued from trial	1 (3.2)	4 (12.9)	3 (9.7)	4 (13.3)	12 (9.8)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by patient	1 (3.2)	2 (6.5)	1 (3.2)	1 (3.3)	5 (4.1)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	2 (6.5)	2 (6.5)	3 (10.0)	7 (5.7)

As seen above, a total of 32 patients received spesolimab i.v. for the treatment of a flare; of these patients, 22 patients (68.8%) received a single 900 mg i.v. dose and 10 patients (31.3%) received 2 doses of spesolimab 900 mg i.v. (double dose). Of the 20 patients who continued with OL maintenance treatment with spesolimab s.c. after flare treatment, 9 patients (45.0%) were escalated to the 300 mg s.c. q4w dosing regimen.

The disposition of patients in the study is also depicted in the figure below.

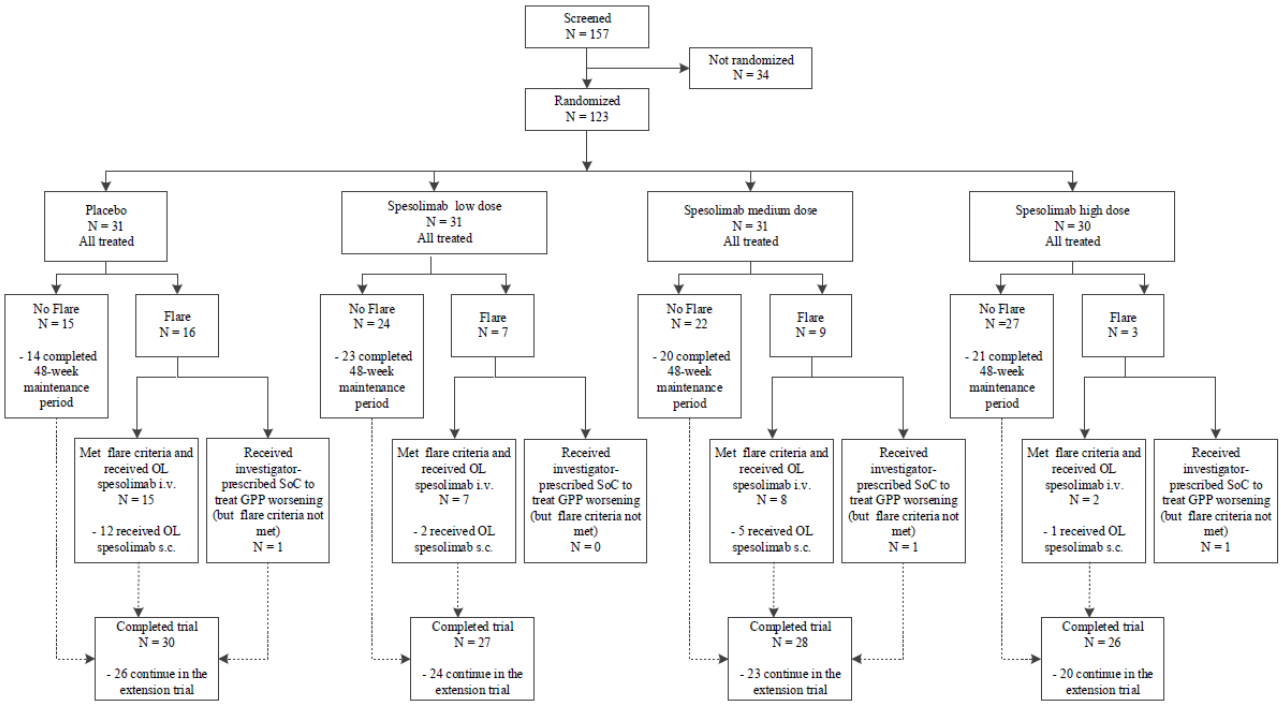


Figure 14. Disposition of patients – Study 1368-0027, ES

- **Recruitment**

The trial was conducted between 08 June 2020 and 23 November 2022.

- **Conduct of the study**

Protocol amendments

A total of 3 global amendments to the CTP were issued after review and approval from relevant HAs/IECs/IRBs.

Global Amendment 1 (dated 29 Jul 2020)

The following main changes were introduced:

- Changes to Section 7, no longer monitoring the event rate, since it is expected that sufficient events would be observed in the target population
- Changes to Section 7.4, changes to randomisation to make sure adolescents were included in each treatment arm

Global Amendment 2 (dated 19 Apr 2021)

The following main changes were introduced:

- Changes to Section 7.2.2, to align with Paediatric Investigational Plan (PIP)
- Changes to Section 7.2.3, descriptive analysis of adults vs. paediatric patients to align with PIP
- Changes to Section 4.1.4 to permit home administration of treatment drug, if necessary, due to COVID-19

Global Amendment 3 (dated 28 Jul 2022)

The following main changes were introduced:

- Changes to Section 5.2.6.1.4, to include peripheral neuropathy as an adverse event of special interest.
- Changes to Section 4.2.2.2, to allow the investigator to determine if a patient should continue rescue therapy.

Impact of the COVID-19 pandemic

The trial began in Jun 2020 and completed in Dec 2022, while the COVID-19 pandemic was ongoing globally. The trial was completed despite the disruptions that occurred, and the objectives were not affected. The following risk mitigation strategies were employed because of COVID-19:

- A risk management plan was set up at the clinical site that detailed specific precautionary measures (e.g. hygienic rules, wearing of face masks, physical distancing). The local requirements were subject to change and the trial procedures were adapted accordingly, when applicable
- Screening of trial participants for SARS-CoV-2 via polymerase chain reaction (PCR) test was performed at screening and prior to admission to site (see also exclusion criteria)
- During the ambulatory visits, patients were allowed to enter the site only after it was confirmed that patients did not have any signs or symptoms of infection (e.g. fever)
- In case SARS-CoV-2 infection was suspected in a subject during trial participation, PCR testing was to be initiated without delay to enable the investigator to take decisions about the next steps
- Global Amendment 2 included a provision to administer the trial medication at the patient's home, if physical visit to the site was not possible, with authorisation of the investigator or designee.

Protocol deviations

Important protocol deviations (iPDs) were defined as those protocol deviations that could potentially affect the efficacy assessments or the patients' rights or safety. Important protocol deviations were defined in the IQRMP, which is stored in the TMF, and were assessed before the locking and unblinding of the data, except for iPDs on trial medication and randomisation, for which the knowledge of the actual treatment received was needed. For these iPDs, the potential cases were determined before unblinding of the data and checked thereafter. A summary of iPDs during this trial is shown in **Table** 16.

Overall, 13 patients (10.6%) were reported with iPDs, with similar proportions of patients in all treatment groups. The most common categories of iPDs were trial medication and randomisation (mostly randomisation order not followed, which were all incorrect entries for the IRT stratification question regarding the use of systemic medication for GPP at randomisation) and safety procedure/SAE reporting. iPDs leading to exclusion from the PPS were reported for 4 patients (3.3%). Of the patients excluded from the PPS, 2 patients were excluded due to incorrect dosing: 1 patient in the spesolimab high dose group received 300 mg on Day 1 instead of 600 mg; and 1 patient was randomised to the placebo group but incorrectly received spesolimab treatment on Day 1, resulting in measurable spesolimab concentrations at Visits 3, 4, and 5.

In this trial, 28 patients (22.8%) were reported with non-important protocol deviations related to COVID-19, with the most common category being late visit due to COVID-19.

Table 16. Patients with important protocol deviations – RS

	Placebo N (%)	Spesolimab low dose (LD 300 mg, 150 mg q12w) N (%)	Spesolimab medium dose (LD 600 mg, 300 mg q12w) N (%)	Spesolimab high dose (LD 600 mg, 300 mg q4w) N (%)	Overall Total N (%)
Number of patients	31 (100.0)	31 (100.0)	31 (100.0)	30 (100.0)	123 (100.0)
Patients with at least 1 iPD[1]	2 (6.5)	3 (9.7)	4 (12.9)	4 (13.3)	13 (10.6)
Patients with at least 1 iPD that led to exclusion from PPS	2 (6.5)	0 (0.0)	1 (3.2)	1 (3.3)	4 (3.3)
C: Trial medication and randomization	1 (3.2)	3 (9.7)	2 (6.5)	2 (6.7)	8 (6.5)
C2: Incorrect dosing[2,3]	1 (3.2)	0 (0.0)	0 (0.0)	1 (3.3)	2 (1.6)
C3: Randomization not followed[2,4]	0 (0.0)	3 (9.7)	2 (6.5)	1 (3.3)	6 (4.9)
D: Concomitant medication	1 (3.2)	0 (0.0)	1 (3.2)	0 (0.0)	2 (1.6)
D2: Prohibited medication use[2,3]	1 (3.2)	0 (0.0)	1 (3.2)	0 (0.0)	2 (1.6)
F: Safety procedure/SAE reporting[2]	0 (0.0)	0 (0.0)	0 (0.0)	3 (10.0)	3 (2.4)
G: Privacy/data protection[2]	0 (0.0)	0 (0.0)	1 (3.2)	0 (0.0)	1 (0.8)

1 Patients may have more than one iPD.
2 PD was identified based on manual review.
3 iPD that led to exclusion from the PPS.
4 Stratification error (Appendix 16.2.3, Listing 1)

Compliance

Study drugs were administered by the investigator or authorised study personnel. In the randomised maintenance treatment period, the mean (SD) of the total injected spesolimab dose was 99.6% (2.7%) of the planned total dose and balanced across the spesolimab treatment groups.

- **Baseline data**

The demographic, disease-related and other baseline-factors of interest are depicted in the tables below.

Table 17. Demographic and baseline data – RS

	Placebo	Spesolimab low dose (LD 300 mg, 150 mg q12w)	Spesolimab medium dose (LD 600 mg, 300 mg q12w)	Spesolimab high dose (LD 600 mg, 300 mg q4w)	Overall Total
Number of patients, N (%)	31 (100.0)	31 (100.0)	31 (100.0)	30 (100.0)	123 (100.0)
Gender, N (%)					
Male	13 (41.9)	11 (35.5)	11 (35.5)	12 (40.0)	47 (38.2)
Female	18 (58.1)	20 (64.5)	20 (64.5)	18 (60.0)	76 (61.8)
Race, N (%)					
Asian	17 (54.8)	20 (64.5)	21 (67.7)	21 (70.0)	79 (64.2)
White	14 (45.2)	11 (35.5)	10 (32.3)	9 (30.0)	44 (35.8)
Ethnicity, N (%)					
Hispanic/Latino	3 (9.7)	3 (9.7)	0 (0.0)	1 (3.3)	7 (5.7)
Not Hispanic/Latino	28 (90.3)	28 (90.3)	31 (100.0)	29 (96.7)	116 (94.3)
Age [years], mean (SD)	39.5 (14.0)	38.9 (16.5)	42.9 (16.7)	40.2 (16.4)	40.4 (15.8)
Adolescents (≥12 to <18), N (%)	2 (6.5)	2 (6.5)	2 (6.5)	2 (6.7)	8 (6.5)
Adults (≥18), N (%)	29 (93.5)	29 (93.5)	29 (93.5)	28 (93.3)	115 (93.5)
<50	23 (74.2)	23 (74.2)	21 (67.7)	22 (73.3)	89 (72.4)
50 to <65	7 (22.6)	6 (19.4)	8 (25.8)	5 (16.7)	26 (21.1)
≥65	1 (3.2)	2 (6.5)	2 (6.5)	3 (10.0)	8 (6.5)
Weight [kg], mean (SD)	75.73 (23.92)	71.07 (23.58)	71.52 (23.01)	68.66 (22.88)	71.77 (23.21)
BMI [kg/m^2], mean (SD)	26.85 (8.28)	26.85 (7.22)	27.38 (8.76)	25.61 (7.25)	26.68 (7.84)
<25, N (%)	14 (45.2)	14 (45.2)	14 (45.2)	19 (63.3)	61 (49.6)
25 to <30, N (%)	9 (29.0)	7 (22.6)	7 (22.6)	5 (16.7)	28 (22.8)
≥30, N (%)	8 (25.8)	10 (32.3)	10 (32.3)	6 (20.0)	34 (27.6)
Renal function based on eGFR/CL$_{CR}$[1], N (%)					
Normal	24 (77.4)	24 (77.4)	17 (54.8)	26 (86.7)	91 (74.0)
Mild impairment	7 (22.6)	6 (19.4)	13 (41.9)	2 (6.7)	28 (22.8)
Moderate impairment	0 (0.0)	1 (3.2)	1 (3.2)	2 (6.7)	4 (3.3)
Baseline potential hepatic impairment[2], N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Concomitant use of systemic GPP medication at randomization, N (%)	22 (71.0)	25 (80.6)	23 (74.2)	22 (73.3)	92 (74.8)
Concurrent plaque psoriasis[3], N (%)	10 (32.3)	10 (32.3)	7 (22.6)	7 (23.3)	34 (27.6)
Concurrent chronic erythrodermic psoriasis, N (%)	0 (0.0)	3 (9.7)	0 (0.0)	0 (0.0)	3 (2.4)

Results for categories "not stated", "unknown", or "missing" are provided in the source table.

BMI: body mass index; ESRD: end stage renal disease.

1 Classification of renal function based on estimated GFR calculated applying CKD-EPI formula: normal renal function (stage 1) ≥90 mL/min/1.73 m^2, mild decrease in GFR (stage 2) = 60 to 89 mL/min/1.73 m^2, moderate decrease in GFR (stage 3) = 30 to 59 mL/min/1.73 m^2, severe decrease in GFR (stage 4) = 15 to 29 mL/min/1.73 m^2, end stage renal disease (stage 5) = <15 mL/min/1.73 m^2 not on dialysis or requiring dialysis. The Bedside Schwartz Equation was applied for adolescents.

2 Defined as International Normalized Ratio ≥2.2 and total serum bilirubin >51.3 µmol/L; see TSAP (Appendix 16.1.9, Table 7.8.7: 1).

3 Concurrent plaque psoriasis meant that the patient had plaque psoriasis during the previous year and the condition was still ongoing at baseline.

Table 18. GPPGA, GPPASI, PSS, and DLQI scores, and JDA GPP severity index at baseline – RS

	Placebo	Spesolimab low dose (LD 300 mg, 150 mg q12w)	Spesolimab medium dose (LD 600 mg, 300 mg q12w)	Spesolimab high dose (LD 600 mg, 300 mg q4w)	Overall Total
Number of patients , N (%)	31 (100.0)	31 (100.0)	31 (100.0)	31 (100.0)	123 (100.0)
GPPASI total score, mean (SD)	3.11 (2.81)	3.03 (3.48)	3.12 (4.16)	3.92 (4.42)	3.29 (3.74)
GPPGA total score, N (%)					
0	4 (12.9)	2 (6.5)	8 (25.8)	3 (10.0)	17 (13.8)
1	27 (87.1)	29 (93.5)	23 (74.2)	27 (90.0)	106 (86.2)
GPPGA pustules, N (%)					
0	21 (67.7)	23 (74.2)	24 (77.4)	20 (66.7)	88 (71.5)
1	10 (32.3)	8 (25.8)	7 (22.6)	10 (33.3)	35 (28.5)
JDA GPP severity index, mean (SD)	2.1 (1.3)	2.0 (1.1)	2.0 (1.4)	2.2 (1.6)	2.1 (1.3)
Mild, N (%)	29 (93.5)	31 (100.0)	31 (100.0)	28 (93.3)	119 (96.7)
Moderate, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)	1 (0.8)
Severe, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing, N (%)	2 (6.5)	0 (0.0)	0 (0.0)	1 (3.3)	3 (2.4)
PSS total score, N	31	31	31	29	122
Mean (SD)	3.6 (2.9)	4.1 (3.8)	3.9 (2.9)	5.3 (3.8)	4.2 (3.4)
DLQI total score, N	31	30	31	29	121
Mean (SD)	7.2 (5.6)	7.6 (6.7)	6.6 (5.6)	11.1 (6.9)	8.1 (6.4)

Patients below the age of 16 years (i.e. 12 to 15 years) did not have to complete the DLQI questionnaire.

DNA sequencing of the IL-36RN, CARD14, and AP1S3 genes was performed for 101 patients in this trial (**Table 19**).

Table 19. Genetic mutations based on genotyping – RS

	Placebo	Spesolimab low dose (LD 300 mg, 150 mg q12w)	Spesolimab medium dose (LD 600 mg, 300 mg q12w)	Spesolimab high dose (LD 600 mg, 300 mg q4w)	Overall Total
	N (%)	N (%)	N (%)	N (%)	N (%)
Number of patients	31 (100.0)	31 (100.0)	31 (100.0)	30 (100.0)	123 (100.0)
Presence of potential pathogenic variation on any of IL-36RN, CARD14, AP1S3					
No	20 (64.5)	14 (45.2)	12 (38.7)	15 (50.0)	61 (49.6)
Yes	6 (19.4)	10 (32.3)	13 (41.9)	11 (36.7)	40 (32.5)
Presence of potential pathogenic IL-36RN variation					
No	22 (71.0)	17 (54.8)	15 (48.4)	19 (63.3)	73 (59.3)
Yes	4 (12.9)	7 (22.6)	10 (32.3)	7 (23.3)	28 (22.8)
Presence of potential pathogenic CARD14 variation					
No	24 (77.4)	21 (67.7)	21 (67.7)	20 (66.7)	86 (69.9)
Yes	2 (6.5)	3 (9.7)	4 (12.9)	6 (20.0)	15 (12.2)
Presence of potential pathogenic AP1S3 variation					
No	26 (83.9)	24 (77.4)	25 (80.6)	25 (83.3)	100 (81.3)
Yes	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)	1 (0.8)

Results for category "DNA sequencing not done" are provided in the source table.

The medical history for GPP is described below.

Table 20. Medical history for GPP – RS

	Placebo	Spesolimab low dose (LD 300 mg, 150 mg q12w)	Spesolimab medium dose (LD 600 mg, 300 mg q12w)	Spesolimab high dose (LD 600 mg, 300 mg q4w)	Overall Total
Number of patients, N (%)	31 (100.0)	31 (100.0)	31 (100.0)	30 (100.0)	123 (100.0)
Time since first diagnosis, N (%)					
≤1 year	3 (9.7)	5 (16.1)	4 (12.9)	4 (13.3)	16 (13.0)
>1 to ≤5 years	10 (32.3)	6 (19.4)	9 (29.0)	9 (30.0)	34 (27.6)
>5 to ≤10 years	7 (22.6)	6 (19.4)	8 (25.8)	8 (26.7)	29 (23.6)
>10 years	11 (35.5)	14 (45.2)	10 (32.3)	9 (30.0)	44 (35.8)
Diagnosis method to confirm GPP, N (%)					
Skin biopsy and histopathological confirmation	15 (48.4)	11 (35.5)	12 (38.7)	9 (30.0)	47 (38.2)
Clinical examination	15 (48.4)	18 (58.1)	17 (54.8)	21 (70.0)	71 (57.7)
Other	1 (3.2)	2 (6.5)	2 (6.5)	0 (0.0)	5 (4.1)
Average number of flares per year					
Mean (SD)	2.4 (1.2)	2.7 (2.3)	1.9 (0.9)	2.4 (1.9)	2.3 (1.6)
Median (Q1, Q3)	2.0 (2.0, 3.0)	2.0 (1.0, 4.0)	2.0 (1.0, 2.0)	2.0 (2.0, 2.0)	2.0 (1.0, 3.0)
Min, max	1, 5	1, 12	0, 4	0, 10	0, 12

With respect to other medical history and baseline conditions, overall, 74% of all patients had at least 1 baseline condition/medical history. The most common dictionary-derived terms were hypertension, psoriasis, and obesity.

With respect to medications for GPP, this is summarised in Table 21 (historical medications for GPP) and Table 22 (systemic medications for GPP at randomisation).

Table 21. Historical medications for GPP (reported for at least 10% of patients overall) – RS

Preferred name	Placebo N (%)	Spesolimab low dose (LD 300 mg, 150 mg q12w) N (%)	Spesolimab medium dose (LD 600 mg, 300 mg q12w) N (%)	Spesolimab high dose (LD 600 mg, 300 mg q4w) N (%)	Overall Total N (%)
Number of patients	31 (100.0)	31 (100.0)	31 (100.0)	30 (100.0)	123 (100.0)
With at least 1 historical medication	30 (96.8)	29 (93.5)	30 (96.8)	26 (86.7)	115 (93.5)
Acitretin	10 (32.3)	17 (54.8)	14 (45.2)	10 (33.3)	51 (41.5)
Methotrexate	17 (54.8)	14 (45.2)	13 (41.9)	6 (20.0)	50 (40.7)
Ciclosporin	8 (25.8)	12 (38.7)	10 (32.3)	8 (26.7)	38 (30.9)
Potassium permanganate	4 (12.9)	7 (22.6)	9 (29.0)	3 (10.0)	23 (18.7)
Betamethasone dipropionate; calcipotriol	5 (16.1)	3 (9.7)	9 (29.0)	5 (16.7)	22 (17.9)
Calcipotriol	7 (22.6)	3 (9.7)	7 (22.6)	5 (16.7)	22 (17.9)
Mometasone furoate	2 (6.5)	6 (19.4)	6 (19.4)	5 (16.7)	19 (15.4)
Betamethasone valerate	3 (9.7)	6 (19.4)	5 (16.1)	4 (13.3)	18 (14.6)
Betamethasone	4 (12.9)	2 (6.5)	8 (25.8)	3 (10.0)	17 (13.8)
Clobetasol propionate	3 (9.7)	7 (22.6)	5 (16.1)	2 (6.7)	17 (13.8)
Paracetamol	3 (9.7)	4 (12.9)	5 (16.1)	5 (16.7)	17 (13.8)
Prednisolone	4 (12.9)	3 (9.7)	3 (9.7)	5 (16.7)	15 (12.2)
Loratadine	5 (16.1)	4 (12.9)	2 (6.5)	3 (10.0)	14 (11.4)
Betamethasone; calcipotriol	4 (12.9)	2 (6.5)	5 (16.1)	2 (6.7)	13 (10.6)
Chlorphenamine maleate	2 (6.5)	5 (16.1)	4 (12.9)	2 (6.7)	13 (10.6)

Table 22. Systemic medications for GPP at randomisation (reported for at least 10% of patients overall) – RS

Preferred name	Placebo	Spesolimab low dose (LD 300 mg, 150 mg q12w)	Spesolimab medium dose (LD 600 mg, 300 mg q12w)	Spesolimab high dose (LD 600 mg, 300 mg q4w)	Overall Total
	N (%)	N (%)	N (%)	N (%)	N (%)
Number of patients	31 (100.0)	31 (100.0)	31 (100.0)	30 (100.0)	123 (100.0)
With at least 1 systemic medication for GPP at randomization	22 (71.0)	25 (80.6)	23 (74.2)	22 (73.3)	92 (74.8)
Acitretin	7 (22.6)	15 (48.4)	14 (45.2)	14 (46.7)	50 (40.7)
Ciclosporin	7 (22.6)	8 (25.8)	7 (22.6)	7 (23.3)	29 (23.6)
Methotrexate	7 (22.6)	4 (12.9)	3 (9.7)	1 (3.3)	15 (12.2)

Concerning other concomitant therapies, overall, 68.3% of patients had at least 1 concomitant medication for indications other than GPP, starting prior to the randomised trial treatment. The most frequently used medications at preferred name level were "emulsifying wax; paraffin, liquid; white soft paraffin", amlodipine, and folic acid.

Overall, 72.4% of patients had at least 1 concomitant medication starting within the randomised maintenance treatment period. The most frequently used concomitant medications at preferred name level were tozinameran and paracetamol. A total of 3 patients had concomitant non-drug therapy starting prior to the randomised maintenance treatment; 8 patients had concomitant non-drug therapy (surgical and medical procedures) starting within the randomised maintenance treatment period.

- **Numbers analysed**

The data analysis sets are shown in the table below, based on the enrolled set (ES). Demographic and baseline data, as well as efficacy analyses, were based on the randomised set (RS). Safety analyses were based on the safety analysis set (SAF). The per-protocol set (PPS) was used for the sensitivity analyses on the primary and key secondary endpoints. Efficacy and safety analyses during the flare treatment period were based on the safety analysis set for flare treatment period (SAF-FT). Efficacy and safety analyses during the OL maintenance treatment period were based on the safety analysis set for OL maintenance treatment period (SAF-MT).

Table 23. Patient analysis sets – RS

	Placebo	Spesolimab low dose (LD 300 mg, 150 mg q12w)	Spesolimab medium dose (LD 600 mg, 300 mg q12w)	Spesolimab high dose (LD 600 mg, 300 mg q4w)	Overall Total
	N (%)	N (%)	N (%)	N (%)	N (%)
Randomized set (RS)	31 (100.0)	31 (100.0)	31 (100.0)	30 (100.0)	123 (100.0)
Safety analysis set (SAF)	31 (100.0)	31 (100.0)	31 (100.0)	30 (100.0)	123 (100.0)
Per-protocol set (PPS)	29 (93.5)	31 (100.0)	30 (96.8)	29 (96.7)	119 (96.7)
Flare treatment period analysis set (SAF-FT)	15 (48.4)	7 (22.6)	8 (25.8)	2 (6.7)	32 (26.0)
OL maintenance treatment period analysis set (SAF-MT)	12 (38.7)	2 (6.5)	5 (16.1)	1 (3.3)	20 (16.3)

1 [redacted] was randomized to the placebo group but incorrectly received spesolimab treatment on Day 1 (Section 11.2.1). Data for this patient was assigned to the spesolimab low dose group in the exposure and safety analysis, as well as in the immunogenicity vs efficacy analysis, i.e. the SAF includes 30 patients in the placebo group and 32 patients in the spesolimab low dose group for these analyses.

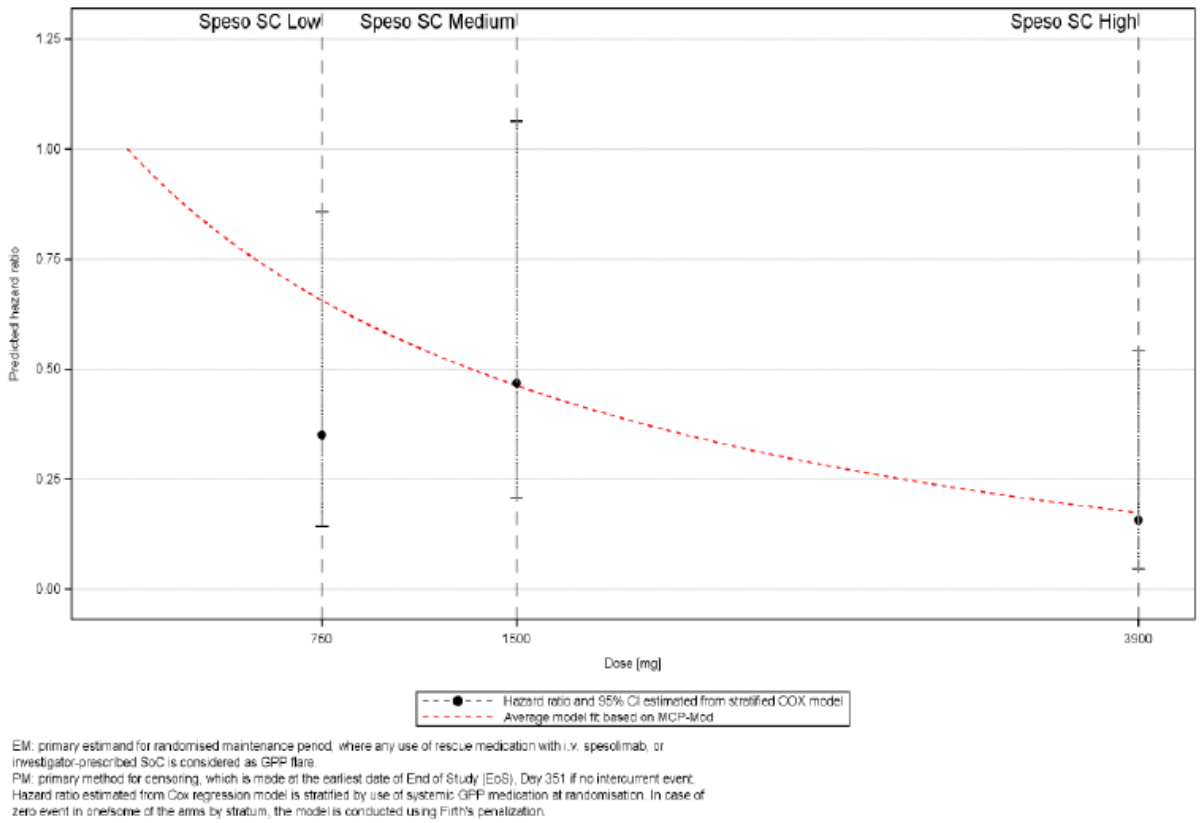
- **Outcomes and estimation**

For the primary objective of the study, a dose response relationship was evaluated.

Evaluation of dose response of spesolimab was determined using a multiple comparison procedure with modelling techniques (MCP-Mod) with respect to achieving a non-flat dose-response curve, while keeping full control of the type I error (alpha) at 0.05 1-sided. The treatment difference for the primary endpoint was estimated using a Cox regression model stratified by the use of systemic GPP medications at randomisation. A non-flat dose response curve is established if at least one dose-response model is statistically significant.

In the primary analysis based on RS (EM-PM), the HR point estimates (95% CI) for MCP-Mod for the spesolimab low, medium, and high dose groups vs placebo were 0.350 (0.143, 0.857), 0.468 (0.206, 1.064), and 0.157 (0.046, 0.541).

The adjusted p-value for each pre-defined model (0.002 for linear, emax1, and emax2; 0.003 for exponential) was statistically significant, thus demonstrating a non-flat dose-response relationship for spesolimab compared with placebo for the primary endpoint.



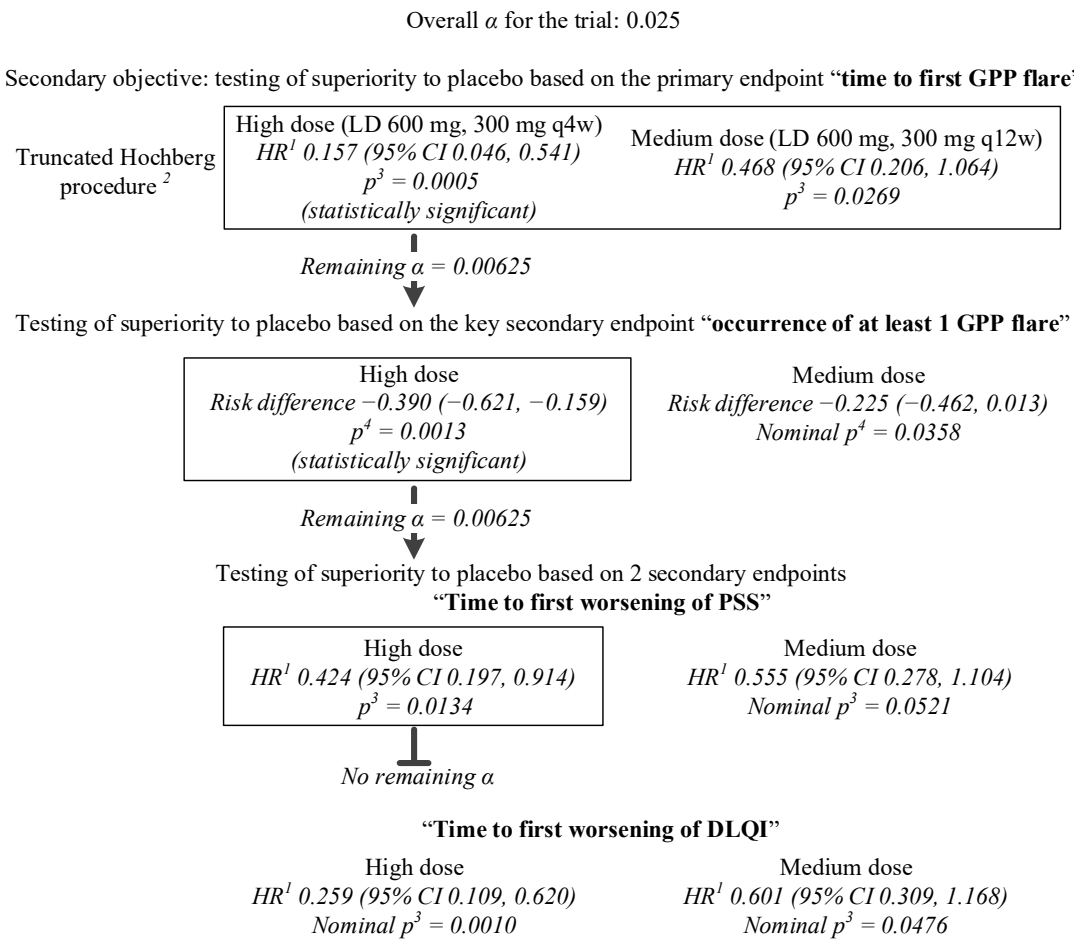
EM: primary estimand for randomised maintenance period, where any use of rescue medication with i.v. spesolimab, or investigator-prescribed SoC is considered as GPP flare.
PM: primary method for censoring, which is made at the earliest date of End of Study (EoS), Day 351 if no intercurrent event.
Hazard ratio estimated from Cox regression model is stratified by use of systemic GPP medication at randomisation. In case of zero event in one/some of the arms by stratum, the model is conducted using Firth's penalization.

Figure 15. Predicted dose response for the time to the first GPP flare up to Week 48 for the averaging model – RS (EM-PM)

Primary and key secondary endpoint

For the primary objective, a dose-response relationship was demonstrated, as stated above.

Subsequently, the confirmatory testing of the secondary objective was carried out, see figure below.



All α-values and p-values were 1-sided; boxes indicate actual confirmatory testing

If the previous test did not reach significance or p-values were not controlled for multiplicity, the subsequent results were considered descriptive and p-values nominal.

1 Cox regression model stratified by the use of systemic GPP medications at randomisation

2 For the primary endpoint: 1) If p-values for both doses had been ≤0.01875, then both comparisons would have been considered statistically significant. 2) If the higher p-value for the 2 comparisons was >0.01875, then the remaining p-value would be tested at an α level of 0.0125. The actual results followed the second scenario and the p-value of the high dose was therefore considered statistically significant (p ≤0.0125).

3 Log-rank test

4 Cochran-Mantel-Haenszel test after multiple imputation, stratified by the use of systemic GPP medications at randomisation

Figure 16. Results of the hierarchical multiple testing procedure

Efficacy results for the primary and key secondary endpoints are depicted in **Table 24** below.

Table 24. Time to the first GPP flare and occurrence of GPP flare up to Week 48 – RS

	Placebo	Spesolimab low dose (LD 300 mg, 150 mg q12w)	Spesolimab medium dose (LD 600 mg, 300 mg q12w)	Spesolimab high dose (LD 600 mg, 300 mg q4w)
Number of patients, N (%)	31 (100.0)	31 (100.0)	31 (100.0)	30 (100.0)
Patients with GPP flares, N (%)	16 (51.6)	7 (22.6)	9 (29.0)	3 (10.0)
Meeting GPP flare criteria	15 (48.4)	7 (22.6)	8 (25.8)	2 (6.7)
Received spesolimab i.v.	15 (48.4)	7 (22.6)	8 (25.8)	2 (6.7)
Spesolimab i.v. treatment as a rescue medication (without meeting GPP flare criteria)	0	0	0	0
Investigator-prescribed SoC to treat GPP worsening without meeting the GPP flare criteria	1 (3.2)	0	1 (3.2)	1 (3.3)
Primary endpoint: time to first GPP flare (EM-PM)				
Event time [week], 10th percentile (95% CI) [1]	1.9 (0.9, 2.9)	4.1 (1.0, 8.7)	4.1 (0.9, 10.7)	n.c. (1.0, n.c.)
Probability of event at Week 48 (Day 337), KM estimate (95% CI)	0.516 (0.356, 0.698)	0.226 (0.115, 0.416)	0.290 (0.163, 0.484)	0.100 (0.033, 0.279)
HR for the time to the first flare vs placebo (95% CI) [2]		0.350 (0.143, 0.857)	0.468 (0.206, 1.064)	0.157 (0.046, 0.541)
p-value [3]		0.0057 (nominal)	0.0269	0.0005
Key secondary endpoint: occurrence of at least 1 GPP flare (EM-MI)				
Proportion with GPP flares (95% CI)	0.516 (0.348, 0.680)	0.226 (0.114, 0.398)	0.297 (0.181, 0.445)	0.127 (0.050, 0.289)
Risk difference for GPP flare occurrence vs placebo (95% CI) [4]		−0.308 (−0.535, −0.081)	−0.225 (−0.462, 0.013)	−0.390 (−0.621, −0.159)
p-value		0.0068 (nominal)	0.0358 (nominal)	0.0013

KM, Kaplan-Meier; n.c., not calculable

EM-PM, primary estimand with GPP flare criteria defined below for the randomised maintenance period using the primary method for censoring

EM-MI, primary estimand with multiple imputation

GPP flare criteria: increase in GPPGA score by ≥2 from baseline and GPPGA pustulation subscore ≥2 up to Week 48. The use of spesolimab i.v. treatment as a rescue medication or investigator-prescribed standard of care (SoC) to treat GPP worsening were considered as onset of GPP flare.

