19 June 2025
EMA/222233/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Spevigo

International non-proprietary name: Spesolimab

Procedure No. EMEA/H/C/005874/X/0011

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):	Solution for injection; Concentrate for solution for infusion
Strength(s):	150 mg, 300 mg and 450 mg
Route(s) of administration:	Subcutaneous use and Intravenous use
Packaging:	pre-filled syringe (glass) and vial (glass)
Package size(s):	1 pre-filled syringe, 2 pre-filled syringes and 2 vials

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List of abbreviations

AE	Adverse event
AR	Assessment report
AUC	Area under the curve
BE	bioequivalence
BI	Boehringer Ingelheim
CI	Confidence interval
C_{max}	Maximum concentration
C_{trough}	Trough concentration
GPP	Generalized Pustular Psoriasis
HCP	Healthcare professional
HFE	Human factors engineering
HS	Hidradenitis suppurativa
HV	Healthy volunteers
IFU	Instructions for use
Ig	Immunoglobulin
IL	Interleukin
IV	intravenous
i.v.	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NSD	Needle safety device
OLE	Open-label extension
PFS	Pre-filled syringe
PFS-NSD-1	A pre-filled syringe equipped with a needle safety device filled with 1 mL of a solution for injection with 150 mg spesolimab/mL formulation (150 mg spesolimab per PFS-NSD-1)
PFS-NSD-2	A pre-filled syringe equipped with a needle safety device filled with 2 mL of a solution for injection with 150 mg spesolimab/mL formulation (300 mg spesolimab per PFS-NSD-2)
PK	Pharmacokinetics
pmbl	periumbilical
PPP	Palmoplantar pustulosis
PT	Preferred Term of MedDRA
Q4W	Once every 4 weeks
SAE	Serious adverse event
SC	Subcutaneous
SCS	Summary of Clinical Safety
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class of MedDRA
SUR	Safety Update Report
UE	Usability engineering

1. Background information on the procedure

1.1. Submission of the dossier

Boehringer Ingelheim International GmbH submitted on 11