1 KM estimate of the time when 10% of the patients had endpoint events

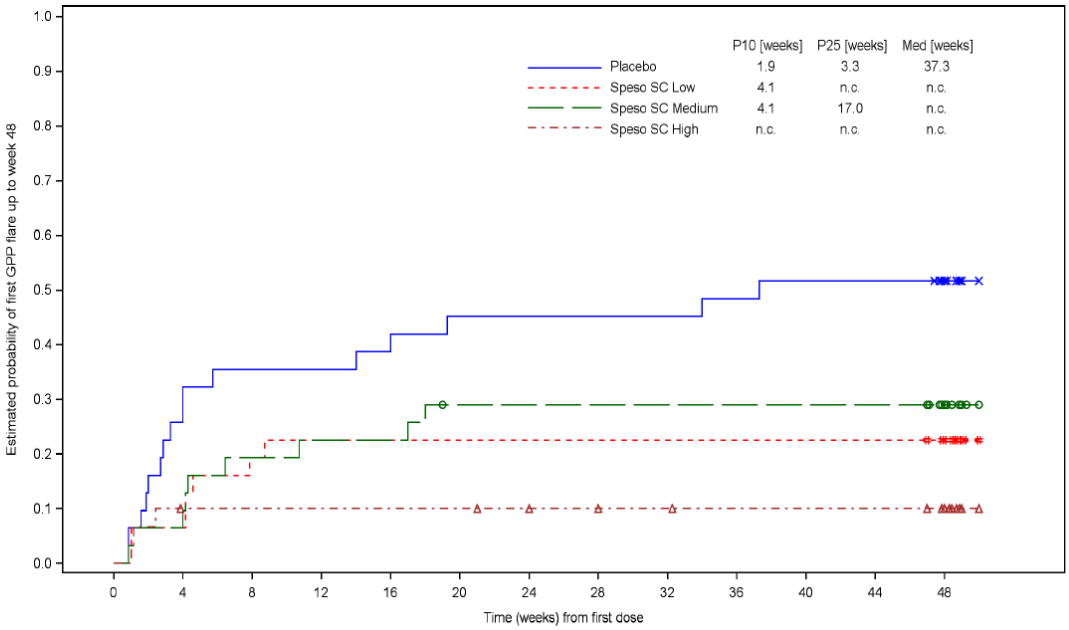
2 Cox regression model stratified by the use of systemic GPP medications at randomisation

3 Log-rank test stratified by the use of systemic GPP medications at randomisation

4 Cochran-Mantel-Haenszel test after multiple imputation, stratified by the use of systemic GPP medications at randomisation

The time course for GPP flare occurrence is depicted below. A separation of the estimated probability of the first GPP flare between spesolimab groups and placebo started in the first 4 weeks after

randomisation and was maintained up to Week 48. After 4 weeks, no flare was reported in the high dose spesolimab group.



Patients at risk

Placebo	31	23	20	20	19	17	17	17	17	16	15	15	11
Speso SC Low	31	29	25	24	24	24	24	24	24	24	24	24	21
Speso SC Medium	31	29	25	24	24	21	21	21	21	21	21	21	14
Speso SC High	30	26	26	26	26	26	25	24	23	22	22	22	18

EM: primary estimand for randomised maintenance period, where any use of rescue medication with i.v. spesolimab, or investigator-prescribed SoC is considered as GPP flare.
PM: primary method for censoring, which is made at the earliest date of End of Study (EoS), Day 351 if no intercurrent event.
Probability of event is estimated by the Kaplan-Meier approach.
n.c. = not calculable.

Following the treatment-policy principle, all data were included in the analysis regardless of treatment discontinuation.

Figure 17. Time to the first GPP flare up to Week 48 – RS (EM-PM)

Sensitivity analyses using alternative censoring method (SM) or patient analysis set (PPS) under the primary estimand, and additional analyses under secondary estimands (EMR or ET) were consistent with the primary analysis for the high dose vs placebo for both the primary and key secondary endpoints (**Figure 18**). A landmark analysis illustrated a lower proportion of patients with flares in the spesolimab high dose group than placebo, evident at Week 12 and continued through Week 48.

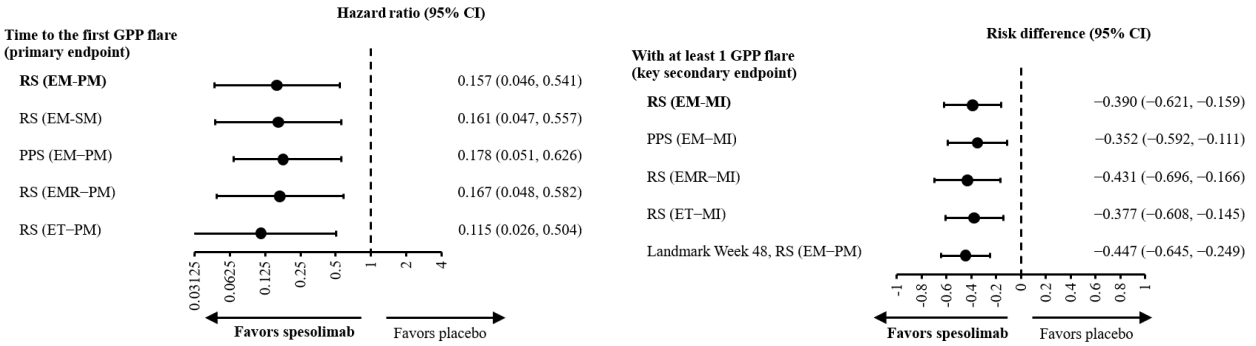


Figure 18. Sensitivity and additional analyses for spesolimab high dose vs placebo for the primary and key secondary endpoints

Secondary endpoints

Time to first worsening of PSS up to Week 48

Statistical significance could not be established for the two secondary endpoints for the spesolimab high dose, time to the first worsening of PSS or DLQI up to Week 48.

Up to Week 48, a total of 56 patients had PSS worsening. The majority (50 patients) met the PSS worsening criterion (4-point increase in total score from baseline), and about half of them (26 patients) received spesolimab i.v. treatment for flares; 5 patients received spesolimab i.v. treatment and 1 patient received investigator-prescribed SoC to treat GPP worsening without meeting PSS worsening criterion.

A lower number of patients in all spesolimab groups than in the placebo group reported PSS worsening up to Week 48 (see *Table 25*). The risk of PSS worsening over 48 weeks was lower with spesolimab high dose compared with placebo (HR 0.424; 95% CI 0.197, 0.914; p = 0.0134), although the required significance level of 0.00625 was not reached.

Table 25. Time to the first worsening of PSS up to Week 48 – RS (EM-PM)

	Placebo	Spesolimab low dose (LD 300 mg, 150 mg q12w)	Spesolimab medium dose (LD 600 mg, 300 mg q12w)	Spesolimab high dose (LD 600 mg, 300 mg q4w)
Number of patients, N (%)	31 (100.0)	31 (100.0)	31 (100.0)	30 (100.0)
Patients with PSS worsening, N (%)	20 (64.5)	12 (38.7)	14 (45.2)	10 (33.3)
Meeting PSS worsening criterion	18 (58.1)	11 (35.5)	12 (38.7)	9 (30.0)
Received spesolimab i.v.	13 (41.9)	5 (16.1)	6 (19.4)	2 (6.7)
Spesolimab i.v. treatment as a rescue medication (without meeting PSS worsening criterion)	2 (6.5)	1 (3.2)	2 (6.5)	0
Investigator-prescribed SoC to treat GPP worsening	0	0	0	1 (3.3)
Event time [week], 25th percentile (95% CI) [1]	3.3 (1.6, 8.6)	5.6 (4.0, 32.0)	7.3 (3.0, 18.1)	9.4 (1.1, n.c.)
Probability of event at Week 48 (Day 337), KM estimate (95% CI)	0.645 (0.481, 0.806)	0.400 (0.250, 0.595)	0.457 (0.301, 0.647)	0.376 (0.223, 0.588)
HR for the time to the first worsening vs placebo (95% CI) [2]		0.459 (0.222, 0.945)	0.555 (0.278, 1.104)	0.424 (0.197, 0.914)
p-value [3]		0.0079 (nominal)	0.0521 (nominal)	0.0134

PSS worsening criterion: 4-point increase in total score from baseline up to Week 48. The use of spesolimab i.v. treatment as a rescue medication or investigator-prescribed SoC to treat GPP worsening were considered as onset of PSS worsening.

Patients with baseline values missing (1 patient in spesolimab high dose group, [redacted] Table 15.1.4: 1 and Appendix 16.2.6, Listing 2) or higher than 12 (maximum score possible is 16; 1 patient each in spesolimab low dose and high dose groups, [redacted] and [redacted]; Appendix 16.2.6, Listing 2) were censored at Day 1.

1 KM estimate of the time when 25% of the patients had endpoint events

2 Cox regression model stratified by the use of systemic GPP medications at randomization

3 Log-rank test stratified by the use of systemic GPP medications at randomization

Time to the first worsening of DLQI up to Week 48

Up to Week 48, a total of 59 patients had DLQI worsening. About half (31 patients) met the DLQI worsening criterion (4-point increase in total score from baseline), and only a few of them (5 patients) received spesolimab i.v. treatment for flares; 27 patients received spesolimab i.v. treatment and 1 patient received investigator-prescribed SoC to treat GPP worsening without meeting DLQI worsening criterion, as DLQI scores were not required to be collected at the time of i.v. treatment.

A lower number of patients in all spesolimab groups than in the placebo group reported DLQI worsening up to Week 48. The risk of DLQI worsening over 48 weeks was lower with spesolimab high dose compared with placebo (HR 0.259; 95% CI 0.109, 0.620; nominal p = 0.0010); see *Table 26*.

Table 26. Time to the first worsening of DLQI up to Week 48 – RS (EM-PM)

	Placebo	Spesolimab low dose (LD 300 mg, 150 mg q12w)	Spesolimab medium dose (LD 600 mg, 300 mg q12w)	Spesolimab high dose (LD 600 mg, 300 mg q4w)
Number of patients, N (%)	31 (100.0)	31 (100.0)	31 (100.0)	30 (100.0)
Patients with DLQI worsening, N (%)	20 (64.5)	16 (51.6)	16 (51.6)	7 (23.3)
Meeting DLQI worsening criterion	6 (19.4)	11 (35.5)	10 (32.3)	4 (13.3)
Received spesolimab i.v.	1 (3.2)	2 (6.5)	2 (6.5)	0
Spesolimab i.v. treatment as a rescue medication (without meeting DLQI worsening criteria)	14 (45.2)	5 (16.1)	6 (19.4)	2 (6.7)
Investigator-prescribed SoC to treat GPP worsening	0	0	0	1 (3.3)
Event time [week], 25th percentile (95% CI) [1]	3.3 (1.6, 5.9)	5.6 (3.0, 11.0)	6.4 (3.0, 36.0)	n.c. (2.4, n.c.)
Probability of event at Week 48 (Day 337), KM estimate (95% CI)	0.645 (0.481, 0.806)	0.533 (0.370, 0.716)	0.495 (0.334, 0.683)	0.247 (0.126, 0.451)
HR for the time to the first worsening vs placebo (95% CI) [2]		0.580 (0.296, 1.136)	0.601 (0.309, 1.168)	0.259 (0.109, 0.620)
p-value [3]		0.0429 (nominal)	0.0476 (nominal)	0.0010 (nominal)

DLQI worsening criterion: 4-point increase in total score from baseline up to Week 48. The use of spesolimab i.v. treatment as a rescue medication or investigator-prescribed SoC to treat GPP worsening were considered as onset of DLQI worsening.

Patients below the age of 16 years (i.e. 12 to 15 years; 1 patient each in spesolimab low dose and high dose groups, [redacted] Table 15.1.4: 1 and Appendix 16.2.6, Listing 2) did not have to complete the DLQI questionnaire, and were censored at Day 1. No other patient had a baseline value missing or higher than 26 (maximum score possible is 30; Table 15.1.4: 1).

1 KM estimate of the time when 25% of the patients had endpoint event

2 Cox regression model stratified by the use of systemic GPP medications at randomization

3 Log-rank test stratified by the use of systemic GPP medications at randomization

Sustained remission up to Week 48

Sustained remission was defined as a patient with a GPPGA score of 0 or 1 (clear or almost clear) at all visits up to Week 48, without intake of rescue medication or investigator-prescribed SoC. The proportion of patients with sustained remission was 0.516 for the spesolimab low dose, 0.452 for the medium dose, 0.633 for the high dose, compared with 0.290 for placebo. The risk difference vs placebo was 0.246 (95% CI 0.013, 0.478) for the spesolimab low dose, 0.166 (95% CI -0.069, 0.401) for the medium dose, and 0.345 (95% CI 0.099, 0.591) for the high dose (*Table 27*).

Table 27. The proportion of patients with sustained remission up to Week 48 – RS (EM-MI)

	Placebo	Spesolimab low dose (LD 300 mg, 150 mg q12w)	Spesolimab medium dose (LD 600 mg, 300 mg q12w)	Spesolimab high dose (LD 600 mg, 300 mg q4w)
Number of patients, N (%)	31 (100.0)	31 (100.0)	31 (100.0)	30 (100.0)
Patients with sustained remission at all available visits, N (%) before imputation	9 (29.0)	16 (51.6)	14 (45.2)	20 (66.7)
With sustained remission at all visits up to Week 48, N (%)	8 (25.8)	12 (38.7)	10 (32.3)	12 (40.0)
Proportion with sustained remission (95% CI)	0.290 (0.161, 0.466)	0.516 (0.348, 0.680)	0.452 (0.292, 0.622)	0.633 (0.471, 0.770)
Risk difference for sustained remission vs placebo (95% CI)		0.246 (0.013, 0.478)	0.166 (-0.069, 0.401)	0.345 (0.099, 0.591)

- **Ancillary analyses**

Subgroup analyses

Subgroup analyses have been presented for the primary and key secondary efficacy endpoints; these analyses were not adjusted for multiple testing.

The primary analysis of the primary endpoint of spesolimab high dose vs. placebo for the time to the first GPP flare up to Week 48 was generally consistent across the subgroups (**Figure 19**). HR point estimates of the subgroups were within the shaded area (i.e. 95% CI of the overall analysis) for all but 3 subgroups: patients with baseline GPPGA of 0 (patients with primary endpoint events: 0 out of 3 for high dose vs 0 out of 4 for placebo), without use of systemic GPP medication at randomisation (2 out of 8 for high dose vs 3 out of 9 for placebo), and in the age category of ≥65 years (1 out of 3 for high dose vs 0 out of 1 for placebo).

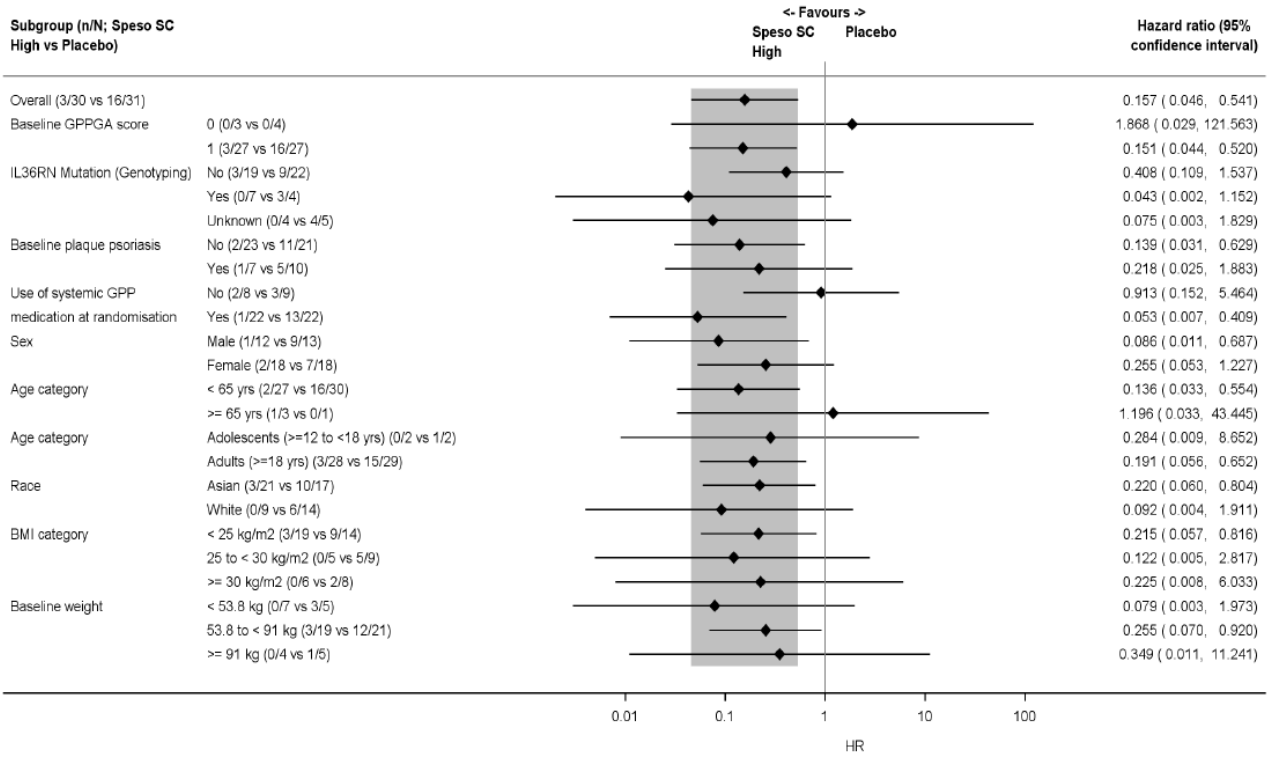


Figure 19. Subgroup analyses for the time to the first GPP flare up to Week 48 for spesolimab high dose vs placebo – RS (EM-PM)

The trends were similar for the key secondary endpoint.

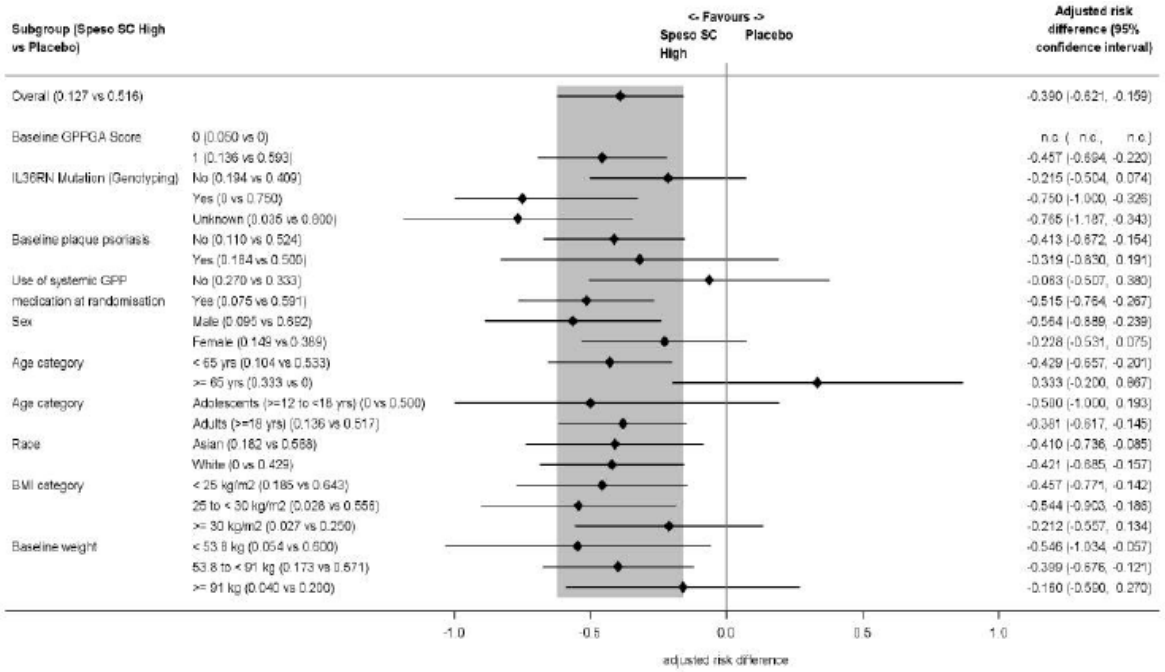
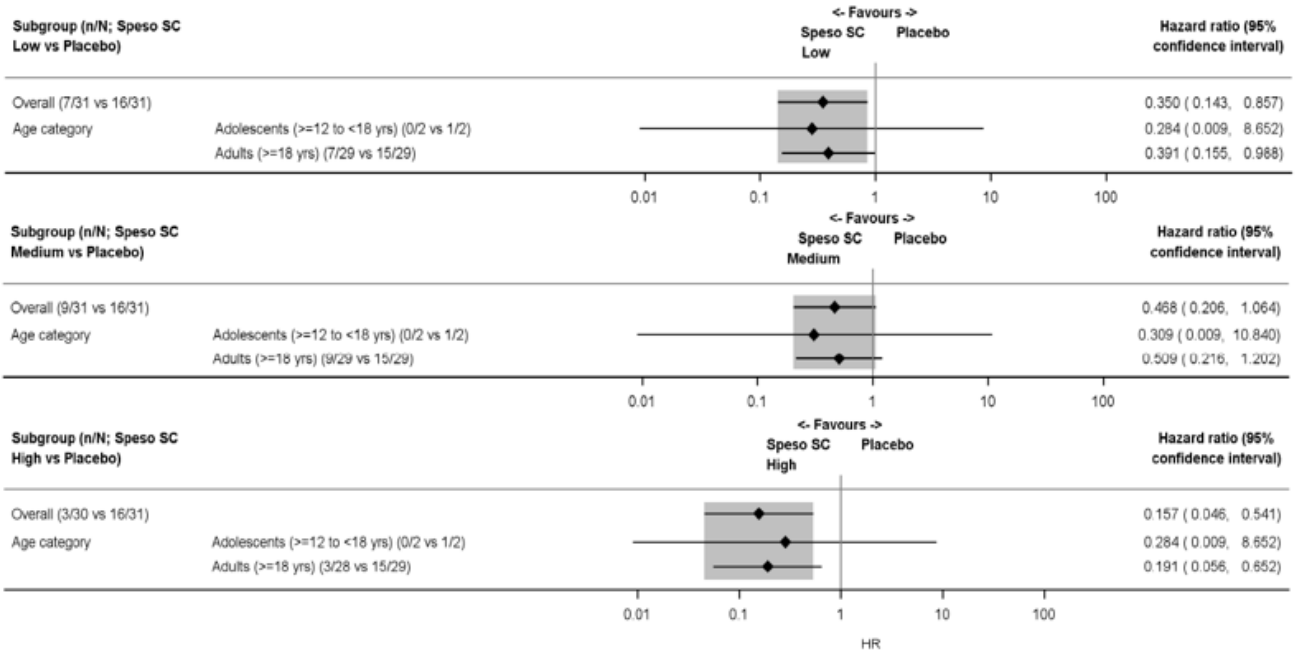


Figure 20. Subgroup analyses for the proportion of patients on spesolimab high dose with at least 1 GPP flare up to Week 48 – RS (EM-MI)

Efficacy in adolescents

A total of eight patients (2 per group) in the study were adolescents, ranging in age from 14 to 17 years at screening.

Only 1 adolescent patient in the placebo group had a GPP flare (reported with PSS worsening and DLQI worsening) and received investigator-prescribed SoC to treat GPP worsening; without meeting the GPP flare criteria. In the spesolimab groups, no adolescent patient had GPP flare, PSS worsening, or DLQI worsening; all 6 of them achieved sustained remission. This was depicted in the following figure.



Firth's penalisation was applied in case of zero event in one or some of the treatment groups.

Figure 21. Time to the first GPP flare up to Week 48 for adolescent and adult patients – RS (EM-PM)

Effect of loading dose, 300 mg vs. 600 mg, up to Week 4

The Applicant presented a display of the proportion of patients with GPP flares, worsening of PSS, or worsening of DLQI up to Week 4 on the basis of the loading dose 300 mg vs. 600 mg group, vs. placebo (**Figure 22**). Both loading doses showed similar trends and were distinguishable from the placebo group by Week 2, regarding the time to the first GPP flare, PSS worsening, or DLQI worsening.

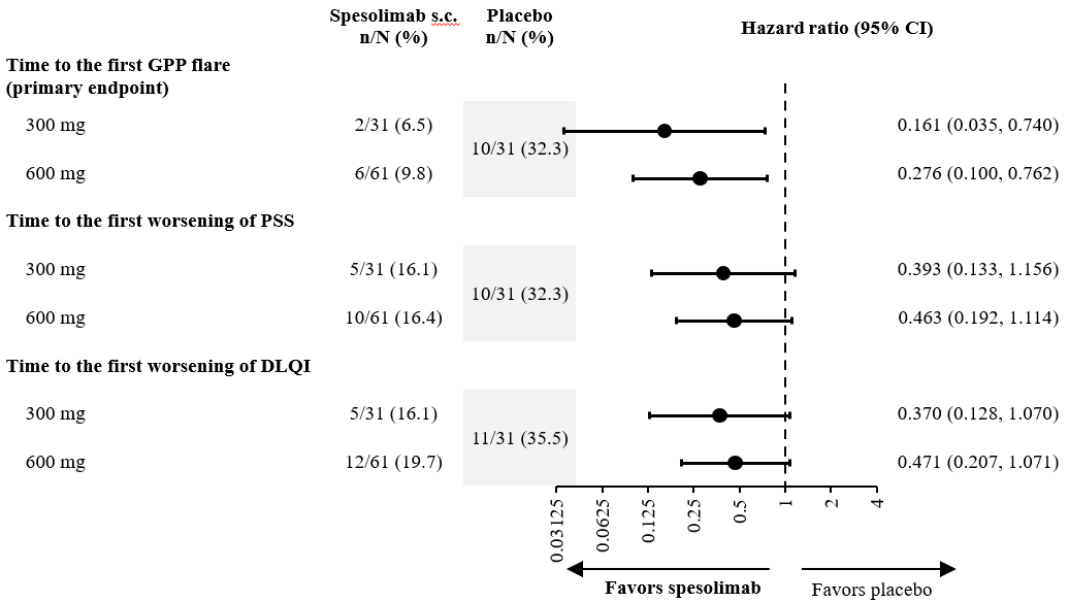


Figure 22. Time to first GPP flare, worsening of PSS, or worsening of DLQI up to Week 4 – RS (EM-PM)

Flare treatment response after spesolimab OL 900 mg i.v. dose as rescue treatment

A total of 32 patients (denoted as the subset SAF-FT) received a spesolimab OL 900 mg i.v. dose (on Day 1) as a rescue treatment for GPP flare; of these patients, 10 received an additional spesolimab OL 900 mg i.v. dose (planned on Day 8). Baseline for the analyses of flare treatment response was the last assessment before the first rescue treatment with spesolimab OL 900 mg i.v. dose.

The results presented focused on "EN-ID8", which regarded the use of investigator-prescribed SoC for GPP as treatment failure/non-response; the use of an additional spesolimab OL i.v. dose, if applicable, was not regarded as treatment failure/non-response and the data after that were not excluded. For the analyses of proportion of patients with response, "OC-ID8" was used in addition, which excluded data after the use of investigator-prescribed SoC for GPP. Investigator-prescribed SoC for GPP was allowed 4 weeks following the first spesolimab OL i.v. dose.

For the 32 patients who received spesolimab i.v. treatment, the probability of a response at Week 1 (Day 8) after the first dose was 0.554 (95% CI 0.388, 0.734; based on EN-ID8-SOC).

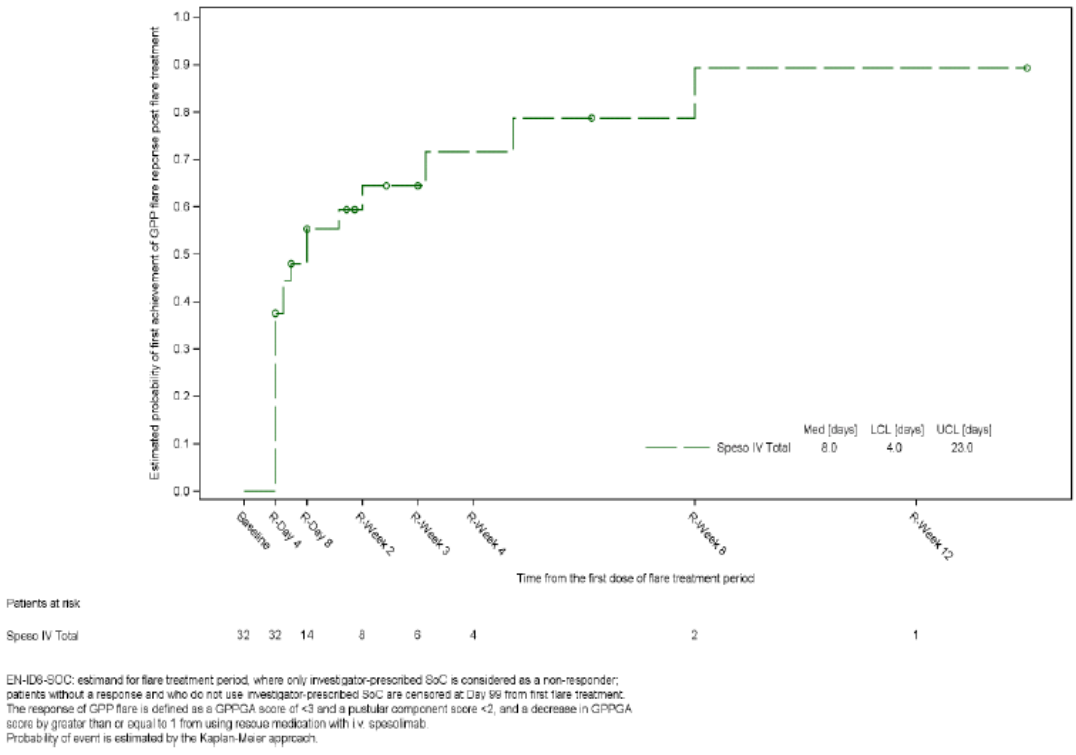


Figure 23. Time to the first response of GPP flare – SAF-FT (EN-ID8-SOC)

After the first spesolimab i.v. dose, a total of 19 of 32 patients (0.594, 95% CI 0.423, 0.745) achieved a response of GPP flare within *2 weeks* (EN-ID8-NRI). The response of GPP flare was defined as a GPPGA score of <3 and a pustular component score <2, and a decrease in GPPGA score by greater than or equal to 1 from using rescue medication with i.v. spesolimab.

A total of 9 of 32 patients (0.281, 95% CI 0.156, 0.454) at Week 1 and 12 patients (0.375, 95% CI 0.229, 0.547) at Week 12 had a *GPPGA total score of 0 or 1* (EN-ID8-NRI). The proportion of patients with GPPGA total score of 0 or 1 increased from the first post-rescue assessment (Day 4) and reached a plateau at around Week 4.

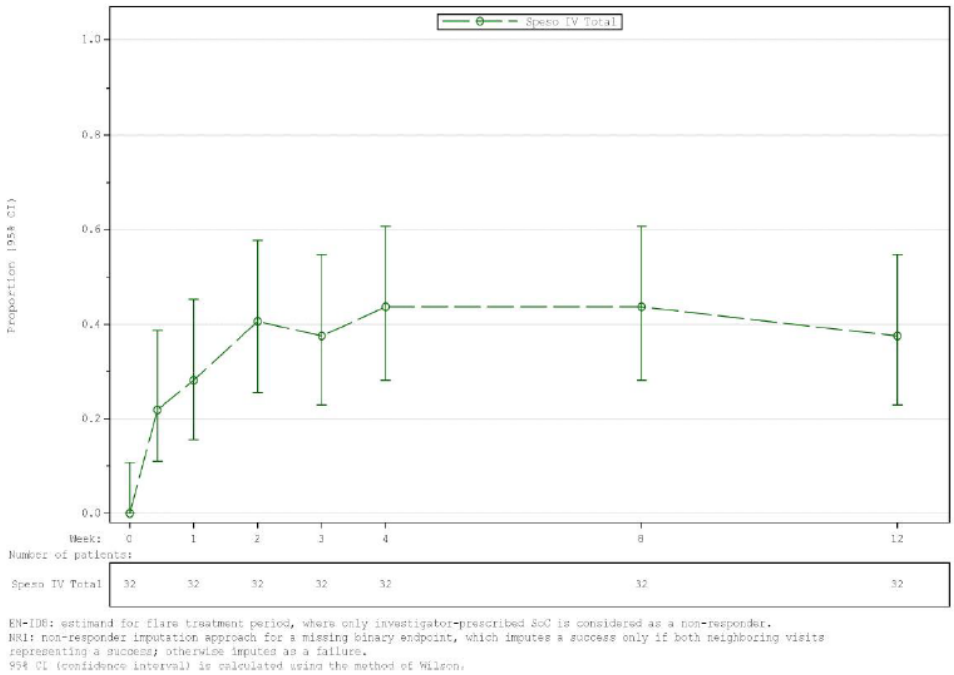


Figure 24. Proportion of patients with GPPGA total score of 0 or 1 up to Week 12 – SAF-FT (EN-ID8-NRI)

For the *GPPGA pustulation sub-score of 0* at Week 1 and up to Week 12, a total of 12 of 32 patients (0.375, 95% CI 0.229, 0.547) at Week 1 and 13 patients (0.406, 95% 0.255, 0.577) at Week 12, had a GPPGA pustulation sub-score of 0 (EN-ID8-NRI).

Analyses of anti-drug antibodies or neutralising antibodies and efficacy

ADA data are also described in the PK AR. However, results related to efficacy are presented here.

Anti-drug antibody (ADA) response was determined for every patient. Immunogenicity of spesolimab was assessed using a multi-tiered approach. All samples were analysed in the ADA screening assay, and only those found to be putative positive in the ADA screening were assessed in the ADA confirmatory assay. Then samples that were confirmed to be positive were titrated (to obtain a titer value).

In total, 123 patients were randomised to receive spesolimab treatments or placebo in this trial. Only 2 of the 123 patients were not ADA evaluable in the trial (one patient in the placebo treatment group had no baseline ADA or PK sample and one patient in the high dose group discontinued the trial early and did not have post-dose ADA or PK samples). The incidence and kinetics of ADA after spesolimab treatment are displayed in *Table 28*.

Table 28. Incidence and kinetics of ADA after any spesolimab treatment

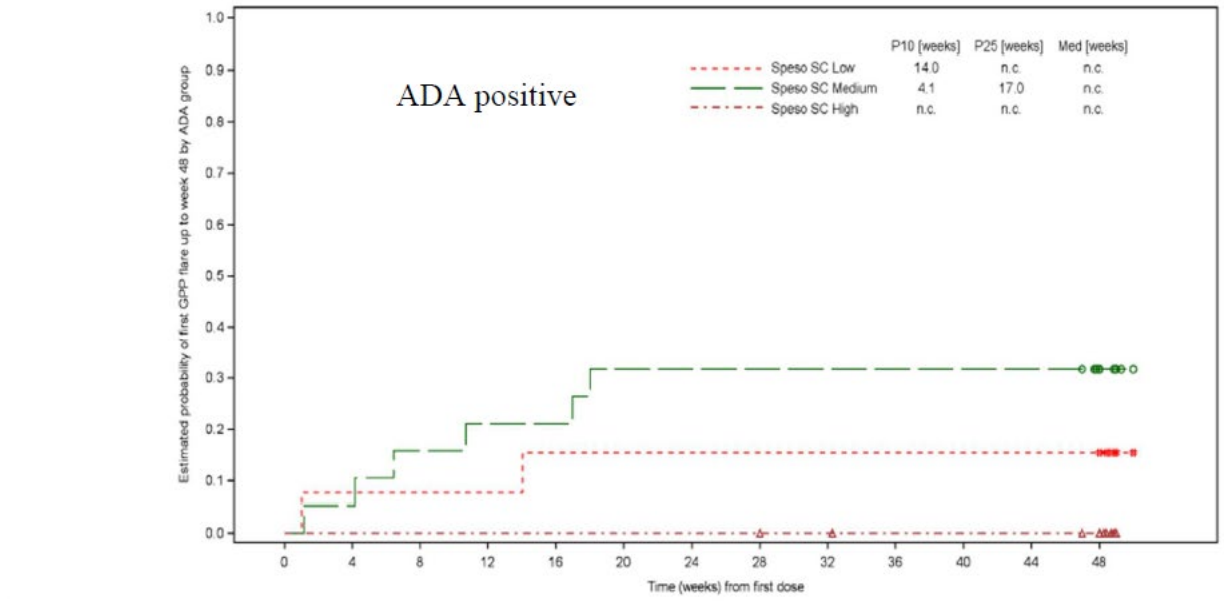
	Placebo	Low dose[1]	Medium dose[1]	High dose[1]
Total, N (%)[2]	15 (100%)	31 (100%)	31 (100%)	29 (100%)
Baseline[3] ADA positive, N (%)	0	2 (6%)	0 (0%)	0 (0%)
ADA negative[4], N (%)	8 (53%)	16 (52%)	10 (32%)	17 (59%)
Treatment-induced or boosted ADA positive[5], N (%)	7 (47%)	14 (45%)	21 (68%)	12 (41%)
Transient positive[6], N (%)	0 (0%)	1 (3%)	2 (6%)	2 (7%)
Potentially persistent positive[7], N (%)	1 (7%)	2 (6%)	1 (3%)	2 (7%)
Persistent positive[8], N (%)	6 (40%)	11 (35%)	18 (58%)	8 (28%)
Patients with maximum titer >4000	6 (40%)	6 (19%)	18 (58%)	7 (24%)
Last sample ADA positive, N (%)	7 (47%)	10 (32%)	18 (58%)	10 (34%)
ADA onset [week][9]	8.6 (2.4, 38.0)	10.6 (4.0, 24.0)	8.0 (1.1, 12.6)	8.0 (3.6, 24.0)
Time of maximum titer [week][9]	30.0 (14.6, 45.7)	21.6 (4.0, 40.0)	18.7 (2.1, 47.0)	20.4 (3.6, 33.0)
Maximum titer	11 500 (2880 – 173 000)	2160 (180 - 173 000)	28 800 (180 - 5 760 000)	5760 (180 - 115 000)
Treatment-induced NAb positive[10], N (%)	7 (47%)	14 (45%)	21 (68%)	10 (34%)
NAb onset [week][9]	8.4 (1.0, 11.5)	11.9 (8.0, 24.0)	8.7 (1.1, 20.0)	10.2 (4.0, 24.0)
Last sample NAb positive, N (%)	6 (40%)	8 (26%)	16 (52%)	8 (26%)

Placebo patients received i.v. spesolimab as rescue possibly followed by s.c. spesolimab treatment.
1 Anyone randomized to this treatment group, including those who received rescue i.v. spesolimab treatment.
2 Spesolimab treated and ADA-evaluable
3 Last sample obtained before initiation of active spesolimab treatment.
4 All samples from a patient were ADA negative throughout the trial.
5 Patient had at least 1 ADA positive sample any time after baseline during the trial.
6 Patients were ADA-positive, and only had one ADA positive sample followed by at least 1 ADA-negative sample 16 or more weeks later; or patients had more than one ADA positive samples but the time period between the first and last ADA positive sample was less than 16 weeks.
7 Patients were ADA positive but did not meet the definition for persistent or transient.
8 Patients were ADA positive, and the time period between the first and last ADA positive sample was equal to or more than 16 weeks.
9 Median (min, max); relative to the start of study, instead of relative to i.v. dosing
10 Patients were treatment induced or boosted ADA-positive and had at least 1 NAb-positive sample after treatment.

Table 29. Patients with at least 1 GPP flare up to Week 48 before and after ADA development – SAF

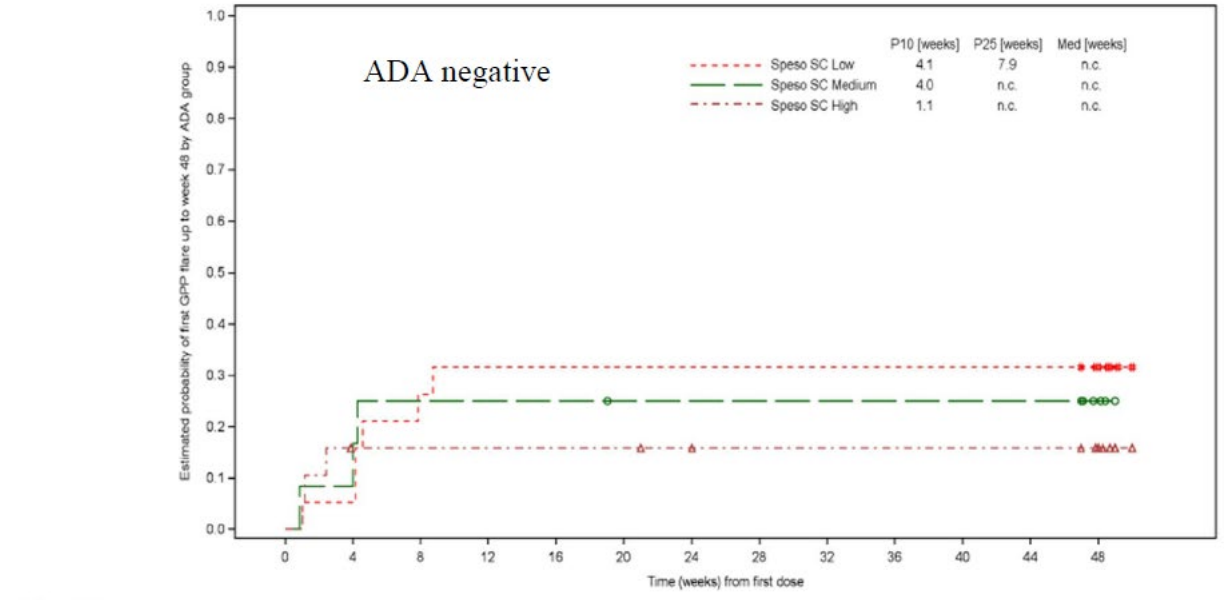
	Spesolimab low dose (LD 300 mg, 150 mg q12w)	Spesolimab medium dose (LD 600 mg, 300 mg q12w)	Spesolimab high dose (LD 600 mg, 300 mg q4w)	Spesolimab total
Number of patients positive for ADA at risk, N (%)	13 (100.0)	16 (100.0)	11 (100.0)	40 (100.0)
Patients with GPP flares after ADA development, N (%)	2 (15.4)	3 (18.8)	0	5 (12.5)
Proportion with GPP flares (95% CI)	0.154 (0.043, 0.422)	0.188 (0.066, 0.430)	0.000 (0.000, 0.259)	0.125 (0.055, 0.261)
Event time [week], 10th percentile (95% CI)	5.3 (0.9, n.c.)	4.9 (3.3, n.c.)	n.c.	5.3 (0.9, n.c.)
Number of patients at risk, N (%)	32 (100.0)	31 (100.0)	30 (100.0)	93 (100.0)
Patients with GPP flares before ADA development, N (%)	6 (18.8)	6 (19.4)	3 (10.0)	15 (16.1)
Proportion with GPP flares (95% CI)	0.188 (0.089, 0.353)	0.194 (0.092, 0.363)	0.100 (0.035, 0.256)	0.161 (0.100, 0.249)
Event time [week], 10th percentile (95% CI)	4.1 (1.0, 8.7)	4.1 (0.9, n.c.)	n.c. (1.0, n.c.)	4.1 (1.1, 8.7)

n.c.: not calculable
Before ADA development included patients with events either before their first ADA positive sample or without ADA positive samples throughout
After ADA development included patients with events from the time point of their first ADA positive sample



Patients at risk

Speso SC Low	13	12	12	12	11	11	11	11	11	11	11	11	11
Speso SC Medium	19	18	16	15	15	13	13	13	13	13	13	13	9
Speso SC High	11	11	11	11	11	11	11	11	10	9	9	9	8



Patients at risk

Speso SC Low	19	18	14	13	13	13	13	13	13	13	13	13	10
Speso SC Medium	12	11	9	9	9	8	8	8	8	8	8	8	5
Speso SC High	19	15	15	15	15	15	14	13	13	13	13	13	10

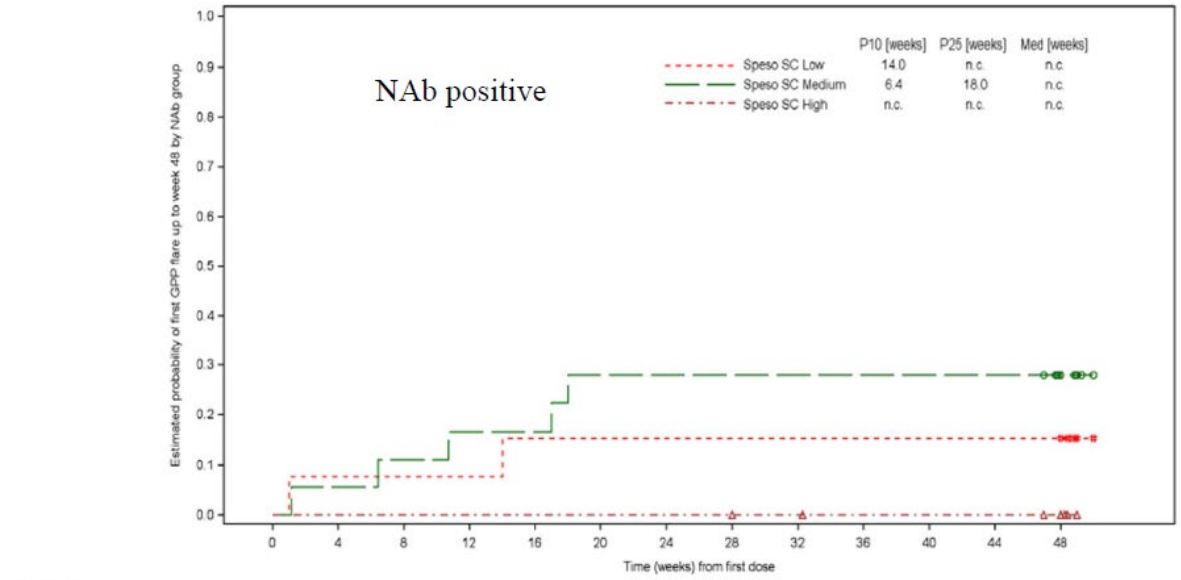
EM: primary estimand for randomised maintenance period, where any use of rescue medication with i.v. spesolimab, or investigator-prescribed SoC is considered as GPP flare.
PM: primary method for handling censoring, where censoring is made at the earliest date of End of Study (EoS), Day 351 if no intercurrent event occurs.
ADA positive is defined as the first occurrence of ADA titer greater than 0 within randomised maintenance period.
Probability of event is estimated by the Kaplan-Meier approach.
n.c. = not calculable.

Figure 25. Time to the first GPP flare up to Week 48 by ADA status – SAF (EM-PM)

Table 30. Patients with at least 1 GPP flare up to Week 48 by NAb status – SAF

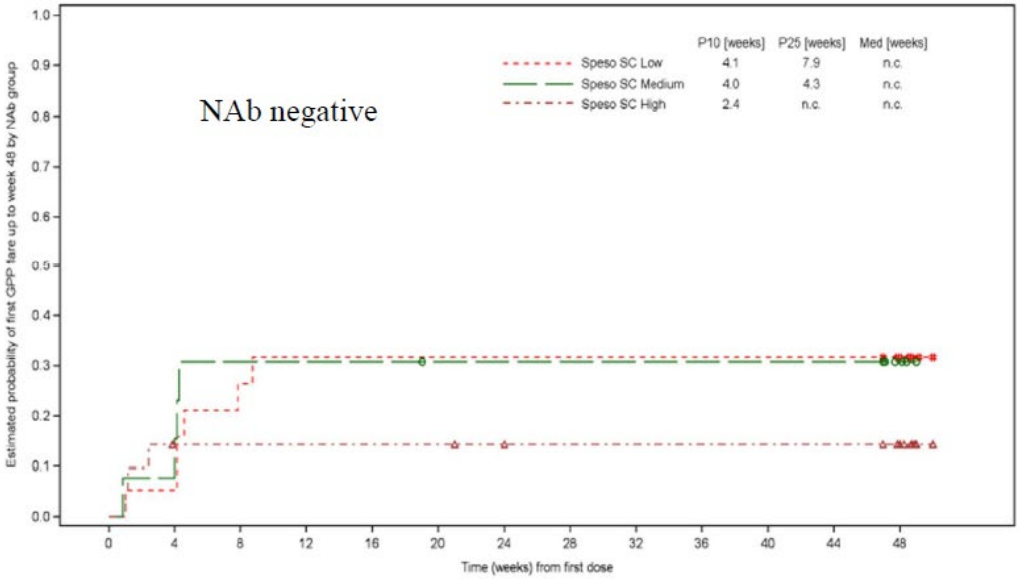
	Spesolimab low dose (LD 300 mg, 150 mg q12w)	Spesolimab medium dose (LD 600 mg, 300 mg q12w)	Spesolimab high dose (LD 600 mg, 300 mg q4w)	Spesolimab total
Patients positive for NAb, N (%)	13 (100.0)	18 (100.0)	9 (100.0)	40 (100.0)
Patients with GPP flares, N (%)	2 (15.4)	5 (27.8)	0	7 (17.5)
Proportion with GPP flares (95% CI)	0.154 (0.043, 0.422)	0.278 (0.125, 0.509)	0.000 (0.000, 0.299)	0.175 (0.087, 0.319)
Event time [week], 10th percentile (95% CI)	14.0 (1.0, n.c.)	6.4 (1.1, 18.0)	n.c. (n.c., n.c.)	12.4 (1.0, n.c.)
Patients negative for NAb, N (%)	19 (100.0)	13 (100.0)	21 (100.0)	53 (100.0)
Patients with GPP flares, N (%)	6 (31.6)	4 (30.8)	3 (14.3)	13 (24.5)
Proportion with GPP flares (95% CI)	0.316 (0.154, 0.540)	0.308 (0.127, 0.576)	0.143 (0.050, 0.346)	0.245 (0.149, 0.376)
Event time [week], 10th percentile (95% CI)	4.1 (1.0, 7.9)	4.0 (0.9, 4.3)	2.4 (1.0, n.c.)	4.0 (0.9, 4.3)

n.c.: not calculable



Patients at risk

Speso SC Low	13	12	12	12	11	11	11	11	11	11	11	11	11
Speso SC Medium	18	17	16	15	15	13	13	13	13	13	13	13	9
Speso SC High	9	9	9	9	9	9	9	9	8	7	7	7	6



Patients at risk

Speso SC Low	19	18	14	13	13	13	13	13	13	13	13	13	10
Speso SC Medium	13	12	9	9	9	8	8	8	8	8	8	8	5
Speso SC High	21	17	17	17	17	17	16	15	15	15	15	15	12

EM: primary estimand for randomised maintenance period, where any use of rescue medication with i.v. spesolimab, or investigator-prescribed SoC is considered as GPP flare.
PM: primary method for handling censoring, where censoring is made at the earliest date of End of Study (EoS), Day 351 if no intercurrent event occurs.
NAb positive is defined as the first occurrence of NAb positive within randomised maintenance period.
Probability of event is estimated by the Kaplan-Meier approach.
n.c. = not calculable.

Figure 26. Time to the first GPP flare up to Week 48 by NAb status – SAF (EM-PM)

In the following figure, flare status and ADA/Nab status over time is presented.

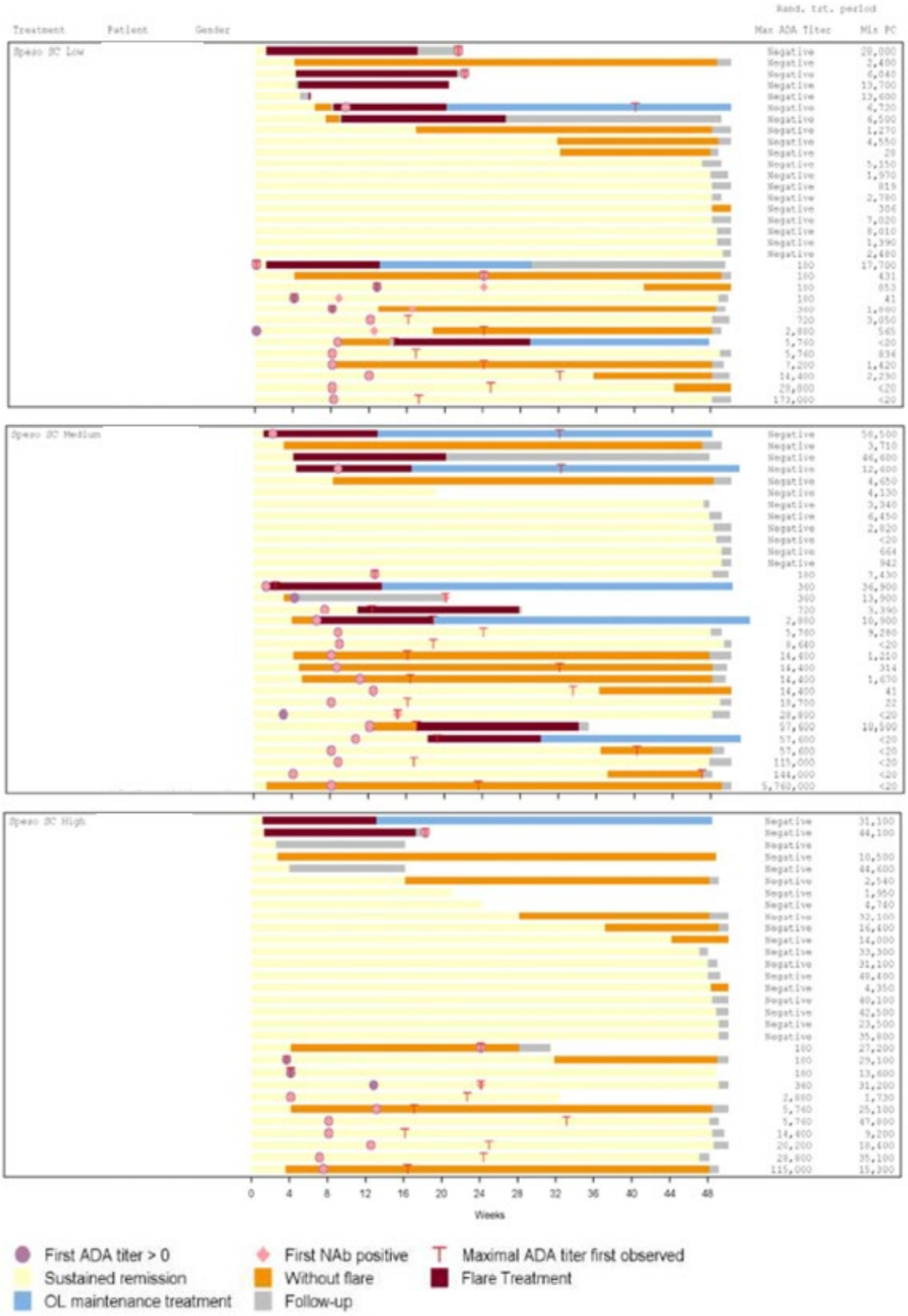


Figure 27. Swimmer plot of flare status and ADA/NAb status by treatment – SAF

- **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).

Table 31 Summary of efficacy for trial 1368-0027

Title: Effisayil 2: Multi-center, randomised, parallel group, double blind, placebo controlled, Phase IIb dose-finding study to evaluate efficacy and safety of BI 655130 (Spesolimab) compared to placebo in preventing generalised pustular psoriasis (GPP) flares in patients with history of GPP			
Study identifier	1368-0027		
Design	Randomised, placebo-controlled, double-blind, parallel-group		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	48 weeks treatment period for the primary analysis Not applicable Patients could continue in the open-label extension trial 1368-0025; otherwise patients were to be followed up for 12 weeks after 48 weeks of treatment period (i.e. 16 weeks after the last dose)	
Hypothesis	Superiority of spesolimab vs placebo		
Treatments groups	Arm 1: spesolimab high dose	Loading dose 600 mg s.c. on Day 1, followed by 300 mg s.c. q4w maintenance treatment for 48 weeks, 30 patients randomised	
	Arm 2: spesolimab medium dose	Loading dose 600 mg s.c. on Day 1, followed by 300 mg s.c. q12w maintenance treatment for 48 weeks, 31 patients randomised	
	Arm 3: spesolimab low dose	Loading dose 300 mg s.c. on Day 1, followed by 150 mg s.c. q12w maintenance treatment for 48 weeks, 31 patients randomised	
	Arm 4: placebo	Loading dose on Day 1, followed by maintenance treatment for 48 weeks, 31 patients randomised	
Endpoints and definitions (for confirmatory endpoints)	Primary endpoint	Time to first GPP flare	Flare defined as an increase in GPPGA score by ≥2 from baseline and GPPGA pustulation subscore ≥2 up to Week 48
	Key secondary endpoint	Occurrence of at least 1 GPP flare	Flare defined as above
	Secondary endpoint	Time to first worsening of PSS	4-point increase in total score from baseline up to Week 48

	Secondary endpoint	Time to first worsening of DLQI	4-point increase in total score from baseline up to Week 48			
Database lock	13 Jan 2023					
Results and Analysis						
Analysis description	Primary Analysis (at Week 48)					
Analysis population and time point description	Randomised set, Week 48					
Descriptive statistics and estimate variability	Treatment group		Placebo	Spesolimab low dose	Spesolimab medium dose	Spesolimab high dose
	Number of patients (%)		31 (100.0)	31 (100.0)	31 (100.0)	30 (100.0)
	With GPP flares, N (%)		16 (51.6)	7 (22.6)	9 (29.0)	3 (10.0)
	Time to the first GPP flare, 10th percentile		1.9 weeks	4.1 weeks	4.1 weeks	n.c. weeks
	95% CI		0.9, 2.9	1.0, 8.7	0.9, 10.7	1.0, n.c.
	Time to the first worsening of PSS, 25th percentile		3.3 weeks	5.6 weeks	7.3 weeks	9.4 weeks
	95% CI		1.6, 8.6	4.0, 32.0	3.0, 18.1	1.1, n.c.
	Time to the first worsening of DLQI, 25th percentile		3.3 weeks	5.6 weeks	6.4 weeks	n.c. weeks
	95% CI		1.6, 5.9	3.0, 11.0	3.0, 36.0	2.4, n.c.
Effect estimate per comparison		Comparison group (vs placebo)		Spesolimab low dose	Spesolimab medium dose	Spesolimab high dose
	Time to first GPP flare	Hazard ratio		0.350	0.468	0.157
		95% CI		0.143, 0.857	0.206, 1.064	0.046, 0.541
		p-value		0.0057 (nominal)	0.0269	0.0005
		Risk difference (%)		−0.308	−0.225	−0.390

	Occurrence of at least 1 GPP flare	95% CI (%)	−0.535, −0.081	−0.462, 0.013	−0.621, −0.159
		p-value	0.0068 (nominal)	0.0358 (nominal)	0.0013
	Time to first worsening of PSS	Hazard ratio	0.459	0.555	0.424
		95% CI	0.222, 0.945	0.278, 1.104	0.197, 0.914
		p-value	0.0079 (nominal)	0.0521 (nominal)	0.0134
	Time to first worsening of DLQI	Hazard ratio	0.580	0.601	0.259
		95% CI	0.296, 1.136	0.309, 1.168	0.109, 0.620
		p-value	0.0429 (nominal)	0.0476 (nominal)	0.0010 (nominal)
Notes	Results for the confirmatory endpoints are included in this table.				

n.c., not calculable

2.6.5.3. Clinical studies in special populations

No studies in special populations have been conducted. Analyses performed based on subgroups is presented in the section *Ancillary analyses*, as well as a paragraph on efficacy data in adolescents.

The Applicant has provided the following table for the current extension application for a display of age distribution in study 1368-0027.

Table 32. Age distribution of spesolimab-treated patients in spesolimab clinical trials in patients with GPP

	Age 65-74 (Older subjects number /total randomised in trial)	Age 75-84 (Older subjects number /total randomised in trial)	Age 85+ (Older subjects number /total randomised in trial)
Controlled trials			
1368-0013 (randomised, placebo-controlled trial)	2 / 53	0 / 53	0 / 53
1368-0027 (randomised, placebo-controlled trial)	6 / 123	1 / 123	0 / 123
Uncontrolled trials			
1368-0011 (open label, single arm trial)	0 / 7	0 / 7	0 / 7
1368-0025[1] (open label extension trial)	6 / 128	0 / 128	0 / 128

1 Patients rolled over from trial 1368-0013 and 1368-0027

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

Pooled GPP trials

Efficacy for patients from pooled and combined GPP trials were analysed by the Applicant, including data from the open-label extension (OLE) study 1368-0025 (see below; *Supportive studies*). In total, 159 patients were treated with spesolimab s.c.; 108 of these patients had been treated for at least 1 year, with 43 of them for at least 2 years, 9 of them for at least 3 years, and the maximum exposure was 3.5 years. With a median exposure to spesolimab s.c. of about 14 months, the treatment effect in the prevention of GPP flares appeared to be sustained and consistent with the randomised period of 48 weeks in 1368-0027. At 2 years of treatment with spesolimab s.c., the probability of a flare was 0.272 (95% CI 0.202, 0.360), lower than with placebo in 1368-0027 at 48 weeks (0.516, 95% CI 0.356, 0.698). The rate of flares was 0.28 per patient per year, lower than the mean of 2.6 (SD 2.23) flares per year reported in the history of these patients.

2.6.5.6. Supportive studies

Human factor study: Spesolimab (Bl 655130): PFS-NSD-1: multi: 150 mg: Human Factors Engineering/Usability Engineering (HFE/UE) Report

The Applicant has submitted a complete HFE/UE analysis of the spesolimab 1 ml Prefilled Syringe with Needle-Safety Device (PFS-NSD-1) according to IEC 62366-1:2015+A1:2020 and FDA guidance "Applying Human Factors and Usability Engineering to Medical Devices".

First, the device's intended users (patients, lay caregivers, and HCPs), uses, and use environments (home use and clinical setting) were defined. Then, known use problems of similar products were assessed to ensure that the design of the PFS-NSD-1 implemented solutions to the problems. Formative usability evaluations were conducted to evaluate the user interface and identify potential interaction difficulties. A summative usability study was performed to validate that the PFS-NSD-1 combination product could be used safely and effectively and was not vulnerable to potentially harmful use errors that could lead to severe injury or death.

During human factors validation, participants who were representative of the intended users of the PFS-NSD-1 attended individual simulated-use testing sessions. The purpose of the HF Validation Study was to demonstrate that the PFS-NSD-1 can be used safely and effectively by the intended users, for the intended uses, in the intended use environments. Critical tasks and success criteria were defined.

The results showed that most assessments were performed without any observed or reported use events. For other tasks, at least one use event was observed or reported during the study and were listed in the report (use errors, close calls and use difficulties), however, for these events the conclusion of the Applicant's evaluation was "No action required.

Study 1368-0025, open-label extension (OLE), interim results

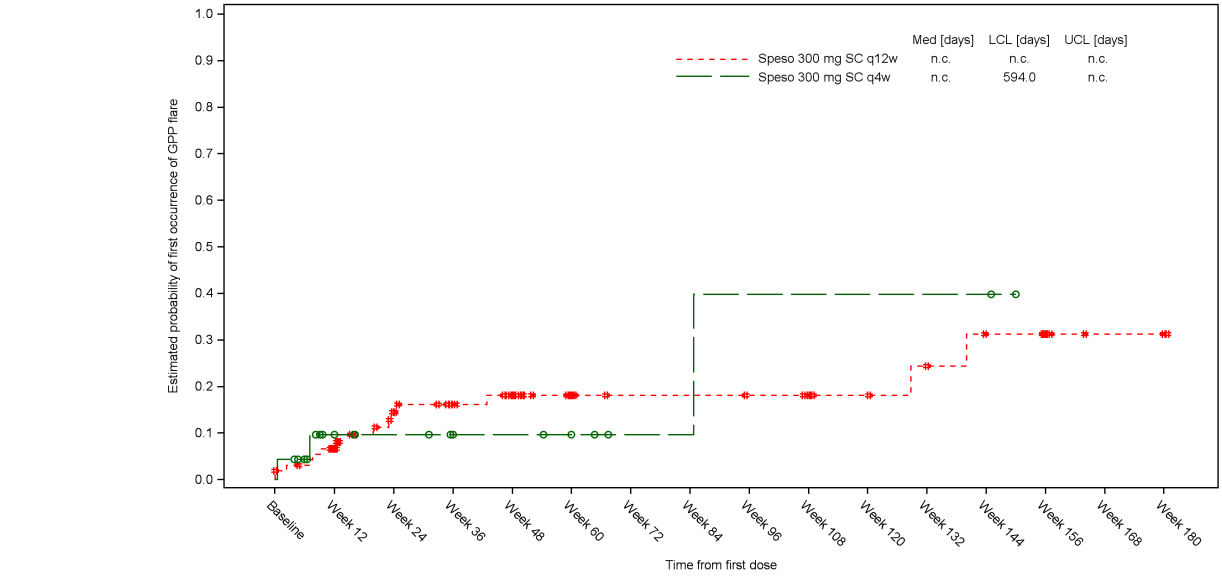
Study 1368-0025 is an ongoing open-label extension (OLE) study with patients coming both from the GPP flare treatment study 1368-0013 and the prevention study 1368-0027.

All patients in 1368-0025 (128 patients) at the analysis cut-off date were from the parent trial 1368-0013 (39 patients) or 1368-0027 (89 patients). Only patients without flare symptoms of moderate or severe intensity were to start with OL spesolimab s.c. maintenance treatment in the extension trial 1368-0025. Patients who had not received any OL spesolimab i.v. treatment in the previous trial were to start with 300 mg q12w, and those who had were to start with 300 mg q4w (q6w before CTP amendment 2). Dose escalation and de-escalation between q4w/q6w and q12w was allowed if pre-

defined criteria based on GPPGA scores were fulfilled. Patients could be treated with spesolimab s.c. for up to 252 weeks in 1368-0025.

At the time of the interim analysis, the median (Q1, Q3) exposure to OL spesolimab s.c. in trial 1368-0025 was 250 (66, 584) days, and in the 1st s.c. maintenance treatment period 163 (43, 422) days. Most patients (N = 105, 82.0% of total) started with 300 mg q12w (of whom 22 patients, 21.0% subsequently escalated to q4w) and 23 patients (18.0% of total) started with q4w/q6w (of whom 3 patients, 13.0% de-escalated to q12w). A total of 12 patients (9.4%; 11 of 105 patients starting with 300 mg q12w and 1 of 23 patients starting with 300 mg q4w/q6w) used spesolimab i.v. for GPP flare treatment.

Preliminary results from the OLE study have been presented in the current submission and are displayed below.



Patients at risk

Speso 300 mg SC q12w	105	74	51	45	39	28	21	21	20	19	14	12	9	6	2	2
Speso 300 mg SC q4w	23	13	10	8	7	6	3	3	2	2	2	2	2	0	0	0

Estimand EM: in addition to GPP flare defined by GPPGA, any use of flare treatment with i.v. Spesolimab, or escape medication will be considered to represent a GPP flare onset.
Estimated rates are based on Kaplan-Meier approach.
Entire treatment period: from start of treatment to the earliest day of treatment REP or cut-off for interim analysis if applicable.
Initial treatment is used for the label.
Speso 300 mg SC q4w refers to the intensified maintenance treatment per CTP version 3.0.
n.c. = not calculable.

Figure 15.2.2.1: 1 Time to first occurrence of GPP flare in entire treatment period - SAF (EM)

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Figure 28. Time to first occurrence of GPP flare in entire treatment period – SAF (EM), Study 1368-0025

Table 33. Summary of patients with GPP flare in entire treatment period – SAF, Study 1368-0025

	Speso 300 mg SC q12w N	%	Speso 300 mg SC q4w N	%	Overall Speso N	%
Number of patients	105		23		128	
Number of patients with first GPP flare	15		3		18	
GPP flare defined by GPPGA*	12	80.0%	3	100.0%	15	83.3%
With i.v. flare treatment	10	66.7%	1	33.3%	11	61.1%
Without i.v. flare treatment	2	13.3%	2	66.7%	4	22.2%
i.v. flare treatment**	1	6.7%	0		1	5.6%
Escape medication***	2	13.3%	0		2	11.1%
Number of patients with second GPP flare	7		1		8	
GPP flare defined by GPPGA*	5	71.4%	0		5	62.5%
With i.v. flare treatment	3	42.9%	0		3	37.5%
Without i.v. flare treatment	2	28.6%	0		2	25.0%
i.v. flare treatment**	0		0		0	
Escape medication***	2	28.6%	1	100.0%	3	37.5%
Number of GPP flares	29		7		36	
GPP flare defined by GPPGA*	23	79.3%	5	71.4%	28	77.8%
With i.v. flare treatment	18	62.1%	2	28.6%	20	55.6%
Without i.v. flare treatment	5	17.2%	3	42.9%	8	22.2%
i.v. flare treatment**	1	3.4%	0		1	2.8%
Escape medication***	5	17.2%	2	28.6%	7	19.4%

Entire treatment period: from start of treatment to the earliest day of treatment REP or cut-off for interim analysis if applicable.
Initial treatment is used for the label.
Speso 300 mg SC q4w refers to the intensified maintenance treatment per CTP version 3.0.
* GPP flare defined by GPPGA per CTP.
** i.v. flare treatment use without meeting GPP flare by GPPGA.
*** Escape medication use without meeting GPP flare by GPPGA.

Source data: Appendix 16.2.6, Listing 3 ctr\t-summry-flare.sas 17FEB2023

2.6.6. Discussion on clinical efficacy

Spevigo (spesolimab) was approved for the treatment of GPP flares in adults in 2022 and the current application concerns the addition of:

- A new indication; for the **prevention** of generalised pustular psoriasis (GPP) flares in adults and adolescents from 12 years of age;
- A new **formulation** and **presentation**; 150 mg solution for injection in pre-filled syringe; and
- An extension of indication to include use in **adolescents** from 12 years of age for the flare treatment indication.

The following two studies are of relevance for the current submission:

- Trial **1368-0027** (Effisayil 2): this pivotal trial investigated efficacy and safety of spesolimab s.c. for flare prevention in patients with a history of GPP. This trial forms the basis for the current MAA and is assessed below.
- Trial **1368-0025** (Effisayil-ON): The objective of this ongoing open-label extension (OLE) trial is to evaluate long-term safety and efficacy of spesolimab s.c. (with the option of spesolimab i.v. for recurring flare treatment) in eligible patients who completed trials 1368-0013 and 1368-0027. Interim data are included in the current MAA.

Design and conduct of clinical studies

Study 1368-0027 (Effisayil 2) was a global, multi-center, double-blind, randomised, placebo-controlled Phase IIb dose-finding trial that evaluated efficacy and safety of 3 s.c. dosing regimens of spesolimab compared with placebo in preventing GPP flares in patients with a history of GPP.

Study population

The inclusion and exclusion criteria are deemed overall relevant for a flare prevention study, however, with some comments related to the protocol-required withdrawal of other GPP treatments. Subjects were to have a diagnosis and documented history of GPP and have at least 2 presentations of moderate to severe GPP flares with fresh pustulation (new appearance or worsening) in the past. At screening and randomisation, patients should however not have an active flare and should have a GPPGA score of 0 or 1.

Patients aged from 12 to 75 years at screening could be included and for all patients, a minimum weight of 40 kg was required. Inclusion of adolescents from 12 years of age in the GPP flare prevention study is in agreement with the PIP for spesolimab in GPP. The upper age limit of 75 years was not explained nor justified; however, the same upper age limit was used in study 1368-0013, the flare treatment study.

Patients were included regardless of their IL36RN mutation status since efficacy has been seen in patients with GPP both with and without the IL36RN mutation. This is in line with the approach used in the flare treatment trial, 1368-0013. For a trial that is intended as the sole confirmatory trial for the prevention indication, it would however have been expected that information on the mutation status should be obtained for *all* subjects. In the Spevigo SmPC, there is no requirement for testing the IL36RN mutation status for initiation of treatment, hence, no issue is raised.

The exclusion criteria are considered adequate to exclude patients at risk, due to infections, pregnancy or other medical conditions, and are overall similar to those applied in the flare treatment study 0013.

Treatments

Eligible patients with GPP were randomised in a 1:1:1:1 ratio to placebo, low (300 mg loading dose, thereafter 150 mg q12w), medium (600 mg loading dose, thereafter 300 mg q12w), or high (600 mg loading dose, thereafter 300 mg q4w) treatment arms. Randomisation was stratified by use of systemic GPP medications at randomisation (yes vs. no), region (Japan vs. non-Japan), and age (adult vs. adolescents).

Study 1368-0027 was defined as a dose finding study and hence included three different dose arms of spesolimab; all with an initial loading dose on Day 1 (600 mg or 300 mg), followed by maintenance dosing either every 4 weeks or every 12 weeks. The posology that is recommended in the SmPC corresponds to the *High dose* arm, i.e. 600 mg s.c. loading dose on Day 1, followed by 300 mg s.c. q4w maintenance treatment. The choice of dose regimen is further discussed below.

The study included a placebo control arm, which is endorsed. In the prevention situation, with availability of i.v. spesolimab and/or other treatments (if needed) upon an acute GPP flare, use of placebo is more straightforward than the situation with acute flare treatment (for which placebo still was included in the pivotal study 0013, albeit with rescue options after one week).

Patients who experienced a GPP flare in this trial were eligible to receive treatment with an open-label dose of i.v. spesolimab 900 mg. Another dose of spesolimab 900 mg i.v. treatment after 1 week could be administered if symptoms persisted according to prespecified criteria. If the patient responded to the spesolimab flare treatment, the patient could continue to receive open label spesolimab s.c. for maintenance. This approach is endorsed.

Allowed and restricted medications in the study have been adequately described, including medications allowed in case of occurrence of an acute GPP flare (e.g. in case of insufficient response to i.v. spesolimab). During the randomised treatment, *all other GPP treatments* had to be withdrawn, with different washout periods specified in the protocol. This included both topical treatments like corticosteroids, as well as biologics and other systemic immunosuppressants. For the commonly used

GPP treatments Methotrexate, Cyclosporine and Retinoids, these had to be stopped on the day of randomisation. This is understood since the Applicant is not aiming for an add-on indication for prevention of GPP flares. However, it can also be viewed as a means to *precipitate* GPP flares, since withdrawal of the usual maintenance treatments can trigger a new flare. The chosen approach was seen as problematic in several aspects. Removal of all background treatments can be adequate in a Phase 2, proof-of-concept (PoC) study. However, study 1368-0027 constitutes both a PoC/dose finding study and the only pivotal efficacy and safety study for the prevention indication, and this approach may not reflect a clinically relevant scenario. Due to the lack of efficacy and safety data on co-treatment with spesolimab and other commonly used GPP treatments, the Applicant was asked to discuss whether it would be relevant to reflect this in the indication wording, similar to the flare treatment indication, by adding the word "monotherapy".

In response to this, the Applicant argued that despite 75% of subjects were using systemic medications for GPP at randomisation, they had a median of 2 flares a year in history. The baseline GPPGA total score was 1 for a majority (86%) of patients. Thus, the GPP treatments provided were insufficient for flare prevention or control of residual symptoms. The Applicant also explained that the study was aimed to be performed in a 'high risk' population in terms of presenting with the clinical event/endpoint in the study, in order to have a feasible sample size and observation time for a study in a rare condition. An expectation of a high flare rate early in the study was even taken into account in the sample size calculation. Hence, the Applicant is aware of treatment withdrawal being a very common reason for experiencing a GPP flare and has used this knowledge in planning the study design. Although leading to a somewhat artificial situation, this is acknowledged and does not *per se* invalidate the adequacy of the study design, or the study results. Since the efficacy results at hand for GPP flare prevention by spesolimab are produced using this study design, the issue is not further pursued.

Objectives and outcomes

The primary objective of the trial was to demonstrate a non-flat dose response curve and evaluate the dose-response relationship for 3 subcutaneous dosing regimens of spesolimab versus placebo, on the primary endpoint, the time to the first GPP flare onset up to Week 48. The secondary objective was to demonstrate superiority versus placebo for each of spesolimab high dose and medium dose on the primary endpoint, as well as the key secondary endpoint; the occurrence of at least one GPP flare up to Week 48.

Being the only clinical study to support the GPP prevention indication, dose finding and demonstration of efficacy have been included in the same study. The study does not have an adaptive design with an initial dose finding part. There seemed to be no (formal) criteria for the decision on which dose regimen to take forward.

The endpoints/outcomes used in this study were similar to those used in study 1368-0013, the GPP flare treatment study that supported the approval of Spevigo. In the initial Spevigo dossier, descriptions and validation data for the GPPGA-based endpoints was included and found acceptable during the MAA evaluation.

The primary endpoint was the time to first GPP flare up to Week 48, with a GPP flare defined as an increase in GPPGA score by ≥2 from baseline and the GPPGA pustulation subscore ≥2. This is deemed as an adequate definition of an acute GPP flare, though it differs somewhat from the definition of a flare in study 1368-0013. In that study, the bar was set higher for defining a GPP flare. The definition used in the current prevention study 1368-0027 was however accepted in the CHMP advice (EMA/CHMP/SAWP/181383/2019), stating that "Given that patients with GPP having low disease activity (GPPGA of 0 or 1) are included, an increase of both GPPGA and pustular sub scale of GPPGA

with at least 2 levels is deemed a relevant representation of a GPP flare." The chosen primary endpoint is therefore relevant and accepted.

Secondary endpoints included time to first worsening of PSS (Psoriasis Symptom Scale) and time to first worsening of DLQI (Dermatology Quality of Life Index); two patient-reported outcomes.

In addition to the primary and secondary endpoints described above, a large number of further endpoints were evaluated, based on e.g. sustained remission, Pain VAS score, GPPASI, EQ-5D-5L, SF-36, WPAI, etc. These were not included in the hierarchical testing strategy and will therefore not be described in this report.

Sample size

The assumptions made regarding the sample size have been described in detail. 120 patients were planned to be recruited so that a power of at least 90% for at least one successful dose of Spesolimab (High or Medium doses) versus placebo on the primary and key secondary endpoints could be achieved under the base scenario. No changes to planned sample size occurred. In summary, the power calculation is considered acceptable.

Randomisation, Blinding

Patients were randomised according to a randomisation plan in a 1:1:1:1 ratio to blinded treatment arms. Stratification of randomisation was performed for concomitant use of systemic GPP medication 4 weeks prior to or at randomisation (yes or no). This stratification factor was used in the analyses.

Stratification factors Region (Japan vs Rest of the world) and Population (Adult vs Adolescents) were implemented for operation purposes only and were not included in the analyses of the efficacy endpoints. Changes regarding randomisation were made in the Global Amendment 1 to ensure at least 2 adolescent patients were included in each randomised treatment arm.

The study procedures to maintain the blind seem overall to be adequate.

Statistical methods

The primary endpoint consisted of a dose finding step and a formal statistical analysis step. For the formal statistical analysis step, hierarchical testing was done at a one-sided alpha level of 0.025. The testing strategy followed a closed testing principle defining five families of endpoints/comparisons. Two hypotheses were tested at the same time in each family. The primary analysis time to first GPP flare up to week 48 weeks was tested for both high spesolimab dose vs placebo and medium spesolimab dose vs placebo, using the same stratified Cox regression model as in the dose finding step. Hazard ratios with 95% CI were presented. P-values from stratified log-rank test [stratified by the systemic concomitant use of GPP medications at randomisation (yes or no)] were also presented. Analyses were based on the randomised set. The testing plan was as follows:

- Scenario 1: If both primary endpoint p-values were ≤0.01875 (one-sided), then both comparisons involving the two Spesolimab dose regimens were declared to be statistically significant and alpha 0.025 would be passed on to the next family.
- Scenario 2: If the maximum of the p-values for the two dose comparisons was >0.01875 (1-sided), then the remaining p-value was to be tested once again at 0.0125 (one-sided level) and declared to be statistically significant if the p-value was ≤0.0125 (1-sided) and alpha 0.00625 would be passed on to the next family.

The actual results followed the second scenario. P-values (High dose p-value = 0.0005 and Medium dose p-value=0.0269) from the log-rank test were presented. Since p-values for the two doses was not ≤0.01875 (1-sided) the two hypotheses were tested once again at 0.0125 (1-sided) significant

level. Based on the description of the second scenario, it is not clear whether only one (the higher) of the p-values for the two comparisons had to be >0.01875 to be able to test the two hypotheses a second time at 0.0125 significant level. In actuality, both hypotheses were tested once again after it was concluded that the higher of the p-values was not >0.01875. The high dose was concluded to be statistically significant and alpha 0.00625 was passed on to the next family. The hierarchical procedure done during this formal statistical analysis step is acceptable.

Kaplan-Meier (KM) estimates of the survival/failure probabilities at 4-week intervals, as well as the median time-to-event, were also presented. Confidence intervals, based on two-sided alpha 0.05 and KM graph were also presented.

Three strategies were applied to intercurrent events: composite strategy, hypothetical strategy and treatment policy. The composite primary estimand was comprised of:

- increase in GPPGA score by ≥ 2 from baseline and pustular component of GPPGA ≥ 2;
- any use of rescue medication with OL i.v. spesolimab, or investigator-prescribed Standard of Care (SoC) to treat GPP worsening.

Hypothetical strategy was applied for use of restricted medication other than as defined in the primary estimands i.e data after use of restricted medication was censored according to the censoring rules described for the primary endpoint. All other intercurrent events except for the rescue medication use of i.v. spesolimab was to be handled using the treatment policy approach. This is acceptable.

Missing data was handled using multiple imputation method for the primary analysis of the key secondary endpoint and the secondary binary endpoint. Missing GPPGA or GPPGA pustulation subscores were not imputed and only observed values were utilised. The imputation of the binary endpoint was only done at a binary level, i.e. success or failure. This is acceptable.

The subgroup analyses were not adjusted for multiple testing, and the effects observed in smaller subgroups were more prone to random variation. This is acceptable.

Results from sensitivity analyses, using alternative censoring method or patient analysis set under the primary estimand, and additional analyses under different estimands were consistent with the primary analysis. The primary analysis of spesolimab high dose vs placebo for the time to the first GPP flare up to Week 48 was generally consistent across the subgroups, therefore the result can be considered robust.

Analysis populations were defined in accordance with ICH E9 guideline. 1 patient was randomised to receive placebo group but instead received Specolimab treatment on Day 1. Data for this patient was assigned to the spesolimab low dose group in the exposure and safety analysis, as well as in the immunogenicity vs efficacy analysis. Since the randomised set was the base for the efficacy analysis, the patient was analysed as randomised in the efficacy analyses. This is acceptable.

An interim analysis of the open-label spesolimab i.v. flare treatment and subsequent maintenance treatment periods was conducted to support the initial spesolimab in GPP flare treatment submission; no unblinding of the randomised s.c. treatment was required.

Changes were made after DBL, the censoring rule of time-to-event endpoints in the analysis of comparison of the effect of loading dose during the first 4 weeks of randomised maintenance period was changed. The subjects without events were censored at the minimum of time of the planned day of Visit 3 (i.e. Day 29) per analysis time window or the time of actual Visit 3 dosing date.

Efficacy data and additional analyses

Participant flow

Out of 157 screened patients, 123 patients were randomised in a 1:1:1:1 ratio to spesolimab low dose, medium dose, high dose and placebo (31 patients per group except 30 in the spesolimab high dose group). All 123 patients were treated and 63.4% (78 patients) completed 48 weeks of randomised treatment period without flare.

A total of 32 patients (26.0%) received OL spesolimab 900 mg i.v. treatment for GPP flares, 15 (48.4%) in the placebo group and 2 (6.7%) in the spesolimab high dose group. Of those who received spesolimab i.v. for the treatment of a flare, 69% (22 patients) received a single 900 mg i.v. dose and 31% (10 patients) received 2 doses of spesolimab 900 mg i.v. (double dose). Thus, in agreement with the approved posology for spesolimab to treat a GPP flare, a single i.v. dose can be sufficient for some subjects while others need an additional dose one week later. About one third of rescued subjects needed two i.v. spesolimab doses.

Out of 20 patients who continued with OL maintenance treatment with spesolimab s.c. after flare treatment, 9 patients (45.0%) were escalated to the 300 mg s.c. q4w dosing regimen. A q12w regimen was the default maintenance regimen according to the protocol, with a possibility to increase frequency to q4w. In the proposed SmPC, the Applicant recommends initiating or re-initiating SC spesolimab dosing 4 weeks after an i.v. flare treatment. The data at hand, albeit very limited, suggest that a large proportion needed to escalate SC dosing from q12w to q4w.

A total of 13 patients (10.6%) prematurely discontinued randomised treatment for reasons other than flare treatment with spesolimab i.v., most of them in the spesolimab high dose group (7 subjects, 23%). Three patients discontinued from the high dose spesolimab group due to AEs.

Of the randomised patients, 111 (90.2%) completed the trial as planned, of whom 93 (75.6%) continued in the extension trial 1368-0025.

The majority of patients were from Asia, excluding Japan (58.5% of randomised patients), and the countries that contributed most randomised patients were Malaysia and China, and also the Russian Federation. A total of 32 (26%) randomised patients were from Europe and 12%were from EU countries (19/157).

Study conduct

Concerning protocol amendments, a total of 3 global amendments to the CTP were issued and their impact is not likely to have been substantial. Risk mitigation strategies employed to deal with the COVID-19 pandemic were described and seem adequate. A possibility to permit home administration of treatment drug, if necessary, was introduced. The compliance with study drug administration was high, with the mean (SD) of the total injected spesolimab doses being 99.6% (2.7%) of the planned total doses and balanced across the spesolimab treatment groups.

Concerning protocol deviations, 13 patients (10.6%) overall were reported with iPDs, with rather similar proportions of patients in all treatment groups (a few more in the high and medium spesolimab dose group compared with the low dose and placebo groups). There were 4 patients (3.3%) for which there were iPDs leading to exclusion from the PPS.

Baseline data

The treatment groups were overall fairly balanced with respect to demographic, disease and other factors, but with some exceptions. The small size of the groups (about 30 per group) however hampers the possibility for the randomisation procedure to completely make the groups even.

There were overall more female (62%) than male (38%) patients included across the treatment arms. All patients were Asian (64%) or White (36%). There was a higher proportion of Asian patients in the High dose Spesolimab group (70% vs. 55% in the placebo group). The mean bodyweight and BMI

were also lower in the High dose Spesolimab group vs. the placebo group (68.7 kg vs. 75.7 kg and 25.6 kg/m^2 vs. 26.9 kg/m^2, respectively), which may have due a general lower body weight in an Asian population. It was unclear whether these imbalances may have affected the outcome of the trial, see further discussions below.

The mean (SD) age was 40.4 (15.8) years. Eight patients (6.5%; 2 per group) were adolescents, ranging from 14 to 17 years at screening. A total of 8 subjects (6.5%) were aged ≥ 65 years.

Slightly below 30% of patients (overall 27.6%) had concurrent plaque psoriasis. Present or past occurrence of psoriasis was reported for 80 patients (65.0%) and arthritis for 10 patients (8.1%).

There was a difference between the placebo group and the spesolimab High dose group in the diagnosis criteria to confirm a GPP diagnosis; in the placebo group, 48% had a skin biopsy and histopathological confirmation and 48% had their diagnosis via clinical examination, whereas in the spesolimab High dose group, 30% had a skin biopsy and histopathological confirmation and 70% had their diagnosis via clinical examination.

With respect to GPP disease criteria, the groups were also fairly well balanced. All patients had a GPPGA total score of 0 (clear; 13.8%) or 1 (almost clear; 86.2%) at baseline, as required by the inclusion criteria. All patients had a GPPGA pustulation subscore of 0 (71.5%) or 1 (28.5%). Thus, a majority of patients had some degree of manifestation of their GPP at inclusion, even if mild. Somewhat less than one third had a GPPGA pustulation subscore of 1, meaning presence of GPP pustules, albeit mild.

The presence of a potential pathogenic IL-36RN variation was reported for 22.8% of patients overall and was lower in the placebo group (12.9%) than in the spesolimab groups (low 22.6%, medium 32.3%, high 23.3%). Otherwise, genetic mutations were generally comparable between the treatment groups. In a study that is pivotal for a new indication, it would have been expected that IL-36RN mutation status had been obtained in the majority of enrolled patients.

Concerning the medical history for GPP, most patients had received their first GPP diagnosis longer than 5 years prior to randomisation. Clinical examination was the most common method for the diagnosis, followed by skin biopsy and histopathological confirmation. The median (Q1, Q3) number of flares per year was 2.0 (1.0, 3.0), with a maximum of 12. These data were generally comparable between the treatment groups.

Overall, 93.5% of patients had at least 1 historical medication for GPP (i.e. medications for GPP that had been stopped prior to screening). A total of almost 75% of subjects used a systemic medication for GPP at randomisation. The most common were acitretin, ciclosporin, and methotrexate. These medications were used within 4 weeks prior to or at randomisation and were discontinued before the start of the randomised study treatment. There was an imbalance in the use of different treatments between the groups, e.g. in the placebo group, equal proportions used acitretin, ciclosporin, and methotrexate, respectively (n=7 for each treatment; 23%), while in the High dose spesolimab group, 47% (n=14) used acitretin, 23% (n=7) used ciclosporin and 3% (1 subject) used methotrexate. The study design requiring a withdrawal of all GPP treatments at randomisation is criticised above. The imbalance of systemic GPP treatments at baseline causes some further concern. More subjects in the High dose spesolimab arm were on acitretin treatment and this retinoid has a long half-life of close to 50 hours (Larsen et al., J Clin Pharmacol. 1991 May;31(5):477-83), while ciclosporin and methotrexate have shorter mean half-lives (7-11 hours and 6-7 hours, respectively). Hence, a concern was raised that almost half of the patients in the High dose spesolimab arm might have had a better protection from GPP flares due to the slowly eliminated acitretin, while a smaller proportion of patients in the placebo arm (23%) had this coverage and more patients were treated with MTX and CsA at baseline,

having shorter half-lives. The Applicant discussed this issue in relation to the study results, see below (*Subgroup analyses*).

Overall, even if the groups were fairly well balanced for several factors, there were also some exceptions. The observed imbalances between the placebo arm and the High dose spesolimab arm in the proportion of Asian vs. White subjects and in body weight and BMI, as well as the imbalance in systemic treatments at baseline and how the GPP diagnosed was confirmed, raised concerns that needed to be addressed. See below.

Outcomes

For the primary endpoint, the spesolimab high dose was statistically significant in reducing the risk of GPP flares compared with placebo in the primary analysis, with an **HR of 0.157** (**95% CI 0.046, 0.541; p = 0.0005**). The medium dose did not reach statistical significance and the key secondary endpoint was only further tested for the high dose.

For the key secondary efficacy endpoint, the spesolimab high dose was statistically significant in reducing the occurrence of GPP flares compared with placebo in the primary analysis (required significance level from multiple testing strategy 0.00625), with an adjusted risk difference of -**0.390** (**95% CI -0.621, -0.159; p = 0.0013**).

Many flares occurred within the first 4 weeks after randomisation. While this is not unexpected, due to the protocol-required withdrawal of existing GPP medications at randomisation that can trigger new GPP flares, it also emphasises the 'artificial' situation with the chosen study design. In the placebo arm, the Kaplan-Meier curve shows a very high rate of GPP flares during the initial 4 weeks after randomisation. The washout of all ongoing systemic GPP treatment, as well as all topical GPP treatments, may have triggered flares at a speed that would likely not have been expected in a normal, clinical situation. As discussed above, the Applicant was aware of this fact and explained that the study was aimed to be performed in a 'high risk' population in terms of presenting with the clinical event/endpoint in the study, in order to have a feasible sample size and observation time for a study in a rare condition. An expectation of a high flare rate early in the study was even taken into account in the sample size calculation. The requirement to withdraw all other GPP treatments however raised the issue of whether spesolimab GPP flare prevention needs to be specified as "monotherapy", similar to the approved GPP flare treatment indication. The wording of the indication is further discussed below.

For other secondary endpoints, i.e. time to the first worsening of PSS up to Week 48 and time to the first worsening of DLQI up to Week 48, formal statistical significance could not be claimed. For time to first worsening of PSS up to Week 48, the required significance level of 0.00625 was not reached for the high dose, hence, confirmatory testing stopped. Nominal p-values were initially presented for these outcomes. Following review of arguments provided by the Applicant, brief results for the PSS and DLQI endpoints was accepted for inclusion in section 5.1 of the SmPC. It was agreed that PSS and DLQI, being patient-reported outcomes, represent outcomes not covered by the primary endpoint. These outcomes can be of interest to prescribers. Also, even if not formally significant in accordance with the pre-specified hierarchical testing procedure, the nominal p-values were fairly low.

Choice of dose

The pivotal study to support the GPP prevention indication was also a dose finding study. As stated above, the primary objective was to demonstrate a non-flat dose response curve, which was achieved. Specific criteria for choosing the dose to recommend in the SmPC have not been found. The Applicant recommends the highest dose regimen for spesolimab in the SmPC, i.e. a 600 mg s.c. loading dose on Day 1, followed by 300 mg s.c. q4w maintenance treatment. The Applicant presented a comparison of the different loading doses used (300 mg vs. 600 mg) on the effect up to Week 4, and most results were numerically similar in the spesolimab loading dose 300 mg group and 600 mg group. Both

loading doses showed similar trends and separated from the placebo group by Week 2. On the basis of efficacy data overall, however, the chosen dose regimen is supported.

Subgroup analyses

For subgroup analyses, the primary analysis of the primary endpoint of spesolimab high dose vs. placebo, as well as for the key secondary endpoint, was generally consistent across various subgroups. These analyses were not adjusted for multiple testing, which is in general not expected or required for these types of analyses. The overall small treatment groups make firm conclusions difficult, and the 95% CIs are very wide for several comparisons. No major cause for concern is apparent for most subgroups. However, for the comparison of patients using systemic GPP medications or not at randomisation, there a difference in HR is noted. For those having a systemic GPP medications at randomisation, the HR (95% CI) is 0.053 (0.007; 0.409), whereas in those not on a systemic GPP medications at randomisation, there is essentially no difference between placebo and high dose spesolimab; HR 0.913 (95% CI 0.152; 5.464). It is however acknowledged that the groups for comparison become very small and firm conclusions are difficult to make, though this may point to the issue of the study design as discussed above, with the required withdrawal of GPP medications.

As mentioned above, some differences between the placebo group and the spesolimab high dose group in different baseline factors were identified. The Applicant has discussed these different factors and provided further analyses.

As for the difference in proportions of Asian patients as well as patients with low mean bodyweight/low BMI in the High dose Spesolimab group vs. the placebo group, the hazard ratios did not show dramatic differences for different subgroups. Some subgroups were small and, consequently and as expected, the 95% CIs were wide.

Also for the GPP diagnosis method, it is acknowledged that skin biopsy and histopathological confirmation was not a criterion for inclusion in the trial and the ERASPEN clinical criteria were applied (which is endorsed). Nevertheless, it can be of interest to find out whether the method of diagnosis affected the outcome. The hazard ratios for patients diagnosed with skin biopsy and histopathological confirmation were similar to those diagnosed with clinical examination for spesolimab high dose vs. placebo (skin biopsy: HR 0.107; 95% CI 0.005, 2.356; clinical examination: 0.185; 95% CI 0.048, 0.708). It is somewhat strange that in the placebo group, patients diagnosed via skin biopsy appeared to have a lower probability of flare than those diagnosed with clinical examination, but this is likely a chance finding.

For the third issue raised, related to observed imbalance of different types of systemic GPP treatments at baseline, the fact that more subjects in the high dose spesolimab arm were on acitretin treatment (47%) vs. in the placebo group (23%), seems not likely to have affected the results. The Applicant refers to data for the placebo arm and subgroups who were on different background treatments. Those in the acitretin group (with potentially longer remaining 'protection' from GPP flares due to the long T½ of acitretin) actually experienced flares earlier than those on CsA or MTX. Still, with only 7 subjects per background treatment (in the placebo group), it is difficult to draw firm conclusions. Nevertheless, it seems difficult to get further based on available data and the issue is not further pursued.

Overall, the Applicant discussed the different points raised and provided additional analyses, which do not raise concerns. Efficacy results by IL-36 mutation status has been included in section 5.1 of the SmPC for the s.c. formulation similar to the information provided in the SmPC for the i.v. formulation.

Adolescents

With respect to efficacy in adolescents, only eight patients in total (2 per group) were included, across an age range from 14 to 17 years at screening. Only 1 adolescent patient in the placebo group had a

GPP flare and received investigator-prescribed SoC to treat GPP worsening, but without meeting the GPP flare criteria. In the spesolimab groups, no adolescent patient had GPP flare, PSS worsening, or DLQI worsening; all 6 of them achieved sustained remission. The Applicant has presented the HRs in adults vs. adolescents, however, due to the very small numbers, the 95% CIs become very wide. Thus, based on the actual results in adolescents, no concern about efficacy is raised, however, the data are very sparse and firm conclusions were difficult to make. On a mechanistic basis, a similar effect in adults and adolescents may be plausible, however, this warranted further discussion and justification.

Within the current submission, not only a prevention indication is sought in adolescents but the age limit for the flare treatment indication (with i.v. spesolimab) has also been changed from 18 to 12 years. There is no data available on the efficacy (or safety) of i.v. flare treatment with spesolimab in adolescents. The Applicant's view is that the benefit-risk balance of spesolimab i.v. treatment for acute GPP flares in adolescent patients with GPP is considered favourable.

The Applicant pointed out that the spesolimab studies in paediatric GPP patients were conducted according to the design, sample size and analyses defined in the paediatric investigation plan (PIP) agreed with the PDCO, which is acknowledged. The Applicant also presented additional information from a literature review, to support that the GPP disease and pathophysiology are similar in adult and paediatric populations.

Literature data does not highlight paediatric-onset GPP as a distinct disease with any specific distinguishing pathophysiological or genetic features compared to adult-onset GPP and the IL-36 pathway is regarded central to GPP pathogenesis in both adult and paediatric patients. In study 1368-0027, 40 patients (32.5%, including the 8 adolescent patients) had been diagnosed with GPP before 18 years of age. The frequency of flares and treatment effect within that subgroup were found to be similar to those diagnosed with GPP as adults, with very similar hazard ratios. This may to some extent support similarity of the disease, although it may not be excluded that the features of a condition may change over time, e.g. when moving from adolescence to adulthood. It is nevertheless acknowledged that available GPP treatments and also GPP treatment guidelines (e.g. in Japan; no specific European treatment guidelines seem to be available for GPP) appear similar for adolescents and adults. The actual results from the 8 adolescents included in the flare prevention study do not give cause for concern as to the effect of spesolimab in adolescents (no GPP flare occurred in any of the spesolimab-treated adolescents) but are naturally too limited to make firm conclusions.

As for the i.v. GPP flare treatment, no data are available in any adolescent patient. The Applicant summarised response by different age cohorts based on pooled data from studies 1368-0013, 1368-0027 and the OLE study 1368-0025. A total of 23 patients were aged 22 or below, and 5 out of 6 patients treated with spesolimab i.v. (83.3%) achieved a response (GPPGA pustulation subscore of 0) by Day 8, which was similar to the overall patients (67.0%). No relationship between age and efficacy of spesolimab in treatment of GPP flares was observed across different age cohorts. While this is a rather crude evaluation, at least it suggests that the effects of spesolimab are not worse in younger vs. older patients, with the caveat that no data exist in adolescents.

With respect to similarity in exposure between adolescents and adults, this is discussed in the Clinical pharmacology section.

Hence, from an efficacy point of view, although no (for i.v. flare treatment) or very limited (for s.c. flare prevention) data exist for spesolimab in adolescents, there is no information to suggest that adolescents and adults would have fundamentally different pathophysiology and treatment effects. Further data will not be requested.

Flare treatment response after receiving i.v. spesolimab as rescue treatment

A total of 32 patients received a spesolimab OL 900 mg i.v. dose (called Day 1) as a rescue treatment for GPP flare and of these, 10 received an additional spesolimab 900 mg i.v. dose (planned on Day 8). For these 32 patients, the probability of a response at Week 1 (Day 8) after the first dose was 0.554 (95% CI 0.388, 0.734; based on EN-ID8-SOC). Results for GPPGA (total score and subscore for pustulation) were presented over time and the proportions of subjects who achieved a GPPGA total score of 0 or 1 or a GPPGA pustulation score of 0 increased mainly over the first 4 weeks after the flare treatment and were around 40%. Based on these data, it seems like a GPP flare can be treated with i.v. spesolimab, one or two doses, in accordance with the already approved SmPC for i.v. spesolimab. Many subjects who experienced a flare and received i.v. spesolimab were in the placebo group (15 out of 32). Thus, these are subjects who are naïve to spesolimab. Seventeen subjects across the three spesolimab arms received i.v. spesolimab as rescue (7 in the low dose, 8 in the medium dose and 2 in the high dose spesolimab groups, respectively).

The Applicant also clarified to what extent patients rescued with i.v. spesolimab for a GPP flare needed additional treatment beyond one or two doses of i.v. spesolimab. More than half of the patients (53.1%) used treatments like topical corticosteroids, methotrexate, cyclosporine, retinoids, and biologics 16 weeks after the last i.v. spesolimab dose. Of these, the majority (12 subjects; 37.5%) used topical corticosteroids, and 4 subjects each (12.5%) used methotrexate, cyclosporine and retinoids. More patients who needed 2 i.v. spesolimab doses (70%) vs. those who needed only one spesolimab i.v. dose (45.5%) also needed additional flare treatments, likely reflecting harder to treat flares. A total of 34% needed additional treatments within the first 4 weeks after the i.v. spesolimab treatment.

Thus, it can be concluded that although spesolimab may effectively treat GPP flares, substantial proportions of patients will still need additional GPP treatments, e.g. topical corticosteroids, but also systemic treatments. This is an observation of interest also in relation to the discussions regarding use of spesolimab as monotherapy or not (see below).

Therapeutic indication

As discussed above, based on the chosen study design requiring withdrawal of all ongoing GPP treatments at randomisation, the issue was raised on the needs to include the word "monotherapy" in the indication wording for GPP prevention, similar to the wording approved for the Spevigo GPP flare treatment indication.

During long-term treatment with spesolimab, the Applicant stated that some patients may need to continue or initiate immunomodulating treatments for other comorbidities. Thus, the Applicant is not in favour of including the word "monotherapy" in the indication wording and is also not supportive of including a warning against concomitant use with immunosuppressants in SmPC section 4.4. The Applicant argued that this fact is already reflected in the SmPC section 5.1, by stating that "At the time of randomisation, 74.8% of patients were treated with systemic therapy for GPP, which was discontinued at the start of the randomised study treatment."

Arguments were also provided that this would be in line with the study design and indication wording in the SmPCs of other immunomodulating drugs. It is agreed that in many phase 3 studies across various indications in this therapeutic area (e.g. plaque psoriasis, atopic dermatitis), exclusion criteria generally state that other immunomodulatory products must be washed out. This rarely warrants a specific monotherapy indication. However, several monoclonal antibody products actually do have either specific and/or more general warnings against concomitant use with other immunosuppressive treatments in section 4.4. For several products it is pointed out that efficacy and safety data for combination therapy are not available. Hence, while an indication wording specifying "monotherapy" seems not necessary in this case, a statement in section 4.4 seems adequate, also in line with the GPP flare treatment SmPC (for i.v. spesolimab). It is acknowledged that experience from the use of

spesolimab combined with other immunosuppressive treatments are available from studies in other indications. However, it cannot be claimed that vast experience of co-treatment exists (especially not for treatments commonly used in GPP) and spesolimab represents a new, so far not well-known mode of action, which warrants some caution. Therefore, a warning should both express the lack of data on co-administration of spesolimab with other products in GPP, as well as a recommendation to taper previous GPP treatments instead of suddenly withdraw them, to reduce the risk of triggering a GPP flare.

It may seem contradictory that "monotherapy" is included in the indication wording for the i.v. spesolimab GPP flare treatment indication but not for the s.c. GPP flare prevention indication. This difference can, however, be justified by the following:

- When initiating spesolimab as a GPP flare prevention treatment, tapering previous GPP treatments would be a sensible approach rather than abrupt withdrawal, to avoid flares in the period before the preventive effect of spesolimab sets in. This would not be compatible with "monotherapy".
- In case GPP flares do occur, additional treatment beyond one or two doses of i.v. spesolimab may be needed for some time after the flare, as was the case in study 1368-0027. In fact, more than 50% of subjects who were treated with i.v. spesolimab for a GPP flare received other treatments as well.
- Some patients may need to continue or initiate immunomodulating treatments for other comorbidities.
- The spesolimab dose for GPP flare treatment is higher (up to two 900 mg i.v. doses one week apart) compared with the GPP flare prevention dose (600 mg s.c. loading dose followed by 300 mg Q4W). Even if the prevention treatment is long-term and continuous, the i.v. flare treatment is performed using a much higher dose (max 1800 mg in one week) and it therefore makes sense to withhold other (immunosuppressive) treatments.

Hence, even if the intention is not to regularly combine spesolimab with other treatments for GPP in the prevention indication, a strict "monotherapy indication" does not seem feasible in this indication. As stated above, adequate wording related to co-administration in sections 4.2, 4.4 and 4.5 is however proposed.

Immunogenicity

Anti-drug antibodies (ADA) formed with a median onset time of 8.0 to 10.6 weeks in ADA-positive patients, after any spesolimab treatment (s.c. or i.v.). In patients initially randomised to spesolimab, ADAs with a titer value >4000 were detected in 6 of 31 patients (19.4%) in the low dose group, 18 of 31 patients (58.1%) in the medium dose group, and 7 of 29 patients (24.1%) in the high dose group. The corresponding percentages of the treatment-induced NAb-positive patients were 45%, 68%, and 34% for the low, medium, and high dose groups. As mentioned above, it is considered appropriate to include overall incidence of ADA (i.e., not only ADAs above a specific titer) and mention that a majority of ADA-positive subjects also developed NAbs. The immunogenicity data presented in the SmPC was amended accordingly. Nevertheless, no obvious correlation between ADA or NAb development and spesolimab's effect in terms of GPP flare occurrence, flare onset time, or sustained remission was observed in the randomised maintenance period.

Study 1368-0025, open-label extension (OLE) study

Interim results from study 1368-0025, an ongoing open-label extension (OLE) study with patients coming both from the GPP flare treatment study 1368-0013 and the prevention study 1368-0027, have been included in the current submission. In that study, the maintenance spesolimab dose regimen could be Q12W or Q4W (or Q6W in an early version of the protocol) depending on whether the subject

had received any OL spesolimab i.v. treatment in the previous trial. Dose escalation and de-escalation between q4w/q6w and q12w was also allowed based on pre-defined criteria based on GPPGA scores. Thus, the posology in the OLE study is not entirely reflective of that proposed in the Spevigo SmPC, being 300 mg Q4W both after initiation with a SC loading dose or following i.v. treatment after an acute GPP flare. Overall, the main part of the study population received spesolimab Q12W, with only 23 patients starting with Q4W/Q6W and three of these had a GPP flare of which one was treated with i.v. spesolimab. Concerning further GPP flares, there was one subject in the Q4W group who had a second flare, and 7 in the Q12W group. Thus, it is difficult to draw conclusions on responsiveness to further flares during spesolimab maintenance treatment.

Device assessment, human factor study

This extension application for Spevigo includes a new mode of administration (SC) and thereby a new device is introduced; a pre-filled syringe with a needle safety device (PFS-NSD). The human factors study/usability report was included in the submission, describing the several steps undertaken to demonstrate safe use of the device. Overall, it was shown that the PFS-NSD is safe and effective for the intended users, intended uses, and in the intended use environments. The device in question is used in other, already marketed products, for home administration of other products. In the clinical efficacy and safety study 1368-0027 evaluating spesolimab for prevention of GPP flares, the patients did not administer spesolimab themselves at home (at least not from information found in the CSR). Some patients with GPP were involved in the formative study and stated that their GPP/PPP symptoms *per se* would not prevent them from performing injections successfully. Hence, even if home administration was not applied within study 1368-0027, it is not expected that patients with GPP would be less suited to use home administration of their medication (if found adequate by the prescriber) compared with e.g. patients with plaque psoriasis, for which many marketed products can by self-administered. Also, there are no safety issues (e.g. serious injection site reactions and/or hypersensitivity) that would speak against self-administration at home. One case of infusion-related reaction has been reported within the spesolimab development program, but this was reported in a patient treated with placebo in trial 0005. Another case within SMQ anaphylactic reaction was reported in trial 0016. The PT was circulatory collapse. It was reported in a woman who attended a visit after an overnight fast. She lost consciousness after a blood draw. Study medication was administered thereafter, without any adverse event. The three serious cases reported within the user-defined adverse event category (UDAEC) 'Systemic hypersensitivity reactions' within studies 0027 or 0025 all had other possible explanations (see section 4.5.1 below). The proposed SmPC recommendation related to self-injection (or injection by care-givers) is therefore supported.

Discussion on the comprehensiveness of data for the prevention of GPP flares in adults and adolescents

Spevigo currently holds a CMA in the currently approved indication treatment of GPP flares in adult patients. At the CHMP request, conditional MA was therefore discussed for the new indication in the prevention of GPP flares in adolescent and adult patients.

The Applicant has provided arguments for viewing the available data as comprehensive; study 1368-0027 was randomised, placebo-controlled and double-blind, conducted across several countries and regions, demonstrating efficacy over 48 weeks with convincing and internally consistent results, the effect being large and with rapid onset, and with a safety profile consistent with the known safety profile already described in the product information.

Mechanistic support is also referred to, e.g. gene expression data from skin samples supporting the therapeutic targeting of IL-36R for the treatment of GPP flares. Also, reductions in serum biomarkers linked to systemic inflammation associated with GPP flares (e.g. CRP, IL-6, neutrophil count) were observed after treatment with spesolimab.

The Applicant's arguments for viewing study 1368-0027 on its own as comprehensive in GPP flare prevention are acknowledged. The size of the study is small and the study did not evaluate co-administration with other GPP treatments, however, as discussed above, this is not deemed to be a major concern. Altogether, while limited in patient numbers, the data for spesolimab in GPP flare prevention is viewed as comprehensive, considering the mechanistic evidence, and with two independent, controlled GPP studies (flare treatment plus prevention) showing convincing efficacy results.

For the initial approval of Spevigo for the treatment of GPP flares, the data was not considered comprehensive, and a CMA was granted. This view was mainly based on the fact that for i.v. spesolimab GPP flare treatment, virtually only data from the treatment of a *single flare* were available at the time of MAA. GPP patients tend to have recurring flares, hence, there was an uncertainty about the efficacy and safety of the product if used to treat recurrent flares. This concern was also raised based on an observed high incidence of ADA formation and a lack of knowledge on the impact of ADA on response to subsequent flares. The post-authorisation study 1368-0120 is planned to provide comprehensive data on spesolimab re-treatment of additional flares, including data on efficacy, safety and antibody formation, as a Specific Obligation. Thus, based on the lack of data on treatment of additional flares at MAA, it is considered justified that data for Spevigo in the initially approved indication were not viewed as comprehensive, while the data available for the indication prevention of GPP flares can be regarded as comprehensive (albeit limited in terms of patient numbers).

Assessment of paediatric data on clinical efficacy

See above.

Additional efficacy data needed in the context of a conditional MA

As discussed above, the data was not considered comprehensive for the initial approval of Spevigo for the treatment of GPP flares in adults. The extrapolation for efficacy and safety from adults to adolescents was supported by similarities in the disease, response to treatment, and plasma exposure levels. However, it is also agreed that the data in the treatment of GPP flares in adolescents from 12 years of age are not considered comprehensive, in line with the adult indication there are uncertainties about the efficacy and safety of the product if used to treat recurrent flares.

To provide comprehensive clinical data on the treatment of subsequent flares, confirmation is currently being generated from trial 1368-120 evaluating efficacy and safety and the impact of immunogenicity of spesolimab i.v. (specific obligation). The main aim of this study is to evaluate the response to recurrent flare(s) treatment with spesolimab i.v. after first flare treatment with spesolimab i.v. The final clinical trial report is expected by January 2028 for provision of comprehensive data. Study 1368-0120 will only enrol adult GPP patients. Thus, no further data in adolescents will be gained in this study, however, based on the already accepted extrapolation from adults to adolescents, data generated in trial 1368-0120 in adults will be regarded applicable to adolescent patients.

2.6.7. Conclusions on the clinical efficacy

In the small, randomised, placebo-controlled dose finding Phase 2 study 1368-0027 for flare prevention in patients with a history of GPP, a statistically significant effect of the proposed high dose regimen of spesolimab in comparison with placebo was observed on the primary endpoint; time to first GPP flare at week 48.

With respect to adolescents, although no (for i.v. flare treatment) or very limited (for s.c. flare prevention) efficacy data exist for spesolimab in adolescents; nonetheless, based on the data

reviewed, there is no information to suggest that adolescents and adults with GPP would have fundamentally different pathophysiology and treatment effects.

In conclusion, CHMP considers that efficacy of spesolimab is supported by the data submitted in the new indication "the prevention of generalised pustular psoriasis (GPP) flares in adults and adolescents from 12 years of age" and in the extension the existing indication in the treatment of GPP in adolescents form 12 years of age as monotherapy.

However, the data for spesolimab in GPP flare re-treatment was not regarded as comprehensive by the CHMP in adolescents in line with the initial MAA in adults.

The CHMP therefore considers the following measures necessary to address the missing efficacy data in the context of a conditional MA should be updated to include adolescents:

In order to confirm the efficacy and safety of spesolimab in the treatment of flares in adult and adolescent patients from 12 years of age 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.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

In support of the safety evaluation, the Applicant primarily refers to the two studies with subcutaneous administration of spesolimab for prevention of a GPP flare, i.e. the placebo-controlled trial 0027 and the extension trial 0025. Supportive data come from the previous trials with intravenous spesolimab for treatment of a GPP flare, and from trials in other indications, in which intravenous as well as subcutaneous spesolimab was administered. Healthy volunteer (HV) data are also available, but there is no new HV data relevant for the safety assessment of current application.

Safety data up to a cut-off date of 08 Jan 2021 was already included in the dossier of the GPP flare treatment MAA and are referred to in this application. Now, safety data from 188 additional patients and 20 additional healthy volunteers are available.

The safety data considered for this application, thus, comprise data from 589 patients and 246 healthy volunteers treated with spesolimab. These include:

- 181 patients with GPP
- 408 patients treated for non-GPP conditions
- 246 healthy volunteers

The total time at risk for spesolimab overall comprises around 840 patient-years:

- GPP: 244.3 patient-years (of these, 8.9 patient-years in adolescents)
- PPP: 327.8 patient-years
- AD: 40.0 patient-years
- HS: 45.7 patient-years
- UC: 96.7 patient-years
- Fistulising CD: 17.7 patient-years

- Healthy volunteers (HVs): 69.7 patient-years

There are 9 completed *placebo-controlled trials* with spesolimab in patients with different diseases. Overall, 445 patients were treated with spesolimab in these trials (s.c. overall: 237 patients, i.v. overall: 243 patients), corresponding to a total time at risk of 162.0 patient years (s.c. overall: 105.0 patient-years, i.v. overall: 57.1 patient-years).

Doses, schedules and route of administration differed between studies and indications. The number of GPP patients treated with the proposed dose schedule of a 600 mg subcutaneous LD followed by 300 mg q4w is 30 from the pivotal Trial no. 0027. Further, 23 patients were treated at the 300 q4w dose in the extension study 0025, which included patients who had previously been treated with spesolimab in Trial 0027 or 0013 (no loading dose needed). Thus, the data is limited in terms of GPP patients treated at the currently proposed dose schedule. Long-term safety data for the proposed maintenance dose or higher are, however, available from the open-label extension trials in other indications.

Data on long-term exposure to spesolimab (i.e. a cumulative time at risk of at least 6 months) is available as follows:

- **≥6 months**: 452 patients (GPP: 138 patients, PPP: 164 patients, AD: 28 patients, HS: 42 patients, UC: 64 patients, fistulising CD: 16 patients)
- **≥1 year**: 295 patients (GPP: 113 patients, PPP: 118 patients, AD: 14 patients, HS: 25 patients, UC: 21 patients, fistulising CD: 4 patients)
- **≥2 years**: 164 patients (GPP: 45 patients, PPP: 98 patients, AD: 7 patients, UC: 12 patients, fistulising CD: 2 patients)
- **≥3 years**: 31 patients (GPP: 18 patients, PPP: 9 patients, UC: 4 patients)

Adolescents

In trial 1368-0027, 8 adolescent patients (2 per treatment group, including placebo), aged 14 to 17 years at randomisation, were randomised and treated. Of these, 7 (including one from the placebo group) rolled over to trial 1368-0025. The inclusion of 8 adolescents in the study was in accordance with the agreed PIP.

No adolescents were included in the trials in other conditions.

Demographics and disease characteristics

Demographics in the GPP trials are summarised in *Table 34*. For disease characteristics, please, refer to the section on Clinical Efficacy.

Table 34. Demographic data in the individual GPP trials – RS/FAS/SAF

	1368-0027	1368-0025	1368-0011	1368-0013
Number of patients, N (%)	123 (100.0)	128 (100.0)	7 (100.0)	53 (100.0)
Male sex, N (%)	47 (38.2)	49 (38.3)	3 (42.9)	17 (32.1)
Race, N (%)				
Asian	79 (64.2)	77 (60.2)	4 (57.1)	29 (54.7)
White	44 (35.8)	51 (39.8)	2 (28.6)	24 (45.3)
Missing	0	0	1 (14.3)	0
Age [years], mean (StD)	40.4 (15.8)	42.2 (14.2)	38.6 (13.8)	43.0 (10.9)
Adolescents (12 to <18 years), N (%)	8 (6.5)	7 (5.5)	0	0
Body weight [kg], mean (StD)	71.77 (23.21)	72.38 (21.01)	62.80 (11.04)	72.03 (24.72)

Patients in trial 1368-0025 rolled over from trials 1368-0013 and 1368-0027

In trial 1368-0027, the use of systemic GPP medication at randomisation was reported for the majority of patients (74.8%), with similar proportions across treatment groups. The most frequently used medications (preferred name) were acitretin (40.7%), followed by ciclosporin (23.6%) and methotrexate (12.2%), which were to be discontinued at the start of the randomised study treatment. Before this trial, the median (Q1, Q3) number of GPP flares per year was 2.

2.6.8.2. Adverse events

Common adverse events in patients with GPP

Pivotal trial 0027 (Effisayil-2)

An overview of AEs in trial 0027 is shown in *Table 35*.

Table 35. Overall summary of AEs in trial 1368-0027 within randomised maintenance treatment period

	Placebo		Spesolimab s.c.							
			Low dose (LD 300 mg, 150 mg q12w)		Medium dose (LD 600 mg, 300 mg q12w)		High dose (LD 600 mg 300 mg q4w)		Total	
	N (%)	Rate/ 100 pt-yrs	N (%)	Rate/ 100 pt-yrs	N (%)	Rate/ 100 pt-yrs	N (%)	Rate/ 100 pt-yrs	N (%)	Rate/ 100 pt-yrs
Number of pts.	30 (100.0)		32 (100.0)		31 (100.0)		30 (100.0)		93 (100.0)	
Time at risk [pt-yrs]	17.7		25.1		22.8		23.9		71.8	
Patients with										
Any AE	26 (86.7)	414.5	29 (90.6)	398.7	29 (93.5)	411.0	26 (86.7)	338.2	84 (90.3)	381.5
Severe AEs[1]	7 (23.3)	45.6	6 (18.8)	25.4	7 (22.6)	31.6	5 (16.7)	21.7	18 (19.4)	26.2
Related AEs[2]	10 (33.3)	74.9	14 (43.8)	86.7	11 (35.5)	65.0	12 (40.0)	76.2	37 (39.8)	75.8
AEs leading to discontinuation[3]	0	0	0	0	2 (6.5)	8.9	3 (10.0)	12.9	5 (5.4)	7.1
AESIs	0	0	1 (3.1)	4.0	1 (3.2)	4.4	0	0	2 (2.2)	2.8
UDAECs	4 (13.3)	25.9	9 (28.1)	46.5	8 (25.8)	41.4	4 (13.3)	17.3	21 (22.6)	34.0
SAEs	1 (3.3)	5.8	5 (15.6)	21.2	1 (3.2)	4.4	3 (10.0)	12.8	9 (9.7)	12.9
Resulted in death	0	0	0	0	0	0	0	0	0	0
Required or prolonged hospitalization	1 (3.3)	5.8	4 (12.5)	16.9	1 (3.2)	4.4	3 (10.0)	12.8	8 (8.6)	11.5
Other medically important	0	0	1 (3.1)	4.0	0	0	0	0	1 (1.1)	1.4

All AEs starting up to the end of time at risk are included. Time at risk: Patients with AEs: start of first AE – start of treatment + 1 day, patients without AE: end of time at risk – start of treatment + 1 day. End of time at risk: the earliest of
(i) date/time before the start of flare rescue treatment with spesolimab i.v.
(ii) date/time of the end of last randomized treatment +112 days
(iii) date/time before the first treatment in OLE trial 1368-0025 if patient rolled over
(iv) last contact date on EoS page if patient did not roll over
1 RCTC grade 3 or 4
2 As assessed by the investigator
3 Of trial medication

All AEs reported for at least 10% of patients in any treatment group on the PT level during the randomised maintenance treatment period are summarised in *Table 36*. For the PTs reported for <10% of patients, no relevant differences were observed between the spesolimab dose groups and the placebo group.

Table 36. AEs reported for at least 10% of patients in any treatment group on the PT level in trial 1368-0027 within randomised maintenance treatment period

SOC PT	Placebo		Spesolimab s.c.							
			Low dose (LD 300 mg, 150 mg q12w)		Medium dose (LD 600 mg, 300 mg q12w)		High dose (LD 600 mg 300 mg q4w)		Total	
	N (%)	Rate/ 100 pt-yrs	N (%)	Rate/ 100 pt-yrs	N (%)	Rate/ 100 pt-yrs	N (%)	Rate/ 100 pt-yrs	N (%)	Rate/ 100 pt-yrs
Number of pts.	30 (100.0)		32 (100.0)		31 (100.0)		30 (100.0)		93 (100.0)	
Patients with any AE	26 (86.7)	414.5	29 (90.6)	398.7	29 (93.5)	411.0	26 (86.7)	338.2	84 (90.3)	381.5
Skin and s.c. tissue disorders	22 (73.3)	192.2	17 (53.1)	89.7	20 (64.5)	127.4	13 (43.3)	69.5	50 (53.8)	93.7
Pustular psoriasis	16 (53.3)	95.8	10 (31.3)	41.9	10 (32.3)	47.2	3 (10.0)	12.7	23 (24.7)	33.5
Psoriasis	3 (10.0)	19.9	4 (12.5)	18.0	5 (16.1)	24.2	4 (13.3)	18.0	13 (14.0)	20.0
Infections and infestations	10 (33.3)	75.2	12 (37.5)	71.0	11 (35.5)	64.1	8 (26.7)	40.5	31 (33.3)	57.6
URTI	4 (13.3)	24.9	3 (9.4)	12.8	6 (19.4)	30.2	0	0	9 (9.7)	13.4
COVID-19	1 (3.3)	5.9	2 (6.3)	8.4	1 (3.2)	4.4	3 (10.0)	13.8	6 (6.5)	8.8
Urinary tract infection	0	0	1 (3.1)	4.1	0	0	4 (13.3)	18.0	5 (5.4)	7.2
General disorders and administration site conditions	3 (10.0)	19.1	9 (28.1)	45.9	8 (25.8)	43.6	8 (26.7)	44.8	25 (26.9)	44.8
Injection site erythema	1 (3.3)	6.1	4 (12.5)	18.7	4 (12.9)	19.3	5 (16.7)	24.7	13 (14.0)	20.8
Investigations	6 (20.0)	43.2	9 (28.1)	48.9	5 (16.1)	24.3	5 (16.7)	24.2	19 (20.4)	31.8
Blood CPK increased	2 (6.7)	12.1	4 (12.5)	17.9	1 (3.2)	4.4	0	0	5 (5.4)	7.3
Musculoskeletal and connective tissue disorders	3 (10.0)	18.2	5 (15.6)	23.3	3 (9.7)	14.5	5 (16.7)	22.7	13 (14.0)	20.3
Arthralgia	1 (3.3)	6.0	4 (12.5)	17.6	1 (3.2)	4.6	3 (10.0)	13.3	8 (8.6)	11.9

CPK = creatine phosphokinase, URTI = upper respiratory tract infection
All AEs starting up to the end of time at risk are included. Time at risk: Patients with AEs: start of first AE – start of treatment + 1 day, patients without AE: end of time at risk – start of treatment + 1 day. End of time at risk: the earliest of (i) date/time before the start of flare rescue treatment with spesolimab i.v.

ii) date/time of the end of last randomised treatent +112 days

iii) date/time before the first treatment in OLE trial 1368-0025 if patient rolled over

iv) last contact date on EoS page if patient did not roll over

During the 48-week randomised maintenance treatment period in trial 1368-0027, the proportions and incidence rates of any AEs were comparable between the spesolimab dose groups and the placebo group.

The proportions of patients with AEs in the SOC "skin and subcutaneous tissue disorders" were lower in the spesolimab groups than in the placebo group, which was mostly driven by the PT pustular psoriasis. Pustular psoriasis was the most frequently reported AE in the spesolimab total group as well as in the placebo group. In the analysis that excludes AEs occurring within 6 days prior to flare treatment the proportions of patients reported with the PT pustular psoriasis was much lower.

The frequency of any infection was balanced between the spesolimab dose groups and the placebo group. On the PT level, the most frequently reported AE in this SOC was upper respiratory tract infection. Most of the AEs related to infection were non-serious, non-severe, and not indicative of opportunistic infections. Three serious events of infection were reported for patients in the spesolimab

low and medium dose groups (see section Serious adverse events below). None of the infection AEs led to treatment discontinuation, and no dose-dependency was observed.

AEs potentially reflecting hypersensitivity were mostly non-serious, occurred with higher frequency in the spesolimab low and medium dose groups than in the spesolimab high dose group and in the placebo group, did not lead to premature discontinuation of trial medication, and did not indicate a dose-dependency.

AEs in the SOC "general disorders and administration site conditions" were reported more frequently in the spesolimab groups than in the placebo group. On the PT level, injection site erythema was the most frequently reported AE in this SOC for the spesolimab groups, with the highest frequency in the spesolimab high dose group.

AEs leading to discontinuation of trial medication, SAEs, and AEs categorised as UDAEC were reported more frequently in some of the spesolimab dose groups than in the placebo group, but no dose response pattern was apparent.

AEs were additionally analysed for the group of patients who received any dose of spesolimab (s.c. or i.v., randomised or open-label). Post-any spesolimab, the overall summary of AE profile was generally comparable to that of the randomised maintenance treatment period, with no new safety findings being observed.

The reported infections are listed in more detail in *Table 37*, on the next page.

Table 37. Frequency (%) and incidence rate (per 100 patient years) of patients with AEs within SOC infections, by treatment – trial 0027

System organ class/ Preferred term	Placebo			Speso SC Low			Speso SC Medium			Speso SC High			Speso SC Total		
	N	%	Rate/100 pt-yrs	N	%	Rate/100 pt-yrs	N	%	Rate/100 pt-yrs	N	%	Rate/100 pt-yrs	N	%	Rate/100 pt-yrs
Number of patients	30	100.0		32	100.0		31	100.0		30	100.0		93	100.0	
Infections and infestations	10	33.3	75.2	12	37.5	71.0	11	35.5	64.1	8	26.7	40.5	31	33.3	57.6
Upper respiratory tract infection	4	13.3	24.9	3	9.4	12.8	6	19.4	30.2	0		0.0	9	9.7	13.4
COVID-19	1	3.3	5.9	2	6.3	8.4	1	3.2	4.4	3	10.0	13.8	6	6.5	8.8
Urinary tract infection	0		0.0	1	3.1	4.1	0		0.0	4	13.3	18.0	5	5.4	7.2
Nasopharyngitis	2	6.7	11.7	1	3.1	4.0	3	9.7	13.9	0		0.0	4	4.3	5.7
Folliculitis	0		0.0	2	6.3	8.5	0		0.0	1	3.3	4.2	3	3.2	4.3
Influenza	0		0.0	2	6.3	8.3	0		0.0	1	3.3	4.2	3	3.2	4.3
Body tinea	0		0.0	0		0.0	1	3.2	4.4	0		0.0	1	1.1	1.4
Cellulitis	0		0.0	1	3.1	4.1	0		0.0	0		0.0	1	1.1	1.4
Conjunctivitis	0		0.0	1	3.1	4.2	0		0.0	0		0.0	1	1.1	1.4
Encephalitis viral	0		0.0	1	3.1	4.1	0		0.0	0		0.0	1	1.1	1.4
Furuncle	0		0.0	1	3.1	4.1	0		0.0	0		0.0	1	1.1	1.4
Genital candidiasis	0		0.0	0		0.0	1	3.2	4.5	0		0.0	1	1.1	1.4
Helicobacter infection	0		0.0	1	3.1	4.1	0		0.0	0		0.0	1	1.1	1.4
Herpes zoster	0		0.0	0		0.0	1	3.2	4.6	0		0.0	1	1.1	1.4
Latent tuberculosis	0		0.0	0		0.0	1	3.2	4.4	0		0.0	1	1.1	1.4
Molluscum contagiosum	0		0.0	0		0.0	1	3.2	4.5	0		0.0	1	1.1	1.4
Pneumonia	0		0.0	1	3.1	4.1	0		0.0	0		0.0	1	1.1	1.4
Pneumonia chlamydial	0		0.0	1	3.1	4.1	0		0.0	0		0.0	1	1.1	1.4
Rash pustular	0		0.0	1	3.1	4.2	0		0.0	0		0.0	1	1.1	1.4
Rubella	0		0.0	0		0.0	1	3.2	4.4	0		0.0	1	1.1	1.4
Skin bacterial infection	0		0.0	0		0.0	1	3.2	4.4	0		0.0	1	1.1	1.4
Skin candida	0		0.0	0		0.0	1	3.2	4.5	0		0.0	1	1.1	1.4
Tinea faciei	0		0.0	0		0.0	1	3.2	4.5	0		0.0	1	1.1	1.4
Tinea pedis	0		0.0	0		0.0	1	3.2	4.4	0		0.0	1	1.1	1.4
Viral infection	0		0.0	0		0.0	0		0.0	1	3.3	4.3	1	1.1	1.4
Viral upper respiratory tract infection	0		0.0	0		0.0	0		0.0	1	3.3	4.2	1	1.1	1.4
Vulvovaginal candidiasis	0		0.0	0		0.0	0		0.0	1	3.3	4.2	1	1.1	1.4
Asymptomatic bacteriuria	1	3.3	5.8	0		0.0	0		0.0	0		0.0	0		0.0
Cystitis	1	3.3	5.9	0		0.0	0		0.0	0		0.0	0		0.0
Oral herpes	1	3.3	6.0	0		0.0	0		0.0	0		0.0	0		0.0
Otitis externa	1	3.3	5.7	0		0.0	0		0.0	0		0.0	0		0.0
Subcutaneous abscess	1	3.3	5.7	0		0.0	0		0.0	0		0.0	0		0.0

Extension trial 0025

In the entire treatment period of this OLE trial, the most frequently reported PTs for patients treated with spesolimab (s.c. with or without i.v.) were pustular psoriasis (14.8%), followed by COVID-19 (9.4%) and upper respiratory tract infection (9.4%) as well as pyrexia (8.6%); all other PTs were reported in <10 patients (*Table 38*).

Table 38. AEs reported for at least 5% of patients on the PT level in trial 1368 0025 during the entire treatment period

SOC PT	N (%)	Rate/100 patient-years
Number of patients	128 (100.0)	
Patients with any AE	76 (59.4)	199.4
Infections and infestations	45 (35.2)	51.1
COVID-19	12 (9.4)	9.5
Upper respiratory tract infection	12 (9.4)	9.4
Nasopharyngitis	8 (6.3)	6.2
Skin and subcutaneous tissue disorders	40 (31.3)	48.4
Pustular psoriasis	19 (14.8)	18.1
Psoriasis	8 (6.3)	6.3
Pruritus	7 (5.5)	5.5
General disorders and administration site conditions	26 (20.3)	26.1
Pyrexia	11 (8.6)	8.8
Injection site pain	9 (7.0)	7.2
Asthenia	7 (5.5)	5.5
Injection site erythema	7 (5.5)	5.5
Nervous system disorders	15 (11.7)	13.0
Headache	8 (6.3)	6.2

Events up to a cut-off date of 01 Dec 2022 are included.
Time at risk: Patients with AEs: start of first AE – start of treatment + 1 day, patients without AE: end of time at risk – start of treatment + 1 day. End of time at risk: min of (day of death, last contact per EoS page, end of defined treatment period)
Entire treatment period: from start of treatment to the earliest day of treatment REP or cut-off date.

Common adverse events in patients with other diseases

Dermatological indications

Based on the data from the placebo-controlled trials in patients with PPP (1368-0015, 1368-0016), AD (1368-0032), and HS (1368-0052), the safety profile of spesolimab was generally comparable with placebo. The safety profile of spesolimab in all available PPP, AD, and HS trials was overall consistent with the profile in patients with GPP. There was a low number of severe or serious cases. Common AEs across trials were (worsening of) the disease under study, injection site reactions, and uncomplicated infections.

Inflammatory bowel disease (IBD)

With the newly available data from the UC trial 1368-0017 (ongoing OLE) up to the cut-off date of 01 Dec 2022 and from the completed trials in patients with fistulising CD 1368-0008 (placebo-controlled) and 1368-0007 (OLE), now data from a total of 132 patients treated with spesolimab in an IBD condition are available.

In the trials in patients with UC, 113 patients were treated with at least 1 dose of spesolimab. Of these, 34 patients received spesolimab s.c. (300 mg q4w), and 111 patients received spesolimab i.v. (with doses of 300 mg SD to 1200 mg q4w). The total time at risk in patients with UC comprises for spesolimab overall 96.7 years and for spesolimab s.c. overall 44.1 years.

In the trials in patients with fistulising CD, 19 patients were treated with at least 1 dose of spesolimab. Of these, 12 patients received spesolimab s.c. (with doses of 300 mg q4w to 600 mg q4w), and 16 patients received spesolimab i.v. (1200 mg q4w). The total time at risk in patients with fistulising CD comprises for spesolimab overall 17.7 years and for spesolimab s.c. overall 10.4 years.

Based on the data from the placebo-controlled trials in patients with UC (1368-0005, 1368-0010) and CD (1368-0008), the safety profile of spesolimab was generally comparable with placebo. The safety profile of spesolimab in all available UC and CD trials was overall consistent with the profile in patients with GPP. There was a low number of severe or serious cases. Common AEs across trials were (worsening of) the disease under study, uncomplicated infections, and skin disorders/injection site reactions.

Grade 3 and Grade 4 adverse events

Trial 0027

Most patients were reported with AEs of worst intensity Rheumatology common toxicity criteria (RCTC) grade 1 or RCTC grade 2. The proportions of patients with severe AEs (RCTC grade 3 or 4) were comparable across the spesolimab dose groups and the placebo group (*Table 39*). However, in the placebo group, most Grade 3 or 4 AEs were pustular psoriasis or psoriasis (except one case of multiple sclerosis), while in the spesolimab groups also other PTs were reported, including three severe infections, drug eruption, breast cancer, pseudohyperkalaemia and cholelithiasis.

Compared with the randomised maintenance period, post any spesolimab treatment three additional patients had AEs of Grade 4. The PTs were urinary tract infection, cellulitis, and septic shock.
Four additional patients had AEs of RCTC grade 3. The PTs included pustular psoriasis, psoriasis, pneumonia, groin pain, and oedema.

All Grade 4 AEs were classified as SAEs and are described in more detail in the section on SAEs below. The infections are further described in the section on UDAECs below.

Table 39. All AEs of RCTC grade 3 or 4 on the PT level in trial 1368-0027 within randomised maintenance treatment period

	Placebo	Spesolimab s.c.			
		Low dose (LD 300 mg, 150 mg q12w)	Medium dose (LD 600 mg, 300 mg q12w)	High dose (LD 600 mg 300 mg q4w)	Total
	N (%)	N (%)	N (%)	N (%)	N (%)
Number of patients	30 (100.0)	32 (100.0)	31 (100.0)	30 (100.0)	93 (100.0)
Patients with any severe AE[1]	7 (23.3)	6 (18.8)	7 (22.6)	5 (16.7)	18 (19.4)
With any AE of RCTC grade 4	1 (3.3)	2 (6.3)	0	2 (6.7)	4 (4.3)
Pustular psoriasis	0	1 (3.1)	0	1 (3.3)	2 (2.2)
Palpitations	0	1 (3.1)	0	0	1 (1.1)
Breast cancer	0	0	0	1 (3.3)	1 (1.1)
Multiple sclerosis	1 (3.3)	0	0	0	0
With any AE of RCTC grade 3	6 (20.0)	4 (12.5)	7 (22.6)	3 (10.0)	14 (15.1)
Pustular psoriasis	4 (13.3)	2 (6.3)	6 (19.4)	1 (3.3)	9 (9.7)
Psoriasis	1 (3.3)	0	0	1 (3.3)	1 (1.1)
Drug eruption	0	1 (3.1)	0	0	1 (1.1)
Encephalitis viral[2]	0	1 (3.1)	0	0	1 (1.1)
Pneumonia	0	1 (3.1)	0	0	1 (1.1)
Skin bacterial infection	0	0	1 (3.2)	0	1 (1.1)
Hypertensive encephalopathy[2]	0	1 (3.1)	0	0	1 (1.1)
Pseudohyperkalaemia	0	0	1 (3.2)	0	1 (1.1)
Cholelithiasis	0	0	0	1 (3.3)	1 (1.1)
Neutropenia	1 (3.3)	0	0	0	0

1 RCTC grade 3 or 4

2 Differential diagnoses of the same clinical picture

All GPP trials

Also in trial 0025, most patients were reported with AEs of worst intensity RCTC grade 1 (mild, 22.7%) or RCTC grade 2 (moderate, 28.9%). Of the 10 patients (7.8%) with severe AEs, 2 patients (1.6%) were reported with AEs of worst intensity RCTC grade 4: 1 patient was reported with cardiac failure and 1 patient was reported with major depression and suicidal ideation (both of RCTC grade 4) as well as major depression and suspected suicide attempt (both of RCTC grade 3). All events were assessed as not related to study drug by the investigators; study drug was continued; the patients required treatment and one patient recovered. Eight patients (6.3%) had at least 1 AE of worst intensity RCTC grade 3, with the pustular psoriasis being the most frequent PT (reported in 4 patients, 3.1%).

In trial 1368-0011, none of the patients was reported with severe AEs. In trial 1368-0013, 1 patient was reported with an AE of RCTC grade 4 (life-threatening); this case of DRESS was also categorised as serious and as a UDAEC. This case was discussed during the original MAA.

The most frequently reported AE of RCTC grade 3 in the spesolimab overall group was pustular psoriasis, which is likely reflective of the patients' GPP flares.

Other indications

In trial 0016 (PPP), of the 14 patients (10.1%) reported with severe AEs, 6 patients were reported with AEs of RCTC grade 4 (life-threatening): acute myocardial infarction and unstable angina in 1 patient (see below), road traffic accident and spinal compression in 1 patient, and rib fracture, traumatic pneumothorax, depression, and foot deformity in 1 patient each.

In trial 0024 (PPP), of the 16 patients (14.8%) with severe AEs, 9 patients were reported with AEs of RCTC grade 4 (life-threatening): chronic cardiac failure, tricuspid valve incompetence, pulmonary

hypertension, endocarditis, pulmonary sepsis, and toxic shock syndrome in 1 patient; Guillain-Barre syndrome (GBS) and colitis in 1 patient; paraspinal abscess and staphylococcal bacteraemia in 1 patient; fall and lower limb fracture in 1 patient; post procedural haemorrhage and obesity in 1 patient; and COVID-19, gangrene, psoriasis, and renal colic in 1 patient each.

In trial 0037 (AD), 4 patients (28.6%) reported with severe AEs. One patient had an AE of RCTC grade 4 (PT: COVID-19 pneumonia). Two patients (14.3%) were reported with SAEs (COVID-19 pneumonia and device related infection in 1 patient each).

In trial 0052 (HS) no severe AEs were reported in the spesolimab group.

In trial 0067 (HS) of the 3 patients (6.7%) with severe AEs, 2 patients were reported with AEs of RCTC grade 4 (life-threatening): acute psychosis and hidradenitis in 1 patient each.

In trial 0017 (UC), of the 6 patients (7.6%) who were reported with severe AEs, 2 patients were reported with AEs of RCTC grade 4 (life-threatening): 1 patient with COVID-19 pneumonia and GBS (see below) and 1 patient with staphylococcal bacteraemia and gastroenteritis.

There were no severe AEs in trial 0008 (CD).

In trial 0007 (fistulising CD) of the 3 patients (25.0%) who were reported with severe AEs, 1 patient was reported with fistula of RCTC grade 4 (life-threatening). This case of fistula of RCTC grade 4 was serious.

Investigator-assessed drug-related adverse events

GPP trials

The most frequently reported AEs assessed as drug related by the investigator in trial 0027 are summarised in *Table 40*.

Table 40. Investigator-assessed drug-related AEs reported for at least 10% of patients in any treatment group on the PT level in trial 1368-0027 within randomised maintenance treatment period

SOC PT	Placebo		Spesolimab s.c.							
			Low dose (LD 300 mg, 150 mg q12w)		Medium dose (LD 600 mg, 300 mg q12w)		High dose (LD 600 mg 300 mg q4w)		Total	
	N (%)	Rate/ 100 pt-yrs	N (%)	Rate/ 100 pt-yrs	N (%)	Rate/ 100 pt-yrs	N (%)	Rate/ 100 pt-yrs	N (%)	Rate/ 100 pt-yrs
Number of pts	30 (100.0)		32 (100.0)		31 (100.0)		30 (100.0)		93 (100.0)	
Patients with any related AE[1]	10 (33.3)	74.9	14 (43.8)	86.7	11 (35.5)	65.0	12 (40.0)	76.2	37 (39.8)	75.8
General disorders and admin. site conditions	3 (10.0)	19.1	6 (18.8)	28.2	5 (16.1)	24.8	6 (20.0)	31.6	17 (18.3)	28.1
Injection site erythema	1 (3.3)	6.1	4 (12.5)	18.7	4 (12.9)	19.3	5 (16.7)	24.7	13 (14.0)	20.8
Skin and s.c. tissue disorders	4 (13.3)	24.1	6 (18.8)	25.2	4 (12.9)	18.8	4 (13.3)	17.9	14 (15.1)	20.8
Pustular psoriasis	3 (10.0)	17.0	5 (15.6)	20.3	2 (6.5)	8.8	2 (6.7)	8.4	9 (9.7)	12.7
Infections and infestations	1 (3.3)	5.7	3 (9.4)	13.2	5 (16.1)	25.1	1 (3.3)	4.2	9 (9.7)	13.6
Upper respiratory tract infection	1 (3.3)	5.7	0	0	4 (12.9)	19.1	0	0	4 (4.3)	5.7

All AEs starting up to the end of time at risk are included. Time at risk: Patients with AEs: start of first AE – start of treatment + 1 day, patients without AE: end of time at risk – start of treatment + 1 day. End of time at risk: the earliest of
(i) date/time before the start of flare rescue treatment with spesolimab i.v.
(ii) date/time of the end of last randomized treatment +112 days
(iii) date/time before the first treatment in OLE trial 1368-0025 if patient rolled over
(iv) last contact date on EoS page if patient did not roll over
1 As assessed by the investigator

After any treatment with spesolimab (s.c. or i.v., randomised or open-label), the same PTs as in the randomised maintenance treatment period were the most frequently reported AEs assessed as drug related by the investigator.

Among the most frequently reported investigator-assessed drug-related AEs across all pooled GPP trials, injection site erythema and upper respiratory tract infection occurred with comparable frequencies in both spesolimab overall groups by parent trial, while the frequencies of pustular psoriasis and injection site pain were higher in patients originating from the flare treatment trial 1368-0013 than in patients originating from the flare prevention trial 1368-0027.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

In the interventional clinical program of spesolimab, one fatal case occurred in a patient with ulcerative colitis participating in trial 1368-0017 (maintenance treatment with SC spesolimab 600 mg q6w). This case was discussed during the initial MAA. 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 hospitalised and died 12 days later. The investigator considered the death related to Covid-19 and not to spesolimab. Based on the information received, also 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 seemed unlikely.

A second fatal case was reported within the spesolimab compassionate use program, and occurred in a male patient, who was treated with a single dose spesolimab for a GPP flare. The case was highly confounded by the patient's complex and grave medical history, his age and co-medications.

Both fatal cases were discussed during the original MAA.

No death occurred in the study 0027.

Other serious adverse events (SAEs)

GPP trials

An overview of all SAEs by GPP trial (except 1368-0011, in which no SAE was reported) is provided in **Table 41.**

In the pivotal trial 0027, the numbers of patients with SAEs were higher in some of the spesolimab groups (low and high dose) than in the placebo group. The number of patients with SAEs in the SOC "skin and subcutaneous tissue disorders" was highest in the spesolimab low dose group (3 patients) compared with 1 patient each in the spesolimab medium and high dose groups and no patient in the placebo group. The most frequently reported SAE in this SOC, pustular psoriasis, was reported for 1 patient in each spesolimab dose group vs. none of the patients in the placebo group. All other SAEs were individual occurrences. SAEs in the SOC "infections and infestations" were reported for 2 patients in the spesolimab low dose group, 1 patient in the spesolimab medium dose group, and none of the patients in the spesolimab high dose group or in the placebo group. The serious infections are described in more detail in the section on User-defined Adverse event Categories (UDAECs) below. After any treatment with spesolimab (s.c. or i.v., randomised or open-label), SAEs were reported in 5 additional patients treated with spesolimab (as compared with the randomised maintenance treatment period). The PTs were pustular psoriasis, urinary tract infection, cellulitis, basal cell carcinoma, and cerebral ischaemia, reported in 1 patient each (see section on UDAECs for more details). One patient randomised to spesolimab medium dose, who was reported with SAEs (pustular psoriasis and skin bacterial infection) in the randomised maintenance treatment period, was reported with additional SAEs (pneumonia, septic shock, and oedema) during the i.v. flare treatment period. All SAEs in this patient were assessed as not related to study drug by the investigator, study drug was continued (OL s.c. maintenance treatment), the patient was treated and recovered.

In trial 0025, 13 patients (10.2%) treated with spesolimab (s.c. with or without i.v.) were reported with SAEs. On the PT level, the most frequently reported SAE was pustular psoriasis (i.e. worsening of the underlying diseases; 4 patients, 3.1%), followed by COVID-19 (2 patients, 1.6%); all other SAEs were individual occurrences and had various PTs (*Table 41*).

Detailed information on SAEs for trial 1368-0013 was discussed during the original MAA for GPP flare treatment. In short, 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 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.

Table 41. Overview of SAEs post-any spesolimab use in trials 1368-0027, 1368-0013, and 1368-0025

SOC PT	1368-0027[1]		1368-0013[2]		1368-0025[3]	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	107 (100.0)		51 (100.0)		128 (100.0)	
Patients with any SAE	14 (13.1)	16.2	13 (25.5)	127.0	13 (10.2)	11.1
Skin and subcutaneous tissue disorders	6 (5.6)	6.7	11 (21.6)	106.0	5 (3.9)	3.9
Pustular psoriasis	4 (3.7)	4.5	9 (17.6)	83.0	4 (3.1)	3.1
Angioedema	1 (0.9)	1.1	0	0	0	0
Drug eruption	1 (0.9)	1.1	0	0	0	0
DRESS	0	0	2 (3.9)	15.9	0	0
Psoriasis	0	0	1 (2.0)	7.8	0	0
Dermatitis exfoliative generalised	0	0	0	0	1 (0.8)	0.7
Infections and infestations	5 (4.7)	5.6	2 (3.9)	15.8	3 (2.3)	2.3
Pneumonia	2 (1.9)	2.2	0	0	1 (0.8)	0.7
COVID-19	0	0	0	0	2 (1.6)	1.5
Urinary tract infection	1 (0.9)	1.1	1 (2.0)	7.8	0	0
Skin bacterial infection	1 (0.9)	1.1	0	0	0	0
Septic shock	1 (0.9)	1.1	0	0	0	0
Cellulitis	1 (0.9)	1.1	0	0	0	0
Encephalitis viral	1 (0.9)	1.1	0	0	0	0
Influenza	0	0	1 (2.0)	7.7	0	0
Neoplasms[5]	2 (1.9)	2.2	1 (2.0)	7.7	2 (1.6)	1.5
Breast cancer	1 (0.9)	1.1	0	0	0	0
Basal cell carcinoma	1 (0.9)	1.1	0	0	1 (0.8)	0.7
Squamous cell carcinoma of the skin	0	0	1 (2.0)	7.7	0	0
Adenocarcinoma	0	0	0	0	1 (0.8)	0.7
Nervous system disorders	2 (1.9)	2.2	0	0	1 (0.8)	0.7
Cerebral ischaemia	1 (0.9)	1.1	0	0	0	0
Hypertensive encephalopathy	1 (0.9)	1.1	0	0	0	0
Bell's palsy	0	0	0	0	1 (0.8)	0.7
Cerebrovascular accident	0	0	0	0	1 (0.8)	0.7
Cardiac disorders	1 (0.9)	1.1	0	0	2 (1.6)	1.5
Palpitations	1 (0.9)	1.1	0	0	0	0
Cardiac failure	0	0	0	0	1 (0.8)	0.7
Sinus tachycardia	0	0	0	0	1 (0.8)	0.7
Hepatobiliary disorders	1 (0.9)	1.1	1 (2.0)	7.8	0	0
Cholelithiasis	1 (0.9)	1.1	0	0	0	0
DILI	0	0	1 (2.0)	7.8	0	0
Gastrointestinal disorders	0	0	0	0	2 (1.6)	1.5
Dental necrosis	0	0	0	0	1 (0.8)	0.7
Nausea	0	0	0	0	1 (0.8)	0.7
Vomiting	0	0	0	0	1 (0.8)	0.7
General dis. and admin. site conditions	1 (0.9)	1.1	0	0	0	0
Oedema	1 (0.9)	1.1	0	0	0	0
Musculoskeletal disorders[4]	0	0	1 (2.0)	7.8	0	0
Arthritis	0	0	1 (2.0)	7.8	0	0
Blood and lymphatic system disorders	0	0	0	0	1 (0.8)	0.7
Anaemia	0	0	0	0	1 (0.8)	0.7
Psychiatric disorders	0	0	0	0	1 (0.8)	0.7
Major depression	0	0	0	0	1 (0.8)	0.7
Suicidal ideation	0	0	0	0	1 (0.8)	0.7
Suspected suicide attempt	0	0	0	0	1 (0.8)	0.7

1 All AEs starting up to the end of time at risk are included. Time at risk: Patients with AEs: start of first AE – start of treatment + 1 day, patients without AE: end of time at risk – start of treatment + 1 day. End of time at risk: the earliest of
(i) date/time of the end of last dose of any study treatment +112 days
(ii) date/time before the first treatment in OLE trial 1368-0025 if patient rolled over
(iii) last contact date on EoS page if patient did not roll over

Studies in other indications

In trial 0016 (PPP), 13 patients (9.4%) were reported with SAEs post-Week 16. On the PT level, all SAEs were individual occurrences.

In trial 0024, 17 patients (15.7%) were reported with SAEs. On the PT level, fall was reported for 2 patients (1.9%); both cases were assessed as not related to trial drug and both patients recovered. All other SAEs were individual occurrences.

In trial 0037 (AD), 2 patients (14.3%) were reported with SAEs (COVID-19 pneumonia and device related infection in 1 patient each).

In trial 0052 (HS), 1 patient in the placebo group had an SAE of suicidal behaviour.

In trial 0067 (HS) 6 patients (13.3%) were reported with SAEs; on the PT level all SAEs were individual occurrences.

In trial 0017, 9 patients (11.4%) were reported with SAEs, of which 1 case (reported as COVID-19 pneumonia and GBS) was fatal. This was the only fatal case reported to the sponsor in all interventional clinical trials with spesolimab to date. This case was already discussed above. Of the remaining 8 patients with SAEs, 4 patients were reported with worsening of ulcerative colitis; the other SAEs were individual occurrences.

In trial 0008 (CD), for 1 patient in the spesolimab group, an SAE of proctalgia was reported.

SAEs falling under the UDAECs are discussed in the section User-defined adverse event categories below.

User-defined adverse event categories (UDAECs)

For a comprehensive assessment of medical topics that were selected in accordance with the expected safety profile of spesolimab and potential safety concerns of spesolimab in the indication of GPP and other potential indication-specific symptoms, MedDRA PT groupings by medical concept were defined. These so-called user-defined adverse event categories (UDAECs) are based on standardised MedDRA queries (SMQs) or BI-customised MedDRA queries (BIcMQs) if no SMQs were available, which collapse multiple MedDRA PTs into clinically relevant categories. Some of the UDAECs were considered relevant for specific populations only. The UDAEC categories and criteria evolved over time, with the safety profile developing Therefore, some UDAECs were analysed retrospectively for all trials using the latest MedDRA version 25.1. The following UDAECs were analysed for the GPP trials:

- Hypersensitivity
- Infections (severe, serious, opportunistic, tuberculosis)
- Malignant tumours
- Malignant skin tumours
- Skin melanomas
- Non-melanoma skin cancer (NMSC)
- Malignancies excluding NMSC
- Peripheral neuropathy

An overview of UDAECs across all placebo-controlled trials in GPP and other indications is provided in Table 42.

Each topic is discussed in some more detail below.

Table 42. Patients with AEs in the UDAECs "hypersensitivity all", "infections all", "malignant tumours", and "peripheral neuropathy" in placebo-controlled periods of double-blind trials 1368-0027, 1368-0013, 1368-0015, 1368-0016, 1368-0032, 1368-0052, 1368-0005, 1368-0010

	GPP				PPP				AD		HS		UC				CD	
Trial no.	**1368-0027**		**1368-0013**		**1368-0015**		**1368-0016**		**1368-0032**		**1368-0052**		**1368-0005**		**1368-0010**		**1368-0008**	
UDAEC[1]	Up to Week 48		Up to Week 1		End of REP		Up to Week 16		Up to Week 16		Up to Week 12		Up to Week 12		End of REP		Up to Week 12	
PT	Placebo	Speso	Placebo	Speso	Placebo	Speso	Placebo	Speso	Placebo	Speso	Placebo	Speso	Placebo	Speso	Placebc	Speso	Placebo	Speso
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Number of patients (100.0%)	123		53		59		152		51		52		97		22		21	
	30	93	18	35	20	39	43	109	18	33	16	36	23	74	7	15	10	11
Hypersensitivity all[1]	3 (10.0)	17 (18.3)	1 (5.6)	3 (8.6)	2 (10.0)	3 (7.7)	4 (9.3)	13 (11.9)	8 (44.4)	11 (33.3)	1 (6.3)	3 (8.3)	1 (4.3)	10 (13.5)	1 (14.3)	2 (13.3)	0	0
DRESS	0	0	0	1 (2.9)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Angioedema	0	1 (1.1)	0	0	0	1 (2.6)	0	0	0	0	0	0	0	0	0	0	0	0
Swollen tongue	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0
Lip oedema	1 (3.3)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Eye oedema	0	0	0	1 (2.9)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Swelling of eyelid	0	0	0	0	0	0	0	0	0	1 (3.0)	0	0	0	0	0	0	0	0
Urticaria	2 (6.7)	2 (2.2)	0	1 (2.9)	0	1 (2.6)	0	1 (0.9)	0	1 (3.0)	0	1 (2.8)	0	1 (1.4)	0	0	0	0
Circulatory collapse	0	0	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0	0	0	0	0
Rash	0	1 (1.1)	0	0	0	0	0	2 (1.8)	1 (5.6)	0	0	0	0	5 (6.8)	1 (14.3)	0	0	0
Rash pustular	0	1 (1.1)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Rash maculo-papular	0	1 (1.1)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pruritus allergic	0	0	0	0	0	0	0	0	0	1 (3.0)	0	0	0	0	0	0	0	0
Drug eruption	0	2 (2.2)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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Trial no.	1368-0027		1368-0013		1368-0015		1368-0016		1368-0032		1368-0052		1368-0005		1368-0010		1368-0008	
UDAEC[1]	Up to Week 48		Up to Week 1		End of REP		Up to Week 16		Up to Week 16		Up to Week 12		Up to Week 12		End of REP		Up to Week 12	
PT	Placebo	Speso	Placebo	Speso	Placebo	Speso	Placebo	Speso	Placebo	Speso	Placebo	Speso	Placebo	Speso	Placebo	Speso	Placebo	Speso
Allergy to vaccine	0	1 (1.1)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Eczema	0	0	0	0	0	0	2 (4.7)	5 (4.6)	0	0	0	1 (2.8)	0	0	0	2 (13.3)	0	0
Dermatitis	0	2 (2.2)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Derm. ex-foliative gen.	0	0	0	0	0	0	0	0	0	1 (3.0)	0	0	0	0	0	0	0	0
Derm. contact	0	3 (3.2)	0	0	1 (5.0)	0	1 (2.3)	1 (0.9)	1 (5.6)	0	0	0	0	0	0	0	0	0
Derm. atopic	0	1 (1.1)	0	0	0	0	0	0	7 (38.9)	9 (27.3)	0	0	0	1 (1.4)	0	0	0	0
Derm. allergic	0	0	1 (5.6)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dermatitis acneiform	0	0	0	0	0	1 (2.6)	0	1 (0.9)	0	0	0	1 (2.8)	0	1 (1.4)	0	0	0	0
Dermatitis perioral	1 (3.3)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hand dermatitis	0	0	0	0	0	0	0	0	0	0	1 (6.3)	0	0	0	0	0	0	0
Rhinitis allergic	0	0	0	0	0	1 (2.6)	0	2 (1.8)	0	0	0	0	0	0	0	0	0	0
Allergic cough	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (1.4)	0	0	0	0
Hypersensitivity	0	0	0	0	0	0	0	0	1 (5.6)	0	0	0	0	0	0	0	0	0
Drug hypersens.	0	1 (1.1)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Inf. rel. reaction	0	0	0	0	1 (5.0)	0	0	0	0	0	0	0	1 (4.3)	2 (2.7)	0	0	0	0
Inj. rel. reaction	0	1 (1.1)	0	0	0	0	1 (2.3)	0	0	0	0	0	0	0	0	0	0	0
Inj. site rash	0	0	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0	0	0	0	0
Inj. site urticaria	0	2 (2.2)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Henoch-Schonlein purpura	0	0	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0	0	0	0	0

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Trial no.	1368-0027		1368-0013		1368-0015		1368-0016		1368-0032		1368-0052		1368-0005		1368-0010		1368-0008	
UDAEC[1]	Up to Week 48		Up to Week 1		End of REP		Up to Week 16		Up to Week 16		Up to Week 12		Up to Week 12		End of REP		Up to Week 12	
PT	Placebo	Speso	Placebo	Speso	Placebo	Speso	Placebo	Speso	Placebo	Speso	Placebo	Speso	Placebo	Speso	Placebo	Speso	Placebo	Speso
Infections all[1]	0	3 (3.2)	0	1 (2.9)	0	0	0	0	0	0	0	0	1 (4.3)	0	1 (14.3)	0	0	0
Urinary tract infection	0	0	0	1 (2.9)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Clostridium difficile colitis	0	0	0	0	0	0	0	0	0	0	0	0	1 (4.3)	0	0	0	0	0
Rectal abscess	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (14.3)	0	0	0
Pneumonia	0	1 (1.1)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Encephalitis viral	0	1 (1.1)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Skin bacterial infection	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Latent tuberculosis	0	1 (1.1)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Malignant tumours[1]	0	1 (1.1)	0	0	0	0	1 (2.3)	0	0	0	0	0	0	0	0	1 (6.7)	0	0
Breast cancer	0	1 (1.1)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Adenocarcinoma of colon	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (6.7)	0	0
Prostate cancer	0	0	0	0	0	0	1 (2.3)	0	0	0	0	0	0	0	0	0	0	0
Peripheral neuropathy[1]	1 (3.3)	0	0	0	0	0	1 (2.3)	1 (0.9)	0	0	0	0	0	0	0	0	0	0
Neuropathy peripheral	0	0	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0	0	0	0	0
Peripheral sensory neuropathy	0	0	0	0	0	0	1 (2.3)	0	0	0	0	0	0	0	0	0	0	0
Multiple sclerosis	1 (3.3)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

MedDRA version 25.1
Derm. = dermatitis, DRESS = drug reaction with eosinophilia and systemic symptoms, gen. = generalized, inf. = infusion, inj. = injection, rel. = related, Speso = spesolimab
Analysis at time of submission. Spesolimab columns are sum of several doses for some trials.

Systemic hypersensitivity reactions

The systematic searches summarised in the UDAEC "hypersensitivity all" also include infusion- and injection site-related reactions and comprise a broad number of PTs, which also include unspecific symptoms potentially indicative of hypersensitivity.

In trial 1368-0027, during the randomised maintenance treatment period, most of the AEs categorised as UDAEC were reported in the UDAEC "hypersensitivity all" (Table 42), with higher numbers of patients in the spesolimab low and medium dose groups (40% and 31%, respectively) than in the spesolimab high dose group and the placebo group (19% and 27%, respectively).

PTs reported for more than 1 patient in the spesolimab total group included dermatitis contact, dermatitis, drug eruption, urticaria, and injection site urticaria. The AEs in the UDAEC "hypersensitivity all" were mostly non-serious, did not lead to premature discontinuation of trial medication and did not indicate dose-dependency. Some of the reported events were clearly attributable to causes other than spesolimab (e.g. verbatim of drug eruption: "rash due to reaction after COVID 19 vaccination"; allergy to vaccine: "allergy to rabies vaccine"; drug hypersensitivity: "suspected allergic reaction after Diclofenac gel back".

Two patients in the spesolimab low dose group were reported with SAEs grouped to the UDAEC "hypersensitivity all":

- Angioedema of eyes, reported in a female patient, started on Day 7 and in temporal association with worsening of GPP and fever. One day later, the patient was administered spesolimab 900 mg i.v. to treat the GPP flare; the angioedema resolved on Day 11 without further treatment. The investigator assessed the event as related to study drug.
- Drug eruption in a female patient was reported to be due to COVID-19 vaccination. Two hours after administration of the vaccine, the patient experienced rash and palpitations (also reported as SAE). Study medication was continued. The rash and palpitations resolved. The investigator assessed both SAEs as not related to study drug.

Post-any spesolimab use, 4 additional patients (i.e. 21 patients in total, 19.6%) were reported with AEs in the UDAEC "hypersensitivity all"; all of these additional AEs were non-serious. One of these non-serious events was acute generalised exanthematous pustulosis (AGEP), reported in a patient two days after start of ciprofloxacin treatment, for which AGEP is a labelled side effect. The investigator assessed the event as not related to study drug, study drug was continued, the patient was treated and recovered.

In the entire treatment period of trial 1368-0025, 15 patients (11.7%) were reported with AEs in the UDAEC "hypersensitivity all". PTs that were reported for more than 1 patient in this trial were rash (3 patients, 2.3%) and allergic rhinitis (2 patients, 1.6%).

For 1 patient (0.8%), the AE in the UDAEC "hypersensitivity all" was serious:

- Dermatitis exfoliative generalised, reported in a male patient, started on Day 467, 3 days after use of amoxicillin/clavulanate for dental infection. Allergy testing confirmed hypersensitivity to both components of the administered antibiotic. The event was assessed as not related to study drug by the investigator, study drug was continued, the patient was treated and recovered on Day 590.

After any spesolimab use in trial 1368-0013, 5 patients (9.8%) were reported with AEs in the UDAEC "hypersensitivity all". PTs that were reported for more than 1 patient in this trial were urticaria and DRESS (reported for 2 patients, 3.9% each). The 2 cases reported as DRESS were serious; in one case the rapid occurrence of symptoms after spesolimab administration makes a causal relationship with

spesolimab implausible, and in the other case, positive rechallenge with spiramycin suggests this antibiotic as an alternative explanation.

In trial 1368-0011, 3 patients were reported with AEs in the UDAEC "hypersensitivity all"; all AEs (eczema in 2 patients and infusion-related reaction in 1 patient) were non-serious.

No new potential DRESS cases were reported, beyond the 2 cases reported in trial 1368-0013. For the SAEs in the UDAEC "hypersensitivity all" reported in 5 patients (2.8%), no clear relationship to spesolimab was observed. The reported hypersensitivity reactions did not suggest a pattern regarding the type of reaction. When also taking the available data in non-GPP conditions into account, injection site reactions were identified as potential ADRs of spesolimab.

Infections (severe, serious, opportunistic)

The systematic searches summarised in the UDAEC "infections all" focused on serious, severe, opportunistic, and tuberculosis infections.

In all GPP trials, according to the CTPs, tuberculosis testing was to be performed as part of the routine testing at screening and at the end of study (except for trial 1368-0011). In the long-term extension trial 1368-0025, routine tuberculosis testing was to be repeated every 48 weeks.

In trial 1368-0027, during the randomised maintenance treatment period, AEs in the UDAEC "infections all (severe, serious or opportunistic)" were reported for a total of 4 patients in the spesolimab low and medium dose groups), i.e. no dose-dependency was observed. None of the infection AEs led to premature discontinuation of trial medication. One patient in the spesolimab medium dose group was reported with non-serious latent tuberculosis (without findings or AEs indicative of a TB reactivation), and 3 patients were reported with serious events:

- Community-acquired pneumonia, reported in a female patient in the spesolimab low dose group, started on Day 208; no pathogen was identified. The investigator assessed the event as related to study drug, study drug was continued, the patient was treated with antibiotics and recovered without complications.
- Encephalitis viral, reported as differential diagnosis in a female patient in the spesolimab low dose group with a history of untreated hypertension, started on Day 74. The patient was hospitalised due to elevated blood pressure (229/109 mmHg). According to the investigator, headache and altered sensorium could rather be explained by the hypertensive emergency and were additionally reported as an SAE of "hypertensive encephalopathy". The lack of nuchal rigidity and photophobia, normal cerebrospinal fluid (CSF) results, except for a slightly elevated protein, normal brain CT, and negative CSF culture for tuberculosis do not seem to support an infectious encephalopathy (either viral or bacterial). The investigator assessed viral encephalitis as related to study drug, study drug was continued, the patient was treated and recovered.
- Skin bacterial infection, reported in a female patient in the spesolimab medium dose group, occurred on Day 31 secondary to a GPP flare (reported as SAE pustular psoriasis, suspected to be triggered by administration of COVID-19 vaccine) that led to skin breakdown. Spesolimab i.v. flare treatment was administered on Days 31 and 38. During the i.v. flare treatment period, the patient was reported with SAEs of septic shock, oedema, and pneumonia, (start Days: 32, 33, and 43). All SAEs in this patient were assessed as not related to study drug by the investigator, study drug was continued (OL s.c. maintenance treatment), the patient was treated and recovered.

Post-any spesolimab use, additional AEs within the UDAEC "infections all" were reported for three patients (one of which is listed above), i.e. for 6 patients in total (5.6%). For both additional patients, the reported events were serious:

- Cellulitis, reported in a female patient with type 2 diabetes mellitus, started on Day 77, one day after spesolimab i.v. administration on Day 76. The patient had oedema, redness, and pain in both lower limbs. The investigator assessed the event as not related to study drug. Diabetes mellitus was considered a risk factor. After treatment with antibiotics the patient recovered. The patient discontinued trial medication (last dose on Day 83) due to lack of efficacy.
- Urinary tract infection, reported in a female patient with type 2 diabetes mellitus and glucosuria, started on Day 211 after spesolimab i.v. single dose administration. The investigator assessed the event as not related to study drug and study drug was continued (OL s.c. maintenance treatment). After treatment with antibiotics the patient recovered.

In the entire treatment period of trial 1368-0025, 3 patients (2.3%) were reported with an AE in the UDAEC "infections all"; all of these AEs were serious:

- COVID-19 (of RCTC grade 2), reported in a female patient with obesity and hypertension, started on Day 147. The patient had not received a booster dose of the COVID-19 vaccine prior to the event. The patient was hospitalised for observation; no oxygen supplementation was required. The investigator assessed the event as not related to study drug, study drug was continued, the patient was treated and recovered.
- COVID-19 (of RCTC grade 2), reported in a female patient with a history of anemia, started on Day 340 (sinus tachycardia was reported as concomitant SAE, with a start on Day 342). The investigator assessed both events as not related to study drug, study drug was continued, the patient was treated and recovered from both events.
- Community-acquired pneumonia, reported in a female patient, started on Day 45. The investigator assessed the event as related to study drug, study drug was continued, the patient was treated and recovered.

After any spesolimab use in trial 1368-0013, 3 patients were reported with AEs in the UDAEC "infections all". The AEs were serious for 2 patients (urinary tract infection, influenza) and non-serious for 1 patient latent tuberculosis, without findings or AEs indicative of a TB reactivation).

In trial 1368-0011, no patient was reported with any AE in the UDAEC "infections all".

In summary, across all pooled GPP trials, 10 of 181 patients (5.5%) were reported with SAEs in the UDAEC "infections all", with pneumonia, urinary tract infection, and COVID-19 reported in more than 1 patient. None of the SAEs led to discontinuation of study drug, all patients recovered without complications, most patients had additional risk factors, and no pattern regarding pathogen or affected organs were seen. The two cases of latent tuberculosis were non-serious and did not lead to reactivation.

When also taking the available data in non-GPP conditions into account (see Clinical AR), serious or opportunistic infections remain an important potential risk of spesolimab.

Malignancies

In trial 1368-0027, during the randomised maintenance treatment period, 1 patient in the spesolimab high dose group was reported with a SAE in the UDAEC "malignant tumours":

- Breast cancer, reported in a female, started on Day 201. The investigator assessed the event as related to study drug and study drug was discontinued. The patient underwent

chemotherapy and unilateral mastectomy and is not yet recovered. Historical medication of this patient included mycophenolate mofetil for 3 years and ciclosporin.

Post-any spesolimab use, 1 additional patient initially randomised to spesolimab medium dose was reported with an AE in the UDAEC "malignant tumours":

- Basal cell carcinoma, reported in a female, started on Day 324 in the OL s.c. maintenance period. The patient had discontinued study drug on Day 225 due to lack of efficacy. The investigator assessed the event as not related to study drug. After excision of the lesion on the nasal wing, the patient recovered.

In trial 1368-0025, 2 patients who had rolled over from trial 1368-0013 were reported with AEs in the UDAEC "malignant tumours":

- Adenocarcinoma (microinvasive carcinoma of the left upper lobe of the lung), reported in a male, started on Day 32 in this OLE trial (and 133 days from the first dose of spesolimab in parent trial 1368-0013). Ground glass nodules of lung had already been detected prior to enrolment in parent trial 1368-0013, but increased in size over time, which led to additional diagnostic procedures. The investigator assessed the event as not related to study drug, study drug was discontinued, the patient underwent anterior segmentectomy of the left upper lobe through video-assisted thoracoscopic surgery and recovered. The patient had a family history of lung cancer.
- Basal cell carcinoma (superficial, on the right thigh), reported in a female, started on Day 752 in this OLE trial (and 843 days from the first dose of spesolimab in the parent trial 1368-0013); fibrous histiocytoma was reported as concomitant non-serious AE. The investigator assessed the basal cell carcinoma as related to study drug, albeit unlikely, and more attributable to other previous treatments (e.g. cyclosporine). Study drug was continued, and after complete excision of the lesion on the same day as the diagnosis, the patient recovered.

Post-any spesolimab use in trial 1368-0013, 1 patient was reported with squamous cell carcinoma of the skin. The patient had a history of acrodermatitis continua of Hallopeau (ACH) covering the entire left hand, suggesting that the skin carcinoma was a progression of the preexisting ACH lesions.

In trial 1368-0011, no patient was reported with any AE grouped to the UDAEC "malignancies".

In summary, across all pooled GPP trials, 5 patients (2.8%) were reported with AEs in the UDAEC "malignant tumours"; all AEs were serious. In some of the cases, time to onset was not plausible and patients had underlying risk factors. The available data, including the data trials in non-GPP conditions, provide insufficient evidence to suggest an increased frequency of malignancies for spesolimab. Malignancy is kept as an important potential risk of spesolimab.

Cardiac safety

AEs in the UDAECs "3-point MACE" and "torsade de pointes" were analysed on trial level for the GPP trials.

In trials 1368-0027 and 1368-0011, none of the patients were reported with AEs in the UDAECs "3-point MACE" or "torsade de pointes".

In trial 1368-0025, 1 patient was reported with an AE in the UDAEC "3-point MACE":

- Cerebrovascular accident, reported in a female, started on Day 220 (Bell's palsy was reported as concomitant SAE). The events were assessed as not related to study drug, study drug was continued, and after treatment, the patient recovered with sequelae.

In trial 1368-0013, 1 patient in the spesolimab group was reported with a non-serious AE of syncope, grouped to the UDAEC "torsade de pointes" (reflecting the broad scope of the respective SMQ) starting on Day 37 during the i.v. infusion of a second dose of spesolimab as OL treatment. The AE was accompanied by hypotension; blood pressure normalised after 10 minutes of infusion interruption and without therapy.

The MAH concludes that when also taking the available data from trials in non-GPP conditions into account (see Clinical AR), there is no indication for an adverse effect of spesolimab on the cardiovascular system.

Peripheral neuropathy

In patients treated with spesolimab in trial 1368-0027 or in any of the other GPP trials, no cases of peripheral neuropathy were reported. One patient in the placebo group of trial 1368-0027 was reported with an SAE of multiple sclerosis grouped to the UDAEC "peripheral neuropathy", which includes a sub-search for "demyelination".

No new cases have been reported in other indications, in addition to the three cases discussed during the original MAA. Peripheral neuropathy remains a potential risk of spesolimab.

Hepatic injury

In the GPP trials 1368-0027, 1368-0025, and 1368-0011, none of the patients were reported with an AESI of hepatic injury.

In trial 1368-0013, 1 patient in the spesolimab group was reported with an AESI of hepatic injury (PTs DRESS and DILI) after one spesolimab dose (treatment of GPP flare). This case was discussed during the original MAA. Although the hepatic injury was assessed as drug related by the investigator, the time course of transaminase elevations and the patient's history of prior reaction to cephalosporins, argue for the concomitantly administered cefuroxime as a potential suspect medication for having caused DILI in this case.

Although in all pooled GPP trials individual patients (7 of 181 patients, 3.9%) had elevations of ALT and/or AST ≥3×ULN, none of the patients had these transaminase elevations together with relevant elevations of AP (≥3×ULN and 2×baseline) and total bilirubin (≥2×ULN and 1.5×baseline) that could indicate a potential Hy's law case.

When also taking the available data from 13 trials in non-GPP conditions into account, the MAH suggests there is no indication for a hepatotoxic effect of spesolimab.

2.6.8.4. Laboratory findings

Within the randomised maintenance treatment period of trial 0027, the number of patients without potential clinically significant abnormalities (PCSA; i.e. who were within normal range at baseline) and then had PCSA (i.e. shifted to either below or above limits of normal) was generally low and occurred with similar frequencies between the spesolimab dose groups and the placebo group for almost all analysed laboratory parameters (i.e. haematology, differentials, coagulation parameters, electrolytes, hepatic and renal parameters, urinalysis, enzyme, substrates, and proteins). For triglycerides, around a fourth of patients without PCSA at baseline had PCSA within the randomised maintenance treatment period, with similar proportions across the spesolimab dose groups and the placebo group. From baseline to end- of treatment, no marked increases or decreases of mean values were observed for any parameter. Post-any spesolimab use, there were no new safety findings.

In trial 0025, the number of patients who were within normal range and then shifted to either below or above limits of normal was generally low. The number of patients with possibly clinically significant abnormalities (PCSA) in laboratory values during the treatment period who did not have any PCSA at baseline was also low. From baseline to end of treatment, no marked increases or decreases of mean values were observed for any parameter.

In the spesolimab overall group for all pooled clinical GPP trials, the proportions of patients without PCSA of laboratory values at baseline who shifted to either low or high PCSA values during the trial were generally very low, except for triglycerides and CRP. As described above, for triglycerides, data from the placebo-controlled trial 1368-0027 showed that similar proportions of patients without PCSA at baseline had PCSA within the randomised treatment periods across the spesolimab dose groups and the placebo group. Moreover, descriptive statistics over time, did not show a trend for a treatment effect. For CRP, high values are a known finding related to the occurrence of GPP flares.

Local tolerability

In trial 0027, 16 patients (17.2%) were reported with local tolerability symptoms after spesolimab injection and 2 patients (6.7%) after placebo. After spesolimab injection: 5 patients (15.6%) in the spesolimab low dose group, 5 patients (16.1%) in the spesolimab medium dose group, and 6 patients (20.0%) in the spesolimab high dose group reported local tolerability symptoms. The most common local tolerability symptom was injection site redness, which was reported in 13 patients (14.0%) after spesolimab injection and 1 patient (3.3%) after placebo. Injection site redness was reported with some dose-dependency after spesolimab injection: 3 patients (9.4%) in the spesolimab low dose group, 4 patients (12.9%) in the spesolimab medium dose group, and 6 patients (20.0%) in the spesolimab high dose group.

All of the local tolerability symptoms in the placebo, spesolimab low dose, and spesolimab medium dose groups were grade 1/mild. One isolated grade 2/moderate local tolerability symptom of injection site urticaria was reported in a patient in the spesolimab high dose group.

Adverse drug reactions for the label

Table 43. Criteria for identification of potential new ADRs

Trials considered		Trial number (condition)	Assessment period (up to)	Data considered
Criterion 1				
Pivotal GPP flare prevention trial		1368-0027 (GPP)	48 weeks	• AEs in ≥3 patients in spesolimab low dose or medium dose or high dose or total + RR >1
Supportive to criterion 1				
Supportive data from all GPP trials		1368-0027, 1368-0025, 1368-0011, 1368-0013 (GPP)	Cut-off date/ end of REP	• Safety data from sensitivity analysis in trial 1368-0027 (excl. 6 days prior to i.v. flare treatment)[1,2] • Safety assessment in trial 1368-0025[2] • Safety assessment in pool of all GPP trials[2]
Criteria 2 and 3				
Other double-blind placebo-controlled trials	***Criterion 2*** ≥100 pts on spesolimab	1368-0016 (PPP)	16 weeks	• AE frequency in spesolimab total ≥5% + RR >1 • AE frequency in spesolimab total ≥2% + RR ≥2
	Criterion 3 15 to <100 pts on spesolimab	1368-0013 (GPP)	1 + 12 weeks	• AE frequency in spesolimab total ≥5% + RR ≥2
		1368-0015 (PPP)	End of REP	
		1368-0032 (AD)	16 weeks	
		1368-0052 (HS)	12 weeks	
		1368-0005 (UC)	12 weeks	
		1368-0010 (UC)	End of REP	
		1368-0008 (CD)	12 weeks	
Supportive to all criteria				
Supportive data from all trials included in the MAA dossier				• All AEs, with a focus on SAEs, Designated Medical Events, and UDAECs[2]
		Completed trials	End of REP	
		Ongoing trials	Cut-off date	

RR = risk ratio for spesolimab vs. placebo
1 To account for events that might reflect the prodromal stage of a flare
2 Descriptively supportive

To identify potential new ADRs of spesolimab in patients with GPP, all safety data for completed and ongoing trials available at the cut-off date (01 Dec 2022) were checked against the criteria for the identification of potential new ADRs summarised in *Table 43*. All completed double-blind placebo-controlled trials, were analysed systematically for imbalances between the spesolimab and the placebo treatment groups.

The focus of ADR detection was on the randomised maintenance period of trial 1368-0027 (criterion 1 in *Table 43*). Supportive data from the pool of all GPP trials were also considered. The placebo-controlled trials in non-GPP conditions were analysed applying criteria 2 or 3 in *Table 43*. In addition, the complete set of trials with spesolimab included in this MAA dossier, including the post-placebo-

controlled periods of the above-mentioned trials as well as the OLE trials in all conditions, was screened for all AEs, with a special focus on SAEs, designated medical events, and UDAECs.

All events/medical concepts that met the criteria for the identification of potential new ADRs on trial level 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 data, vital signs, and dedicated pharmacokinetic/dynamic analyses. Relevant aspects for the determination of a causal association were considered, including mechanistic plausibility, time to onset, and lack of confounding factors or alternative explanations. Numerical consistency across trials was also taken into consideration.

Table 44 summarises those events/medical concepts (PTs or PT groupings):

- That met any of the criteria described above in at least 2 of the 9 double-blind placebo-controlled trials and
- For which the number of trials where the respective PTs or PT groupings were more frequent for spesolimab than placebo was higher as compared to the number of trials where the respective PT/PT grouping were less frequent for spesolimab than placebo.

Based on the methods described above, no new ADRs in addition to those already known in the treatment of GPP flares that are specific to spesolimab s.c. for GPP flare prevention were identified.

Table 44. Events/medical concepts that met any of the criteria 1 to 3 for identification of potential new ADRs in ≥2 double-blind placebo-controlled trials and had a higher frequency for spesolimab than placebo in more trials than vice versa

Medical concept	ADR detection criteria met in N of 9 trials	Comments
Acne[1]	4	Low frequency in GPP pool, high background incidence, no dose-dependency, no mechanistic plausibility (pustular reduction by spesolimab); on trial level reported with higher frequency for spesolimab vs. placebo in 4 dermatological and 2 IBD trials
Headache[1]	4	Inconsistent finding[2], high background incidence, concurrent AEs as alternative explanations (e.g. toothache, eye inflammation, GPP flare), no pattern in time to onset
Pyrexia[1]	3	Inconsistent finding[2], not confirmed by measurement of body temperature as vital sign, mostly in close temporal relationship to GPP flare/COVID-19 vaccination/upper respiratory or urinary tract infection
Diarrhoea[1]	3	This gastrointestinal disorder was reported on trial level with higher frequency for spesolimab vs. placebo in more dermatological trials (N=4) than in IBD trials (N=1); however, reported in a low number of patients. Inconsistent finding[2], high background incidence, no dose-dependency
Psoriasis[1]	3	Reported exclusively in dermatological trials (with most cases in GPP trial 1368-0027, where frequency of psoriasis at baseline was high), no dose-dependency
Arthralgia[1]	2	Inconsistent finding[2], alternative explanations in concurrent conditions (e.g. GPP, general pain conditions, etc.) or medical history (e.g. obesity, psoriatic arthropathy, synovitis, decreased bone density), no dose-dependency, highly variable time to onset (2 days to >2 years)
Back pain[1]	2	Inconsistent finding[2], low frequency in GPP pool, high background incidence, no dose-dependency
Hypertension[1]	2	Inconsistent finding[2], not confirmed by measurement of blood pressure as vital sign, high background incidence, no dose-dependency, low numbers and difference to placebo in individual trials
Viral infectious disorders[3]	2	Inconsistent finding[2], high background incidence, no specific pattern
Gastrointestinal infection[3]	2	Inconsistent finding[2]; reported with highest frequency in a small IBD trial (UC: 1368-0010), i.e. confounded by the indication, and with very low numbers across all trials
Skin infection[3]	2	Inconsistent finding[2], low numbers and small difference to placebo in individual trials; on trial level reported with higher frequency for spesolimab vs. placebo in 4 dermatological trials (i.e. the condition might be a risk factor)
Injection site reactions – procedural[3]	2	Inconsistent finding[2], overall very low numbers (2 for placebo and 6 for spesolimab-treated subjects across all trials)

[1] PT,
[2] In at least 1 trial, the proportion of patients with the respective PT/PT grouping was higher in the placebo group than in the spesolimab group,
[3] PT grouping

2.6.8.5. Safety in special populations

In trial 1368-0027, AEs during the randomised maintenance treatment period as well as post-any spesolimab treatment were analysed in subgroups as defined in *Table 45*, except for subgroups with too few patients: As no patients with hepatic impairment were included in the trial, the analysis by hepatic impairment status was not performed. All patients were Asian or White, therefore the analysis by race included only these 2 race categories.

Table 45. Definition of subgroup analyses for safety in trial 1368 0027

Subgroup	Categories
Sex	Female vs. male
Age	<65 years vs. ≥65 years
Adolescent vs. adult	12 to <18 years vs. ≥18 years
Race	Asian vs. White vs. Other[4]
Body mass index (BMI)	<25 vs. 25 to <30 vs. ≥30 kg/m^2
Weight	<53.8 kg vs. 53.8 to <91 kg vs. ≥91 kg[1]
Ongoing plaque psoriasis at baseline	Yes vs. no
Baseline GPPGA total score	0 vs. 1
Use of systemic GPP medication at randomisation	Yes vs. no
Mutation status in IL-36RN	Yes vs. no
Renal impairment[2]	Normal renal function vs. mild vs. moderate[4] vs. severe[4] impairment vs. ESRD[4]
Hepatic impairment	Yes[3,4] vs. no

Subgroup analyses performed
1 Based on the body weight values corresponding to the range of 80% to 125% of steady-state $AUC_{0-\tau}$ (any dosing regimen) using 70 kg as reference according to the population PK model
2 For adults, based on eGFR applying CKD-EPI formula: normal renal function (stage 1) ≥90 mL/min/1.73m^2, mild decrease in GFR (stage 2) = 60-89 mL/min/1.73m^2, moderate decrease in GFR (stage 3) = 30-59 mL/min/1.73m^2, severe decrease in GFR (stage 4) = 15-29 mL/min/1.73m^2, end stage renal disease (stage 5) = <15 mL/min/1.73m^2 not on dialysis or requiring dialysis. For adolescents, Bedside Schwartz equation was applied.
3 Defined as International Normalised ratio ≥2.2 and total serum bilirubin >51.3 µmol/L
4 Number of patients in this category <8

In addition, the following subgroups were analysed for the pooled safety data from all GPP trials (SAF-ISS3p): sex, age (including additionally the categories <50 years vs. 50 to <65 years vs. 65 to <75 years vs. ≥75 years), race, BMI, weight, region (USA/Canada vs. Asia vs. Europe vs. Rest of World), ongoing plaque psoriasis at baseline, and concomitant immunosuppressant use (yes vs. no).

The trends in frequencies and incidence rates of AEs between spesolimab and placebo for the subgroups were generally consistent with those of the overall population of the trial, with the limitation of small group sizes for some subgroups.

There was no indication of differences between the categories in the subgroups of sex, age, race, plaque psoriasis at baseline, IL-36RN mutation status, BMI, weight, or renal function. However, the sample sizes within subgroups were relatively small and there were imbalances between the subgroups in multiple categories. Consequently, AEs and SAEs tended to be reported more frequently in the subgroups with higher numbers of patients.

Considering these limitations, possible differences were observed in the rate of AEs between patients with systemic GPP medication at randomisation (yes vs. no) and who received spesolimab of 501.9 vs. 196.1/100 patient-years; however, for patients with systemic GPP medications use at randomisation, the rates of AEs were comparable between spesolimab and placebo (501.9 vs. 421.2/100 patient-

years). In this subgroup, for patients treated with spesolimab, there was no difference in the rate of SAEs (13.2 vs. 11.9/100 patient-years).

Similarly, SAEs were reported at a higher rate in patients with baseline GPPGA total score of 1 at baseline (15.1/100 patient-years) than in patients with baseline GPPGA total score of 0 (0/100 patient-years), which could reflect patients with greater severity of GPP. Of note, the number of patients with a GPPGA total score of 0 at baseline was small.

Adolescents

Altogether 8 adolescents, aged 14 to 17 years at randomisation, have been included in the spesolimab development program. All were included in the GPP prevention study 0027, with 2 subjects per dose group, including placebo. Of these, 7 continued to the extension trial 0025. One of the subjects in the placebo group did not continue. Therefore, a total of 7 adolescent subjects have been exposed to spesolimab. The total time at risk for the 7 adolescents who were exposed to spesolimab was 8.9 years, i.e. a mean of 1.3 years per subject.

Within the randomised maintenance treatment period of Trial 0027, all of the 8 adolescent patients were reported with AEs. In the spesolimab groups, the exposure-adjusted incidence rates were lower in adolescents than in adults.

All AEs were non-serious, except for 1 case of community-acquired pneumonia in a patient in the spesolimab low dose group, which belonged to the UDAEC "infections all" and is discussed in more detail in the section of UDAECs above. Non-serious AEs under the SOC "infections and infestations" were reported in 1 patient of the spesolimab low dose group, 2 patients of the spesolimab medium dose group, and 1 patient each in the spesolimab high dose group and the placebo group. The other non-serious AEs in the spesolimab dose groups were distributed across different SOCs; 1 non-serious case of dermatitis in a patient in the spesolimab low dose group was categorised as UDAEC "hypersensitivity all". This patient in the spesolimab low dose group, who was reported with dermatitis after ADA development, and another patient in the spesolimab high dose group, with no potential hypersensitivity event, were the only adolescent patients who developed ADA.

None of the AEs led to discontinuation of trial medication.

Among the 7 patients continuing to trial 1368-0025, 3 patients were reported with non-serious AEs (exacerbation of psoriasis: 1 patient, acne and plaque psoriasis: 1 patient, folliculitis pityrosporon: 1 patient). All AEs reported in adolescent patients in trials 1368-0027 and 1368-0025 are listed in Table 46.

Table 46. Listing of AEs in adolescent patients in trials 1368-0027 and 1368-0025

Patient no. 1368-0027 *Roll over*	Age [years]/ Sex/body weight [kg]	Treatment at AE onset	Lowest level term	Start-stop date	Re-lated	Action with drug	Treatment/ outcome	Serious	Comment
Initial randomization in trial 1368-0027: Placebo									
continued in OLE trial		Placebo	Injection site redness, warmth Pain injection site	1-1	Yes	None	No/Rec	-	
			Fatigue, headache, nausea	8-11	-	None	No/Rec	-	
			Exacerbation of psoriasis	148-394[1]	-	None	Yes/Not Rec	-	
			COVID-19	154-164	-	None	Yes/Rec	-	
			Hypertriglyceridaemia	176-204	-	None	No/Rec	-	
			RBC urine positive	204-287	-	None	No/Rec	-	
			Indeterminate tuberculosis test	344-393	-	None	No/Rec	-	2 indeterminate Quantiferon tests; PCR TB in sputum and 3rd Quantiferon neg.
did not continue in OLE trial		Placebo	Pustular psoriasis	2-85	-	None	Yes/Rec	-	Family's decision to stop study drug
Initial randomization in trial 1368-0027: Spesolimab low dose									
continued in OLE trial		Speso low dose	Dermatitis NOS[2]	130-321	-	None	Yes/Rec	-	
			Plaque psoriasis	168-856[1]	-	None	Yes/Not Rec	-	
			Community-acquired pneumonia[2]	208-230	Yes	None	Yes/Rec	Yes	No pathogen identified. No known risk factors.
		1368-0025: Speso 300 mg q12w	Exacerbation of psoriasis	361-856	-	None	Yes/Not Rec	-	
continued in OLE trial		Spesolimab low dose	Furuncle	139-141	-	None	Yes/Rec with sequelae	-	
			Folliculitis	141-150	-	None	Yes/Rec	-	
			Upper respiratory tract infection	252-254	-	None	Yes/Rec	-	
Initial randomization in trial 1368-0027: spesolimab medium dose									
continued in OLE trial		Speso medium dose	Upper respiratory tract infection	280-284	-	None	Yes/Rec	-	
			Skin erythema desquamative	283-335	-	None	No/Not Rec	-	
		1368-0025: Speso 300 mg q12w	Acne	601-846	-	None	Yes/Not Rec	-	
			Plaque psoriasis	649-846	-	None	No/Not Rec	-	
continued in OLE trial		Speso medium dose	Headache	112-113	-	None	Yes/Rec	-	
			Hyperuricaemia	198-225	-	None	No/Rec	-	
			Common cold	295-303	-	None	Yes/Rec	-	
			Upper respiratory tract infection	330-331	Yes	None	Yes/Rec	-	
Initial randomization in trial 1368-0027: spesolimab high dose									
continued in OLE trial		Speso high dose	Hyperglycemia	171-437[1]	-	None	No/Not Rec	-	Patient was advised to do a healthy life-style
			Dog bite	277-284	-	None	Yes/Rec	-	
		1368-0025: Speso 300 mg q12w	Folliculitis pityrosporon	423-431	-	None	No/Rec	-	
continued in OLE trial		Speso high dose	Pain injection site	2-4	Yes	None	No/Rec	-	
			Injection site redness	120-120	Yes	None	No/Rec	-	
			Injection site erythema	141-141, 172-172, 197-197, 261-261	Yes	None	No/Rec	-	

1 Partial or missing date imputed
2 Categorized as UDAEC

2.6.8.6. Immunological events

In all trials in patients with GPP and other diseases, ADAs were tested. NAb were assessed in all patient trials in GPP and other dermatological indications, except trials 1368-0011 and 1368-0015, and in trial 1368-0008 in patients with fistulising CD.

The influence of ADA and NAb formation on safety in the clinical trials was mainly assessed based on AEs grouped to the UDAEC "hypersensitivity all".

All findings that were available by the cut-off date of the GPP flare treatment submission was summarised in the ISI for GPP flare treatment and discussed during the original MAA. In summary, 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. Population PK analysis indicated that ADA titers > 4000 may lead to decreased plasma concentrations. A total of 24% of patients had a maximum ADA titer greater than 4000. Across studies, the frequency and incidence rate of hypersensitivity events was comparable before and after ADA/NAb development. 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.

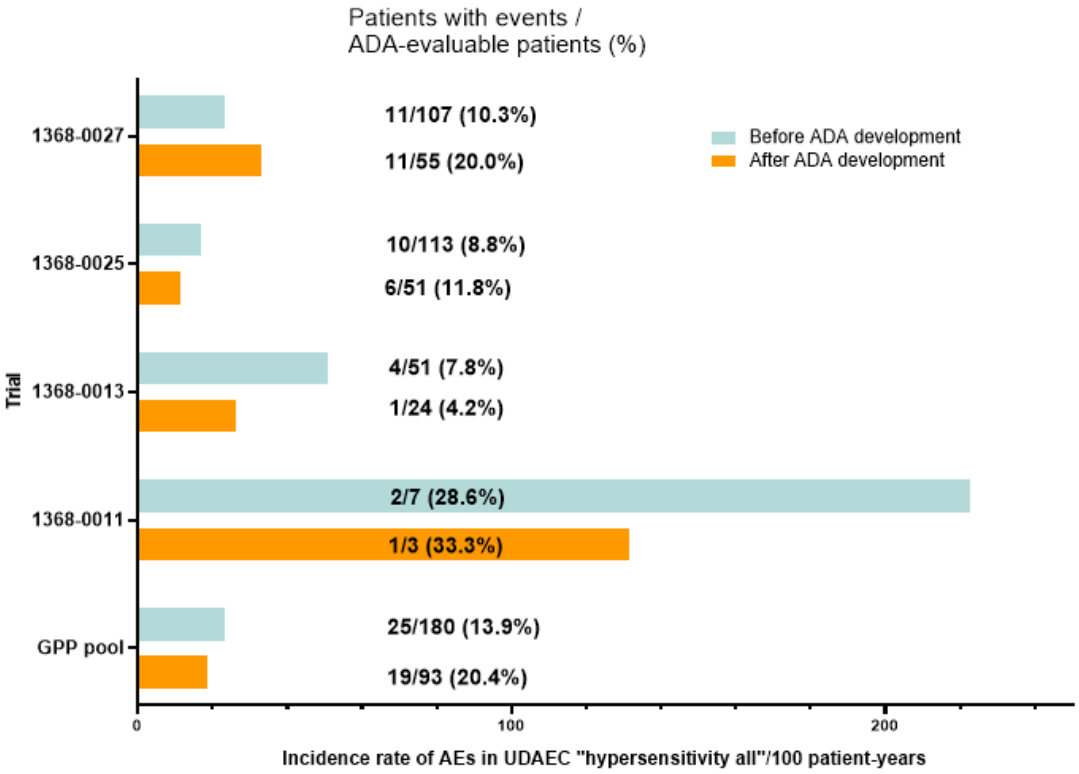
In the randomised maintenance treatment period of trial 1368-0027, the proportions and time-adjusted incidence rates of AEs grouped to the UDAEC "hypersensitivity all" were comparable before and after ADA development in each of the spesolimab dose groups, with a trend to lower numbers of patients with ADA in the higher dose groups (*Table 47*). The same trend was seen for NAb vs. AEs grouped to the UDAEC "hypersensitivity all".

Table 47. Trial 1368-0027: Immunogenicity of spesolimab

	N (%)			
	High dose[1]	Medium dose[1]	Low dose[1]	Placebo[1] who received rescue i.v. spesolimab (possibly followed by s.c. speso trt)
Total[2]	29 (100%)	31 (100%)	31 (100%)	15 (100%)
Baseline[3] ADA positive	0 (0%)	0 (0%)	2 (6%)	0
ADA negative[4]	17 (59%)	10 (32%)	16 (52%)	8 (53%)
Treatment-induced or boosted ADA positive[5]	12 (41%)	21 (68%)	14 (45%)	7 (47%)
Transient positive[6]	2 (7%)	2 (6%)	1 (3%)	0 (0%)
Potentially persistent positive[7]	2 (7%)	1 (3%)	2 (6%)	1 (7%)
Persistent positive[8]	8 (28%)	18 (58%)	11 (35%)	6 (40%)
Patients with maximum titer >4000	7 (24%)	18 (58%)	6 (19%)	6 (40%)
Patients with maximum titer >4000 and NAb positive	7 (24%)	18 (58%)	6 (19%)	6 (40%)
Last sample ADA positive	10 (34%)	18 (58%)	10 (32%)	7 (47%)
ADA onset [week]*	8.0 (3.6, 24.0)	8.0 (1.1, 12.6)	10.6 (4.0, 24.0)	3.9 (1.0, 8.6)[10]
Time of maximum titer [week]*	20.4 (3.6, 33.0)	18.7 (2.1, 47.0)	21.6 (4.0, 40.0)	25.6 (11.6, 42.0)[10]
Maximum titer*	5760 (180 - 115 000)	28800 (180 - 5 760 000)	2160 (180 - 173 000)	11500 (2880 - 173 000)
Treatment-induced NAb positive[9]	10 (34%)	21 (68%)	14 (45%)	7 (47%)
NAb onset [week]*	10.2 (4.0, 24.0)	8.7 (1.1, 20.0)	11.9 (8.0, 24.0)	8.4 (1.0, 11.5)
Last sample NAb positive	8 (28%)	16 (52%)	8 (26%)	6 (40%)

[1] anyone randomized to the spesolimab treatment groups; for patients randomized to placebo, only those who received rescue i.v. spesolimab treatment. Note that one patient randomized to placebo incorrectly received a single s.c. spesolimab 150 mg on Day 1. This patient [redacted] also received i.v. spesolimab treatment and was ADA and NAb-positive.
[2] spesolimab treated and ADA-evaluable
[3] last sample obtained before initiation of active spesolimab treatment
[4,5,6,7,8,9]: as defined in the MAH's integrated summary of immunogenicity
[10] relative to the first active spesolimab dosing. Relative to the start of the study, the median (range) for the ADA onset and time of maximum titer were 8.6 (2.4, 38.0) weeks and 30.0 (14.6, 45.7) weeks, as reported in the CTR.
*Median (min, max)

When taking the results post-any spesolimab use in all trials included in this MAA into account, in most trials, the frequency and incidence rate of hypersensitivity events was comparable before and after ADA/NAb development. The same was true post-any spesolimab across all GPP trials as well as for the pool of all GPP trials; see **Figure 29**. In addition, swimmer plots including information on time to first ADA/NAb development and time to first occurrence of hypersensitivity AEs and local tolerability events (if applicable) were reviewed for all patients from all GPP trials. In summary, there was no indication for a relationship between potential hypersensitivity events and the presence of ADA/NAb.



Hypersensitivity events = AEs in UDAEC "hypersensitivity all". Before ADA development: patients with hypersensitivity event before their first ADA positive sample or without ADA positive samples throughout. After ADA development: patients with hypersensitivity event from the time point of their first ADA positive sample onwards.

Figure 29. Summary of exposure-adjusted incidence rate of hypersensitivity events post-any spesolimab use by ADA development across spesolimab trials in patients with GPP (individual trials and pooled).

2.6.8.7. Safety related to drug-drug interactions and other interactions

Up to now, no formal drug interaction trials with spesolimab have been performed.

Concomitant immunosuppressants

GPP trials

In GPP trials, concomitant immunosuppressants (including corticosteroids, methotrexate, ciclosporin, and biologics) were used by 81/181 (44.8%) of the patients in the spesolimab overall group (by parent trial 1368-0027: 35.5%, by parent trial 1368-0013: 66%) during treatment.

An overview of AEs in the GPP trials in patients with or without concomitant immunosuppressants is shown in *Table 48*.

Table 48. Overall summary of treatment−emergent adverse events, by concomitant immunosuppressant use in GPP trials

	Concomitant Immunosuppressant Use: No				Yes			
	Speso Overall				Speso Overall			
	N	%	Time at risk [pt-yrs]	Rate/100 pt-yrs	N	%	Time at risk [pt-yrs]	Rate/100 pt-yrs
Number of subjects	100	100.0	135.3		81	100.0	109.1	
Subjects with any AE	87	87.0	27.5	316.4	79	97.5	8.6	920.4
Subjects with severe AEs (RCTC grade 3 or 4)	11	11.0	124.4	8.8	29	35.8	73.6	39.4
Subjects with investigator defined drug-related AEs	39	39.0	85.4	45.7	52	64.2	40.2	129.4
Subjects with AEs leading to discontinuation of trial drug	3	3.0	134.7	2.2	8	9.9	106.8	7.5
Subjects with AESIs	3	3.0	131.2	2.3	2	2.5	105.9	1.9
Subjects with serious AEs	17	17.0	118.8	14.3	21	25.9	76.5	27.4
Results in Death	0		135.3	0.0	0		109.1	0.0
Is Life Threatening	2	2.0	134.2	1.5	1	1.2	108.4	0.9
Persist or Signif Disability/Incapacity	0		135.3	0.0	0		109.1	0.0
Requires or Prolongs Hospitalization	14	14.0	120.3	11.6	18	22.2	77.2	23.3
Congenital Anomaly or Birth Defect	0		135.3	0.0	0		109.1	0.0
Other Medically Important Serious Event	4	4.0	133.0	3.0	3	3.7	108.4	2.8
Subjects with other significant AEs (according to project definition)	1	1.0	135.0	0.7	6	7.4	107.4	5.6

A comparison with placebo is shown in *Table 49*.

Table 49. Event rate before/without and with use of non-topical immunosuppressants in the pre-flare period of trial 1368-0027 – GPP prevention trial

	Placebo			Spesolimab s.c. overall		
	N (%)[1]	Time at risk (Pt-yrs)[2]	Rate/ 100 Pt-yrs[3]	N (%)[1]	Time at risk (Pt-yrs)[2]	Rate/ 100 Pt-yrs[3]
Total number of patients[4]	30			93		
Patients before[5,6] or without IS use	14 (100.0)			56 (100.0)		
Patients with event before[5,6] or without IS use						
Any AE	11 (78.6)	2.9	384.5	45 (80.4)	15.3	293.7
Severe AEs (RCTC grade 3 or 4)	4 (28.6)	5.1	78.5	6 (10.7)	40.0	15.0
SAEs	1 (7.1)	6.0	16.8	4 (7.1)	40.0	10.0
AEs in the SOC infections and infestations	3 (21.4)	5.7	52.7	16 (28.6)	32.9	48.6
AEs in the UDAEC infections all	0	6.3	0	1 (1.8)	40.1	2.5
Patients with IS use[6,7]	19 (100.0)			44 (100.0)		
Patients with event after IS use[6,7]						
Any AE	15 (78.9)	3.5	423.7	39 (88.6)	6.7	580.0
Severe AEs (RCTC grade 3 or 4)	2 (10.5)	9.6	20.9	8 (18.2)	24.6	32.5
SAEs	0	10.5	0	4 (9.1)	25.5	15.7
AEs in the SOC infections and infestations	6 (31.6)	7.1	84.4	14 (31.8)	18.8	74.6
AEs in the UDAEC infections all	0	10.5	0	2 (4.5)	25.8	7.8

EoS = End of study, IS = immunosuppressant, OL(E) = open-label (extension), pt-yrs = patient-years
1 Percentages are calculated using total number of patients in the category/treatment class as the denominator
2 Patients with AE: start of 1st AE - start of period + 1 day; patients without AE: end of time at risk - start of period + 1 day
3 Number of patients with the respective events per treatment divided by time at risk expressed as [100 patient-years]
4 Total number of patients refers to patients with and without immunosuppressant use
5 Pre-IS period: AE from 1st treatment administration to (day 337, the day before any OL spesolimab i.v. rescue dose, the last randomised treatment + 112 days before 1st IS use if applicable, day of EoS if patients were not rolled over, or day before first dose in OLE study if pts were rolled over)
6 A patient can be included in both categories
7 Post-IS period: 1st IS administration to (day 337, the day before any OL spesolimab i.v. rescue dose, the last randomised treatment + 112 days, the day of EoS if patients were not rolled over, or the day before 1st dose in OLE study if patients were rolled over). For patients with 1st IS taken on or before 1st treatment dose, only the post-IS period can be defined for AE reporting. IS use excludes IS use >14 days before 1st dose of trial medication

Trials in other indications

In PPP trials, concomitant immunosuppressants were used by 25/108 (23.1%) patients during treatment. In the HS extension trial 0067, concomitant immunosuppressants were used by 12/45 (26.7%) patients during treatment. In the UC extension trial 0017, concomitant immunosuppressants were used by73/79 (92.4%) patients during treatment. Patients in AD and CD trials did not receive concomitant immunosuppressants.

Comparison with placebo

An overview of AEs by concomitant immunosuppressant use in all placebo-controlled trials with spesolimab is shown in *Table 50*.

Table 50. Event rate before/without and with use of non-topical immuno-suppressants in the pool of all placebo-controlled trials included in SAF-ISS1p

	Placebo			Spesolimab overall		
	N (%)[1]	Time at risk (Pt-yrs)[2]	Rate/ 100 Pt-yrs[3]	N (%)[1]	Time at risk (Pt-yrs)[2]	Rate/ 100 Pt-yrs[3]
Total number of patients[4]	185			445		
Patients before[5,6] or without IS use[8]	122 (100.0)			308 (100.0)		
Patients with event before[5,6] or without IS use						
Any AE	94 (77.0)	13.7	687.1	235 (76.3)	39.9	589.0
Severe AEs (RCTC grade 3 or 4)	9 (7.4)	32.7	27.5	23 (7.5)	101.8	22.6
SAEs	7 (5.7)	33.7	20.8	16 (5.2)	102.6	15.6
AEs in the SOC infections and infestations	35 (28.7)	26.0	134.5	87 (28.2)	82.4	105.6
AEs in the UDAEC infections all	0	34.7	0	2 (0.6)	103.9	1.9
Patients with IS use[6,7]	82 (100.0)			181 (100.0)		
Patients with event after IS use[6,7]						
Any AE	57 (69.5)	9.9	577.5	129 (71.3)	22.7	568.0
Severe AEs (RCTC grade 3 or 4)	15 (18.3)	21.3	70.4	18 (9.9)	54.3	33.1
SAEs	7 (8.5)	23.6	29.7	13 (7.2)	55.4	23.5
AEs in the SOC infections and infestations	19 (23.2)	18.0	105.6	54 (29.8)	45.2	119.3
AEs in the UDAEC infections all	2 (2.4)	23.8	8.4	2 (1.1)	57.0	3.5

EoS = End of study, IS = immunosuppressant, OL(E) = open-label (extension), pt-yrs = patient-years
1 Percentages are calculated using total number of subjects in the category/treatment class as the denominator
2 Patients with AE: start of 1st AE - start of period + 1 day; patients without AE: end of time at risk - start of period + 1 day
3 Number of patients with the respective events per treatment divided by time at risk expressed as [100 patient-years]
4 Total number of patients refers to patients with and without immunosuppressant use
5 Pre-IS period: AE from 1st treatment administration to (day before 1st IS use if applicable, end of treatment period)
6 A patient can be included in both categories
7 Post-IS period: 1st IS administration to end of treatment period. For patients with 1st IS taken on or before 1st treatment dose, only the post-IS period can be defined for AE reporting. IS use excludes IS use >14 days before 1st dose of trial medication

2.6.8.8. Discontinuation due to adverse events

During the randomised period of trial 0027, three patients in the spesolimab high dose group and 2 patients in the spesolimab medium dose groups vs. none of the patients in the spesolimab low dose or placebo groups were reported with AEs leading to discontinuation (*Table 51*). Pustular psoriasis (potentially reflective of a GPP flare) was reported for 2 patients (1 patient each in the spesolimab high and medium dose groups). The other AEs leading to discontinuation of trial medication were individual occurrences (*Table 51*).

After any treatment with spesolimab (s.c. or i.v., randomised or open-label), 4 additional patients reported with AEs leading to discontinuation from either the OL i.v. flare treatment period (1 patient [0.9%] each with pustular psoriasis, erythema, or guttate psoriasis) or the OL s.c. MT period (1 patient [0.9%] with pustular psoriasis).

Table 51. AEs leading to discontinuation of trial medication in trial 1368-0027 within randomised maintenance treatment period.

SOC PT	Placebo		Spesolimab s.c.							
			Low dose (LD 300 mg, 150 mg q12w)		Medium dose (LD 600 mg, 300 mg q12w)		High dose (LD 600 mg 300 mg q4w)		Total	
	N (%)	Rate/ 100 pt-yrs	N (%)	Rate/ 100 pt-yrs	N (%)	Rate/ 100 pt-yrs	N (%)	Rate/ 100 pt-yrs	N (%)	Rate/ 100 pt-yrs
Number of patients	30 (100.0)		32 (100.0)		31 (100.0)		30 (100.0)		93 (100.0)	
Patients with any AEs leading to discontinuation[1]	0	0	0	0	2 (6.5)	8.9	3 (10.0)	12.9	5 (5.4)	7.1
Skin and s.c. tissue disorders	0	0	0	0	1 (3.2)	4.4	2 (6.7)	8.6	3 (3.2)	4.2
Pustular psoriasis	0	0	0	0	1 (3.2)[2]	4.4	1 (3.3)	4.2	2 (2.2)	2.8
Psoriasis	0	0	0	0	0	0	1 (3.3)	4.2	1 (1.1)	1.4
Neoplasms[3]	0	0	0	0	0	0	1 (3.3)	4.2	1 (1.1)	1.4
Breast cancer	0	0	0	0	0	0	1 (3.3)	4.2	1 (1.1)	1.4
Musculoskeletal and connective tissue disorders	0	0	0	0	1 (3.2)	4.4	0	0	1 (1.1)	1.4
Psoriatic arthropathy	0	0	0	0	1 (3.2)	4.4	0	0	1 (1.1)	1.4

All AEs starting up to the end of time at risk are included. Time at risk: Patients with AEs: start of first AE – start of treatment + 1 day, patients without AE: end of time at risk – start of treatment + 1 day. End of time at risk: the earliest of
(i) date/time before the start of flare rescue treatment with spesolimab i.v.
(ii) date/time of the end of last randomized treatment +112 days
(iii) date/time before the first treatment in OLE trial 1368-0025 if patient rolled over
(iv) last contact date on EoS page if patient did not roll over

1 Of trial medication

2 Patient [redacted] discontinued from the flare treatment period due to pustular psoriasis with onset during the randomized maintenance treatment period (Day 15). This patient received the first dose of spesolimab s.c. on Day 1 and a dose of spesolimab i.v. for flare treatment on Day 29. The AE leading to discontinuation was counted in the randomized maintenance treatment period

3 SOC "Neoplasms benign, malignant and unspecified (incl cysts and polyps)"

In trial 0025, AEs leading to discontinuation of trial medication were reported for 2 patients (1.6%); the respective PTs were adenocarcinoma and psoriasis, reported for 1 patient each (0.8%).

Administration of spesolimab was a single i.v. administration in trial 1368-0011 and a single or double dose i.v. administration in trial 1368-0013; in both trials, none of the patients was reported with AEs leading to discontinuation of trial medication.

2.6.8.9. Post marketing experience

No new safety issues were identified during assessment of the latest PSUR (data lock point 01 Sep 2023).

2.6.9. Discussion on clinical safety

During the original MAA for the intravenous formulation of spesolimab, it was concluded that in placebo-controlled trials with spesolimab in different indications, there were few notable differences in adverse events profile between treatment groups. The most notable exception was infections, which was in many studies more commonly reported in spesolimab-treated patients than in the placebo groups. The data included in the original MAA further showed that, except for AEs attributed to the underlying disease, the AE profile was largely similar and manageable across studies and indications, including studies with subcutaneous maintenance treatment. Altogether, the previous safety assessment did not give raise to any major safety concerns regarding the administration of one or two doses of 900 mg IV spesolimab for the treatment of adult patients with a GPP flare.

In support of the safety evaluation for the new route of administration, the new, continuous dose regimen and the new patient population (adolescents) proposed in the current application for prevention of GPP flares, the MAH primarily refers to the placebo-controlled, dose-finding trial 0027 and the open-label extension trial 0025, both with subcutaneous administration of spesolimab for prevention of GPP flares.

In the pivotal trial (0027), three different doses of spesolimab were tested: a loading dose (LD) of 300 mg followed by 150 mg q12w; LD of 600 mg followed by 300 mg q12w; and LD 600 mg followed by 300 mg q4w, respectively. The highest dose, a LD of 600 mg followed by 300 mg q4w, was chosen for the extension trial (0025) and is also the recommended dose in the SmPC. The number of subjects in the GPP trials that were treated at the high maintenance dose is small: a total of 30 patients in the pivotal trial and 23 patients in the extension trial. There is some overlap between the 30 patients treated at the high dose in study 0027 and the 23 patients treated at this dose in the extension study. Data for the lower doses in trial 0027 is considered supportive.

Data on maintenance treatment with the high dose or higher (300 mg or 600 mg every 4 week) is, however, available from studies in other indications. Across studies, a total of 589 subjects have been exposed to at least one dose of spesolimab. Data on long-term treatment with spesolimab (> 1 year) is available from a total of 295 patients (113 with GPP) through the different studies and indications. A majority of the 295 patients have received doses of 300 mg q4w or higher, although mostly in studies in other indications than GPP. As previous and currently available data indicate that the safety profile of spesolimab is similar across indications, safety data from studies in other indications are considered supportive for the current application.

A total of 7 adolescents have been exposed to spesolimab, all in the GPP prevention trials 0027 and 0025. The total time at risk for the 7 adolescents exposed to spesolimab is 8.9 years.

Common adverse events

Infections were commonly reported in all treatment groups in Trial 0027. The most commonly reported infections were those that might be expected in the general population: Upper respiratory tract infection, urinary tract infection, nasopharyngitis, influenza and Covid-19. All other infection preferred terms (PTs) were single occurrences. Contrary to what was observed in Trial 0013 supporting the original MAA, in Trial 0027 there was no difference in the frequency of infection between placebo and spesolimab overall (33.3% per group). Serious infections were, however, only observed in the spesolimab-treated groups in Trial 0027 (n=3) (SmPC section 4.8).

Other common adverse events were reactions related to the underlying pustular psoriasis, local reactions (injection site erythema) and arthralgia. Accordingly, injection-site reaction is a listed ADR in the SmPC. Arthralgia is a commonly reported AE in several of the spesolimab studies, which was discussed already during the original MAA. As arthralgia is commonly associated with the disorders in

which spesolimab is evaluated, and as, across studies, the rates of arthralgia were overall similar between spesolimab and placebo groups, a causal relationship with spesolimab cannot be established. It is therefore acceptable not to include arthralgia in the ADR table in the SmPC.

In Trial 0027, most patients were reported with AEs of worst intensity Rheumatology common toxicity criteria (RCTC) grade 1 or RCTC grade 2. The proportions of patients with severe AEs (RCTC grade 3 or 4) were comparable across the spesolimab dose groups and the placebo group. However, in the placebo group, most Grade 3 or 4 AEs were pustular psoriasis or psoriasis, while in the spesolimab groups also other PTs were reported, including three severe infections, drug eruption, breast cancer, pseudohyperkalaemia and cholelithiasis. Apart from three serious infections, the events were single occurrences and of various nature. Many events had other possible explanations and, at present, causality with spesolimab cannot be assessed for these events.

Altogether two fatal cases have been reported in subjects treated with spesolimab, one within the interventional clinical trial program and one within the compassionate use program. Both cases were discussed during the assessment of the original MAA. A causal relationship with spesolimab was not concluded.

During assessment of the original MAA, the observed SAEs across studies were thoroughly discussed. It was concluded that, by then, available data was not sufficient to support addition of any of the observed SAEs as ADR in the SmPC; however, some of the observed events were considered potential risks that need to be followed-up and are listed as safety concerns in the RMP (serious infection, malignancy, peripheral neuropathy). The additional data presented in the current application does not change the previous conclusion.

Data presented at the original MAA indicated that the majority of AEs leading to discontinuation was related to the underlying disease. Although the new data on discontinuations, provided with the current application, was not comprehensively presented for other disease than GPP, the GPP data indicate a similar pattern as was observed at the original MAA.

Thus, overall, no new safety concerns were identified based on the data presented in the current application.

User-defined adverse event categories (UDAECs)

The following UDAECs were discussed:

- Hypersensitivity
- Infections (severe, serious, opportunistic, tuberculosis)
- Malignancy
- Peripheral neuropathy
- Cardiac safety
- Hepatic toxicity

These UDAECs were also discussed during the original MAA.

Most observed hypersensitivity reactions were mild and were mainly local reactions. The new cases reported under this UDAEC (systemic reactions) had other likely explanations. The two cases of DRESS and one case of anaphylaxis reported in the original application were not apparently associated with spesolimab. No new cases of DRESS or anaphylaxis have been reported in the current application. Of note, the MAH suggests that for the new GPP flare prevention indication, the pre-filled syringe for subcutaneous administration is suitable for self-administration at home. It is agreed that currently available data on the risk for systemic or serious hypersensitivity reactions do not give raise to concern regarding the self-administration of subcutaneous spesolimab.

Based on the immunomodulatory mechanism of action of spesolimab, an increased risk for serious infections or malignancy cannot be excluded. Across all pooled GPP trials, 10 of 181 patients (5.5%) were reported with SAEs in the UDAEC "infections (severe, serious or opportunistic)", with pneumonia, urinary tract infection, and COVID-19 reported in more than one patient. None of the infection SAEs led to discontinuation of study drug.

Most of the reported malignancies were considered not related to trial medication and some patients had underlying risk factors.

No new cases of GBS or peripheral neuropathy have been reported in the dataset provided with the current application.

There is currently no indication for an adverse effect of spesolimab on the cardiovascular system, or that spesolimab causes hepatic injury.

Altogether, the new data on UDAECs provided with the current application do not change the conclusions drawn during assessment of the original MAA for intravenous spesolimab. Thus, presently, a causal association with spesolimab and the UDAECs cannot be established. However, 'Systemic hypersensitivity reaction', 'Serious, severe or opportunistic infection', 'Malignancy', and 'Peripheral neuropathy' remain important potential risks. Except for Systemic hypersensitivity reactions, specific adverse reaction follow-up questionnaires are in place for further characterisation of these risks post-marketing. Careful follow-up of these potential risks is considered particularly important considering the currently applied maintenance treatment indication, which may potentially be life-long, and – with the indication extended to adolescents – be initiated early in life.

Immunogenicity

Despite a relatively high degree of development of ADAs and NAbs, no clear differences in the rate of hypersensitivity or allergic reactions were observed in spesolimab-treated subjects before and after development of ADAs. This trend was observed also in the data submitted with the original MAA and no new conclusions are drawn.

Concomitant treatment with other immunosuppressants

The MAH has presented a comparison of safety data from patients with and without concomitant use of other non-topical immunosuppressants (IS:s) in placebo-controlled spesolimab studies, for all indications as well as for GPP studies separately. The MAH defined 'concomitant IS use' as including IS treatment that was stopped within 14 days before start of spesolimab, as some residual effect is expected. This means that in such patients, only the first spesolimab dose can be considered to have been given concomitantly with another IS. In the GPP patients, the majority of patients defined as 'with concomitant IS use' had discontinued the other IS before start of spesolimab. Data from these patients may have diluted the overall results when looking over the whole spesolimab treatment period.

More than half of the patients treated with concomitant IS were treated with corticosteroids, alone or in combination with other IS. Only a small number of patients (33 in the spesolimab groups) were treated with concomitant IS biologics.

In general, across studies in different indications, there were no notable differences between the four groups (placebo with/without concomitant IS and spesolimab with/without concomitant IS). In particular, the rate of any infection (SOC infections and infestations) was largely similar between groups, and indeed highest in the placebo group without concomitant IS. The rate of 'severe, serious, opportunistic infections and tuberculosis', i.e. the UDAEC 'infections' was low in all groups, and highest in the placebo group with concomitant IS. The rate of severe AEs and SAEs were higher in the groups with concomitant IS than without, but was higher in the placebo group than in the spesolimab group.

Data from the GPP prevention study 0027 indicated a possibly increased risk for infection (any) with IS than without, but this was seen to a similar degree in the placebo and the spesolimab group. As mentioned above, the data on concomitant IS use from this study are difficult to interpret due to the fact that most subject with concomitant IS had discontinued there IS before start of spesolimab. Further, definite conclusions are difficult to draw due to the relatively low number of patients using concomitant IS, the variety of concomitant ISs used in the spesolimab studies, differences in doses and schedules, and differences in study populations. The limited data on potential risks at co-administration with other ISs is therefore described in section 4.4 and 4.5 of the SmPC. A strict warning against concomitant use of other immunosuppressive therapy in the SmPC for GPP flare prevention is, however, not appropriate as during maintenance treatment, patients may need such other treatment for their GPP as well as for other conditions. Further, the available safety data, albeit the limitations mentioned above, do not raise concerns regarding a potentiated risk for serious/severe events, infections or other, at such co-administration, except that an increased risk for ADRs would generally be expected at an increased drug burden.

SmPC

The safety information in the proposed SmPC for the subcutaneous formulation intended for prevention of GPP flares differs, in some respect, from the previously approved SmPC for the intravenous formulation.

Section 4.4

The warnings concerning infusion related reactions (IRR) and on the lack of data on re-treatment of a new flare that are given in the previously approved SmPC for the intravenous formulation have been removed in the proposed SmPC for the subcutaneous formulation, which is adequate.

Section 4.8

The MAH does not suggest addition of any new reactions in the ADR table in section 4.8 of the new SmPC for the 150 mg solution for injection in pre-filled syringe, as compared with the previously approved SmPC for the 450 mg concentrate for solution for infusion. This is accepted, based on the new data presented.

Assessment of paediatric data on clinical safety

In total 8 adolescents, aged 14 to 17 years at randomisation, have been included in the spesolimab development program. All were included in the GPP prevention Trial 0027, with 2 subjects per dose group (low, intermediate and high dose), including placebo. Of these, 7 subjects continued to the extension trial 0025 where they were treated with the high dose 300 mg q4w. One of the subjects in the placebo group did not continue. Therefore, a total of 7 adolescent subjects have been exposed to spesolimab. The total time at risk for the 7 adolescents exposed to spesolimab is 8.9 years.

There is no data with the 900 mg IV dose for treatment of a GPP flare in adolescents.

It is noted that the number of adolescents included in Trial 0027 is in accordance with the agreed PIP (at least 8 subjects, 2 per dose group). The PDCO agreed with the MAH that as there are no differences in GPP disease characteristics between adolescents and adults. Further, non-clinical studies have not indicated any off-target effects, and the PDCO saw no reason to suspect a difference in susceptibility to AEs from IL36 inhibition. Therefore, it was concluded that the focus of the paediatric development should be to confirm similar exposure to spesolimab in a smaller number of subjects.

Among the 7 adolescent subjects exposed to s.c. spesolimab in Trials 0027 and 0025, the reported adverse events were in line with what has been reported in adults. There was one SAE; a serious

infection (pneumonia), which was considered treatment-related. This occurred during the placebo-controlled period of Trial 0027 in a subject treated with the spesolimab low dose.

Other infections and other reactions potentially related to immunosuppression that were reported in adolescents were a common cold (considered unrelated by the investigator), two cases of upper respiratory tract infections in the low- and medium dose groups, respectively (one of these was considered related), and one case of folliculitis pityrosporon (considered unrelated). The latter occurred during the extension trial 0025, i.e. during high dose treatment. A narrative for this subject was not provided with the interim report, as the AE was not an SAE or an UDAEC. It is likely not possible to assess a causal relationship in this case.

Further there was one case of Covid-19 infection, but this occurred in trial 0027 in a subject treated with placebo.

In response to questions, the MAH has further discussed the B/R in adolescents, suggesting that the disease pathophysiology and mechanism of action of spesolimab targeting IL-36R can be assumed to be similar between adolescent and adult patients. From a safety perspective, the MAH discussed primarily the risk for infections, suggesting that as the immune system is assumed to be fully developed in adolescence, no differences in the risk for infection is expected. A more active immune system in adolescents than in adults could possibly lead to a higher rate of hypersensitivity reactions. However, this risk is not at present considered to outweigh the benefits of the treatment in adolescents. Indeed, no correlation has been observed between ADA positivity and risk for hypersensitivity reactions. Further, the reported hypersensitivity reactions that have been considered at least possibly related to spesolimab have been local reactions of mild-moderate intensity.

Based on the immunomodulatory mechanism of action of spesolimab, an increased risk of malignancy cannot be excluded. The rate of reported malignancies in the spesolimab studies was not higher than in the general population, but the currently available data may not be sufficient to evaluate this risk, as an increased risk for malignancy may not be seen until after several years of use of the product. Malignancy is therefore listed as an important potential risk in the RMP. For adolescents, the possibly increased risk for future malignancy is a concern related to the potential longer-term treatment and longer life-expectancy in adolescents after initiation of treatment, than in adults. Nevertheless, it is acknowledged that it is still a theoretical risk, while GPP is a serious, potentially life-threatening condition affecting quality of life. Alternative treatments for GPP flares are sparse and not without safety problems, including risk for malignancy. The theoretical risk of malignancy may not, at present, be considered to outweigh the expected benefits of the product in adolescents. The risk for malignancy should, however, be carefully followed in future PSURs, and re-assessment of the benefit/risk will thereby be regularly made.

Altogether, from a safety perspective it is agreed that safety data from adults can be extrapolated to adolescents, via matching plasma exposure levels. As discussed under Clinical Efficacy above, also efficacy data can likely be extrapolated from adults to adolescents, given similarity in the disease presentation.

The population pharmacokinetic and exposure-response analyses show similarity in pharmacokinetics between adults and adolescents except in the smallest weight group of 30-40 kg. Based on modelling and simulation (see pharmacokinetic assessment), the exposure in this weight group with the 300 mg q4w dose is predicted to exceed the range observed in adults in the GPP prevention studies by 2-fold. Of note, patients with a body weight of <40 kg were excluded from trial 1368-0027. Use in patients weighing <40 kg is listed as Missing information in the RMP. The modelling and simulation indicates that halving the dose in patients weighing 30-40 kg will provide plasma exposures almost entirely within the range of exposures observed in adults at the 300 mg q4w dose. Therefore, a halved dose is expected to be sufficiently efficient in patients weighing 30-40 kg. Further, given potential risks of

long-term immunosuppression, the smallest patients should not be overdosed. Therefore, the halved dose is recommended for patients weighing 30-40 kg. As the instructions for use (IFU) is based on the human factors engineering (HFE) summative study for a 2-count pack, the medication should be administered by a Health Care Professional (HCP) for those weighing <40 kg (SmPC section 4.2 and 5.2).

Additional safety data needed in the context of a conditional MA

Additional safety data will be provided from the ongoing post-authorisation trial (1368-120; the SOB) in the treatment of GPP flares by applying extrapolation from adults to adolescents.

2.6.10. Conclusions on the clinical safety

No new safety concerns have been identified from the data provided with the current application in the adult population. Data in adolescents is very limited, but a different susceptibility to ADRs of IL36 inhibition, as compared with adults, might not be expected. The extrapolation of safety data from adults to adolescents via PK/exposure data is acceptable. Further safety data will be generated from the ongoing post-authorisation trial (1368-120; the SOB) in the treatment of GPP flares by applying extrapolation from adults to adolescents.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 52 Summary of 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
	Use in patients with body weight <40 kg

2.7.2. Pharmacovigilance plan

Table 53 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
PASS 1368-0128 Spesolimab Post-Authorisation Safety Study (PASS) for Use in Patients with Generalised Pustular Psoriasis (GPP) Planned	The primary objective is to estimate incidence rates of safety events of interest (serious or opportunistic infections, systemic hypersensitivity reaction, peripheral neuropathy and malignancies) among adult and adolescent (aged ≥12 years) patients initiating spesolimab for treatment of GPP and, if feasible, compare to relevant, contemporaneous cohorts of patients initiating other treatments for GPP (biologics or systemic immunomodulatory and anti-inflammatory agents (non-biologics)) in the routine clinical care setting.	Serious or opportunistic infections, systemic hypersensitivity reaction, peripheral neuropathy, malignancies	Final report	31 Dec 2031

2.7.3. Risk minimisation measures

Table 54 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
None		
Important potential risks		
Serious or opportunistic infections	*Routine risk minimisation measures* EU-SmPC section 4.3, 4.4 PL section 2 Prescription only medicine GPP flare prevention: In case a loading dose is needed, this should be administered by a healthcare professional. For subsequent doses, if the healthcare professional determines that it is appropriate, patients may self-inject or caregivers may administer the Spevigo pre-filled syringe after proper training in subcutaneous injection technique. GPP flare treatment: Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form None *Additional pharmacovigilance activities* PASS 1368-0128 (final report 31 Dec 2031)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risks (cont'd)		
Systemic hypersensitivity reaction	*Routine risk minimisation measures* EU-SmPC sections 4.3, 4.4 PL section 2 Prescription only medicine GPP flare prevention: In case a loading dose is needed, this should be administered by a healthcare professional. For subsequent doses, if the healthcare professional determines that it is appropriate, patients may self-inject or caregivers may administer the Spevigo pre-filled syringe after proper training in subcutaneous injection technique. GPP flare treatment: Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form (DRESS) *Additional pharmacovigilance activities* PASS 1368-0128 (final report 31 Dec 2031)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risks (cont'd)		
Malignancy	*Routine risk minimisation measures* None Prescription only medicine GPP flare prevention: In case a loading dose is needed, this should be administered by a healthcare professional. For subsequent doses, if the healthcare professional determines that it is appropriate, patients may self-inject or caregivers may administer the Spevigo pre-filled syringe after proper training in subcutaneous injection technique. GPP flare treatment: Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form *Additional pharmacovigilance activities* PASS 1368-0128 (final report 31 Dec 2031)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risks (cont'd)		
Peripheral neuropathy	*Routine risk minimisation measures* EU-SmPC section 4.4 PL section 2 Prescription only medicine GPP flare prevention: In case a loading dose is needed, this should be administered by a healthcare professional. For subsequent doses, if the healthcare professional determines that it is appropriate, patients may self-inject or caregivers may administer the Spevigo pre-filled syringe after proper training in subcutaneous injection technique. GPP flare treatment: Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* None *Additional pharmacovigilance activities* PASS 1368-0128 (final report 31 Dec 2031)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information		
Pregnant or breast-feeding women	*Routine risk minimisation measures* EU-SmPC section 4.6 PL section 2 Prescription only medicine GPP flare prevention: In case a loading dose is needed, this should be administered by a healthcare professional. For subsequent doses, if the healthcare professional determines that it is appropriate, patients may self-inject or caregivers may administer the Spevigo pre-filled syringe after proper training in subcutaneous injection technique. GPP flare treatment: Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* None *Additional pharmacovigilance activities* None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information (cont'd)		
Use in patients with body weight <40 kg	*Routine risk minimisation measures* EU-SmPC section 4.2 Prescription only medicine GPP flare prevention: In case a loading dose is needed, this should be administered by a healthcare professional. For subsequent doses, if the healthcare professional determines that it is appropriate, patients may self-inject or caregivers may administer the Spevigo pre-filled syringe after proper training in subcutaneous injection technique. GPP flare treatment: Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* None *Additional pharmacovigilance activities* PASS 1368-0128 (final report 31 Dec 2031)

2.7.4. Conclusion

The CHMP considered that the risk management plan version 2.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH 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 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.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Spevigo 150 mg solution for injection in the pre-filled syringe. The bridging report submitted by the MAH has been found acceptable.

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 contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is approved under a conditional marketing authorisation [REG Art 14-a].

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

The current application concerns an extension of the previously approved generalised pustular psoriasis (GPP) flare treatment indication for the Spevigo 450 mg concentrate for solution for infusion, to include adolescents as follows:

- Spevigo is indicated for the treatment of generalised pustular psoriasis (GPP) flares in adults ***and adolescents from 12 years of age as monotherapy.***

In addition, a new pharmaceutical form for subcutaneous administration, Spevigo 150 mg solution for injection in pre-filled syringe, and a new indication is applied for:

- ***Spevigo is indicated for the prevention of generalised pustular psoriasis (GPP) flares in adults and adolescents from 12 years of age.***

3.1.2. Available therapies and unmet medical need

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. GPP flares 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.

Spevigo is already approved for treatment of a GPP flare. To date, there are no approved therapies specifically indicated for the prevention of GPP flares. For the use of non-targeted immunomodulatory therapies (e.g. methotrexate, cyclosporine, retinoids, systemic corticosteroids), there is limited evidence on efficacy. There had been no randomised, controlled clinical trials for the prevention of GPP flares (including with biologics). Most of these therapies used in clinical practice are associated with toxicities that make them inappropriate for continuous use.

3.1.3. Main clinical studies

The current application is primarily based on the following studies:

- Trial **1368-0027** (Effisayil 2): this pivotal trial investigated efficacy and safety of spesolimab s.c. for flare prevention in patients with a history of GPP. This trial forms the basis for the current MAA and is assessed below.
- Trial **1368-0025** (Effisayil-ON): The objective of this ongoing open-label extension (OLE) trial is to evaluate long-term safety and efficacy of spesolimab s.c. (with the option of spesolimab i.v. for recurring flare treatment) in eligible patients who completed trials 1368-0013 and 1368-0027. Interim data are included in the current MAA.

Supportive safety data are available from studies with spesolimab in other indications.

Study **1368-0027** was a global, multi-center, double-blind, randomised, placebo-controlled Phase IIb dose-finding trial that evaluated efficacy and safety of 3 s.c. dosing regimens of spesolimab compared with placebo in preventing GPP flares in patients with a history of GPP. A total of 123 patients were randomised in a 1:1:1:1 ratio to spesolimab low dose, medium dose, high dose and placebo (31 patients per group except 30 in the spesolimab high dose group). During the randomised treatment, all other GPP treatments had to be withdrawn, with different washout periods according to the protocol. The commonly used GPP treatments methotrexate, cyclosporine and retinoids had to be stopped on the day of randomisation. The primary efficacy endpoint was the time to first GPP flare up to Week 48. Intravenous spesolimab was used to treat GPP flares.

3.2. Favourable effects

For the primary efficacy endpoint (time to the first GPP flare onset up to Week 48), the spesolimab high dose was statistically significant in reducing the risk of GPP flares compared with placebo in the primary analysis, with an HR of 0.157 (95% CI 0.046, 0.541; p = 0.0005). In the placebo group, 16 out of 31 subjects had a GPP flare vs. 3 out of 30 in the spesolimab high dose arm (corresponding to the recommended posology in the SmPC).

The hazard ratio of spesolimab 600 mg loading dose (used for the high and medium dose groups) vs. placebo was 0.276 (95% CI 0.100, 0.762) in the first 4 weeks, comparable with the effect of the high dose up to 48 weeks as mentioned above (HR 0.157, 95% CI 0.046, 0.541).

For the key secondary efficacy endpoint, the spesolimab high dose was statistically significant in reducing the occurrence of GPP flares compared with placebo in the primary analysis (required significance level from multiple testing strategy 0.00625), with an adjusted risk difference of -0.390 (95% CI -0.621, -0.159; p = 0.0013).

For secondary endpoints, the risk of PSS worsening over 48 weeks was lower with spesolimab high dose compared with placebo (HR 0.424; 95% CI 0.197, 0.914; p = 0.0134), although the required significance level of 0.00625 was not reached.

Also for the secondary endpoint time to worsening of DLQI, the risk of DLQI worsening over 48 weeks was lower with spesolimab high dose compared with placebo (HR 0.259; 95% CI 0.109, 0.620; nominal p = 0.0010).

With respect to adolescent patients, no adolescent had GPP flare, PSS worsening, or DLQI worsening; the 6 spesolimab-treated subjects achieved sustained remission, while 1 out of 2 adolescents receiving placebo had a GPP flare.

3.3. Uncertainties and limitations about favourable effects

The extension application to support a GPP prevention indication for spesolimab is based on one, small (n=123 randomised), Phase 2, dose finding study. The comparison of relevance for the proposed posology relies on 30 patients treated with the high dose spesolimab regimen vs. 31 patients receiving placebo.

During the randomised treatment, all other GPP treatments had to be withdrawn, with different washout periods according to the protocol. This included both topical treatments like corticosteroids, as well as biologics and other systemic immunosuppressants. The commonly used GPP treatments methotrexate, cyclosporine and retinoids had to be stopped on the day of randomisation. This study design can precipitate GPP flares, since withdrawal of the usual maintenance treatments is known to be a trigger for new flares. Consequently, many flares occurred within the first 4 weeks after randomisation, especially in the placebo group. The Applicant has discussed and justified this somewhat 'artificial' study design approach and whether it might have inflated the effect size. Despite 75% of subjects were using systemic medications for GPP at randomisation, they had a median of 2 flares a year in history and the baseline GPPGA total score was 1 for a majority (86%) of patients. Thus, the GPP treatments provided were insufficient for flare prevention or control of residual symptoms. The Applicant explained that the study was aimed to be performed in a 'high risk' population in terms of presenting with the clinical event/endpoint in the study, in order to have a feasible sample size and observation time for a study in a rare condition. The Applicant also points out that the HR ratio for the 600 mg loading dose (used for the high and medium dose groups) vs. placebo in the first 4 weeks was comparable with the effect of the high dose up to 48 weeks. Thus, data do not suggest that the effect size was inflated in the first 4 weeks. Although leading to a somewhat artificial situation, the reasons behind the choice of study design are acknowledged and does not *per se* invalidate the adequacy of the study design, or the study results. This however raised the question as to how spesolimab is intended to be used in clinical practice; see discussion below related to the wording of the indication.

3.4. Unfavourable effects

Infections were commonly reported in all treatment groups in Trial 0027. During the 48-week placebo-controlled period, there was no difference in the frequency of infection between placebo and spesolimab overall (33.3% per group). The most commonly reported infections were those expected in a general population, such as upper respiratory tract infection, urinary tract infection, nasopharyngitis, influenza and Covid-19. Serious infections (n=3) were only reported in the spesolimab-treated groups in this study. The production information has been updated accordingly.

Other common adverse events in spesolimab across studies were reactions related to the underlying disease and local reactions (injection site erythema). There was no clear dose dependency in rates of common AEs. Overall, in placebo-controlled trials in different indications there were few notable differences between treatment groups.

In study 0027, most patients were reported with AEs of worst intensity Rheumatology common toxicity criteria (RCTC) grade 1 or RCTC grade 2. The proportions of patients with severe AEs (RCTC grade 3 or 4) were comparable across the spesolimab dose groups and the placebo group.

In trial 0027, the numbers of patients with SAEs were higher in some of the spesolimab groups (low and high dose) than in the placebo group. The most frequently reported SAEs were within the SOC skin and subcutaneous tissue disorders (n=5) and infections (n=3). In trial 0025, 13 patients reported with an SAE. Of these, 3 were within the SOC Infections (2 cases of Covid-19, one case of pneumonia). On the PT level, the most frequently reported SAE was pustular psoriasis (i.e. worsening of the underlying diseases; 4 patients, 3.1%), followed by COVID-19 (2 patients, 1.6%); all other SAEs were individual occurrences and had various PTs. None of the infection SAEs led to discontinuation of study drug, and all patients recovered without complications. SAEs in the category "hypersensitivity" were reported in 5 patients (2.8%) in the GPP studies; no clear causal relationship with spesolimab was observed.

Across studies in different AEs leading to treatment discontinuation was reported in about 3-9% of patients treated with spesolimab. Most of the AEs leading to discontinuation were related to the underlying disease.

A relatively high degree of development of ADAs and NAbs towards spesolimab was observed. As in the original MAA, no consistent differences in the rate of hypersensitivity or allergic reactions were observed in spesolimab-treated subjects before and after development of ADAs.

No new safety concerns were identified from the new safety data for adult patients that was provided with the current application.

During spesolimab development, a total of 7 adolescents have been exposed to spesolimab, all in the GPP prevention trials 0027 and 0025. The total time at risk for the 7 adolescents exposed to spesolimab is 8.9 years. The reported adverse events in adolescents were in line with what has been reported in adults. There was one SAE, a serious infection (community-acquired pneumonia), which was considered treatment-related. This occurred in study 0027 in a subject treated with the spesolimab low dose. The patient was treated with antibiotics and recovered without complications. Pneumonia is a user-defined adverse event category (UDAEC) and the new data presented in this application do not change the conclusions drawn during the assessment of the original MAA, and no update to the product information is required at this time.

3.5. Uncertainties and limitations about unfavourable effects

The main uncertainty for the current application relates to the very small number of adolescent patients included in the spesolimab safety database. The uncertainties around some of the potential risks at long-term treatment, such as malignancy, is of particular concern for this patient population. However, as there is no obvious reason to expect a different susceptibility to ADRs of IL36 inhibition in adolescents as compared with adults, it is accepted that safety results from adults can be extrapolated to adolescents via PK/exposure data. The potential risk for malignancy is currently considered to be outweighed by the expected benefits of treatment in adolescents, taking into account that a GPP flare is a potentially life-threatening condition and that alternative treatments are sparse and not without safety problems, including risk for malignancy. Malignancy is an important potential risk listed in the RMP which is being monitored in routine and additional pharmacovigilance activities (e.g. PSURs, PASS 1268-0128) (see also below).

Based on the antibody nature of and the mechanism of action for spesolimab, important potential risks listed in the RMP are serious or opportunistic infections, systemic hypersensitivity reactions, and malignancy. Further, peripheral neuropathy is listed as a potential risk, as a few cases have been

described during spesolimab development. Currently available data is not sufficient for an assessment of whether a causal relationship between spesolimab and these risks is at least a reasonable possibility. Careful follow-up of the potential risks is considered particularly important considering the currently applied prevention indication, when treatment may potentially be life-long. Considering the severity of the disease, further characterisation of these risks post-marketing is acceptable.

Reduced dose regimens are recommended for patients weighing between 30-40 kg. PK simulations showed that administration of the typical adult dose (600 mg loading dose followed by 300 mg Q4W for s.c. and 900 mg i.v.) to patients 30-40 kg would result in 2-fold higher exposure than what is observed in adults in GPP studies. Given the potential risks with long-term immunosuppression, and as added benefit is not expected with a higher exposure in this group, reduced regimens (300 mg loading dose followed by 150 mg Q4W for s.c. spesolimab and 450 mg for i.v. spesolimab) are more appropriate in this group, since this leads to PK exposures comparable to the target exposure range established in GPP studies. Nevertheless, "Use in patients with a body weight < 40 kg" has been included as a Missing information in the RMP, as patients were excluded from the spesolimab trials.

3.6. Effects Table

Table 55 Effects Table for the prevention of GPP flares (report date 31 March 2023)

Effect	Short description	Unit	Treatment Spesolimab high dose (n=30)	Control Placebo (n=31 RS, n=30 SAF)	Uncertainties / Strength of evidence	References
Favourable Effects						
Time to first GPP flare up to Week 48	Patients with GPP flares	N (%)	3 (10.0)	16 (51.6)	HR for the time to the first flare vs. placebo (95% CI): 0.157 (0.046; 0.541) p=0.0005	Study 0027
Occurrence of GPP flare up to Week 48	Proportion with GPP flares	Proportion (95% CI)	0.127 (0.050; 0.289)	0.516 (0.348; 0.680)	Risk difference for GPP flare occurrence vs. placebo (95% CI): -0.390 (-0.621; -0.159) p=0.0013	
Time to first worsening of PSS	Patients with PSS worsening	N (%)	10 (33.3)	20 (64.5)	HR for time to the first worsening vs. placebo (95% CI): 0.424 (0.197; 0.914) p=0.0134 Not reaching required significance level of 0.00625	
Unfavourable Effects						
Infection	Includes all PTs under the SOC Infections and infestations	N (%)	8 (26.7)	10 (33.3)	Small study	Study 0027
Serious infection	SAE	N (%)	0 (0)	0 (0)		
Pustular psoria	PT	N (%)	3 (10.0)	16 (53.3)		

Effect	Short description	Unit	Treatment Spesolimab high dose (n=30)	Control Placebo (n=31 RS, n=30 SAF)	Uncertainties / Strength of evidence	References
sis						
Psoriasis	PT	N (%)	4 (13.3)	3 (10.0)		
Injection site erythema	PT	N (%)	5 (16.7)	1 (3.3)		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A statistically significant and clinically relevant effect of the proposed high dose regimen of spesolimab in comparison with placebo was observed on the primary endpoint, time to first GPP flare at week 48, in study 1368-0027. Concerns were raised in relation to the study design, requiring withdrawal of all other GPP treatments at baseline, which created an "artificial" situation with a high rate of GPP flares in the placebo group during the first 4 weeks after randomisation. However, the data show that s.c. spesolimab treatment indeed protects from early as well as later GPP flares and it is considered that a preventive effective of spesolimab has been shown.

A question was raised on whether the indication wording should specify use as "monotherapy" for the GPP flare prevention indication in line with the wording for the treatment indication. It is acknowledged that the intention is not to regularly combine spesolimab with other treatments for GPP in the prevention indication. However, a strict "monotherapy indication" does not seem adequate considering that at initiation of spesolimab prevention therapy a tapering of previous GPP treatments is recommended to avoid precipitation of a flare. Also, during upcoming flares additional treatments may be needed. Adequate wording related to the limited experience of co-administration with other (immunosuppressive) treatments in sections 4.2, 4.4 and 4.5 is however proposed.

Efficacy data to support the new proposed indication in adolescents (both treatment and prevention of GPP) is very limited, however, extrapolation from adults to adolescents has been sufficiently substantiated.

Despite the limitations of the safety data presented, i.e. a small number of GPP patients treated at the proposed dose, which makes the safety assessment dependent on data from studies in other indications and with different dose schedules, safety data are considered sufficient to support a marketing authorisation for use of spesolimab for prevention of GPP flares in adult and adolescent patients. Overall, no major safety concerns have been identified. Potential effects of long-term immunosuppression remains to be elucidated, but taking into account the rarity and the severity of the disease, and the demonstrated efficacy of spesolimab, this can be made post-marketing. Further, it is accepted that safety data may be extrapolated to adolescents from adults via exposure data.

3.7.2. Balance of benefits and risks

Study 1368-0027 showed a statistically significant and clinically relevant effect of the proposed dose regimen of spesolimab vs. placebo on the time to first GPP flare. While the chosen approach to other GPP medications may not fully reflect a real-life clinical scenario, this does not preclude a conclusion

about the GPP preventive effects of spesolimab. No major safety concerns have been identified. The potential risks are not considered to outweigh the benefit of treatment in this severe disease.

Sufficient justification for extrapolation from adults to adolescents via exposure data has been provided, thus, despite very limited data in adolescents, the benefit/risk balance of spesolimab for the treatment and prevention of GPP flares by spesolimab is positive. However, based on the predicted higher exposure in patients weighing 30-40 kg, a lower dose is recommended to this group, considering the potential risks with long-term immunosuppression, and as added benefit is not expected with a higher exposure in this group.

3.7.3. Additional considerations on the benefit-risk balance

Spevigo currently holds a conditional marketing approval for the treatment of generalised pustular psoriasis (GPP) flares in adults.

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was proposed by the CHMP during the assessment, after having consulted the applicant for the extension of indication in the treatment of GPP flare in adolescent patients from 12 years of age.

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, as discussed above.
- 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 main aim of this study is to evaluate the response to recurrent flare(s) treatment with spesolimab i.v. after first flare treatment with spesolimab i.v. The final clinical trial report is expected by January 2028 for provision of comprehensive data. Study 1368-0120 will only enrol adult GPP patients. Thus, no further data in adolescents will be gained in this study, however, based on the already accepted extrapolation from adults to adolescents, data generated in trial 1368-0120 in adults will be regarded applicable to adolescent patients. Thus, trial 1368-0120 is expected to provide comprehensive and relevant data on the efficacy and safety of subsequent flare treatment with spesolimab i.v. for patients aged 12 years and above.

- Unmet medical needs will be addressed, as this is the first targeted therapy for GPP flare/s in adolescents.

Systemic treatments used off-label for paediatric patients with GPP include oral acitretin, ciclosporin, and methotrexate. These current off-label treatment options are associated with significant limitations in safety: teratogenicity of retinoids, premature epiphyseal closure with acitretin; renal toxicity of ciclosporin; liver toxicity of methotrexate.

In pivotal trial 1368-0013 in the initial MAA, 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 in adults and adolescents. 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.

GPP condition is similar in adolescents and adults. 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 was shown to address the high unmet medical need by rapidly improving GPP pustulation while having beneficial effects on other (systemic) symptoms and patient-reported outcomes relevant for GPP flares, with manageable risks that are justifiable in the light of the disease’s severity. As spesolimab is effective and safe in the treatment of GPP flares, which are associated with significant impairment of the quality of life of patients and their families, the societal burdens of consumption of resource-intensive healthcare services (including 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 additional data are still required.

3.8. Conclusions

The overall benefit/risk balance of Spevigo is positive, subject to the conditions stated in 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 150 mg solution for injection in pre-filled syringe is favourable in the following indication(s):

Spevigo is indicated for the prevention of generalised pustular psoriasis (GPP) flares in adults and adolescents from 12 years of age.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Spevigo 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).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports 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.

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.

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 and adolescent patients from 12 years of age 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.	January 2028

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0049/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

Variations requested		Type	Annexes affected
X.02.V	Annex I_2.(e) Change or addition of a new route of administration	Line Extension	I, IIIA, IIIB and A
X.02.IV	Annex I_2.(d) Change or addition of a new pharmaceutical form	Line Extension	I, IIIA, IIIB and A
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, IIIA, IIIB and A
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication for 150 mg solution for injection in PFS to include the prevention of generalised pustular psoriasis (GPP) flares in adults and adolescents from 12 years of age based on the results from Effisayil 2 (1368-0027), a randomised, double-blind, placebo-controlled phase II b study of spesolimab for subcutaneous administration in adult and adolescent patients with a history of GPP. As a consequence, sections 1, 2, 3, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 6.2, 6.3, 6.4, 6.5, 6.6 and 7 have been updated. The PL is updated accordingly.

Extension of indication for 450 mg concentrate for solution for infusion to include the treatment of generalised pustular psoriasis (GPP) flares in adolescents from 12 years of age as monotherapy. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 6.6 have been updated. Minor editorial changes have been introduced throughout the PI. The PL is updated accordingly. In addition, the details of the local representative for Norway have been updated. In addition, the details of the local representative for Norway have been updated. The RMP version 2.2 has also been submitted.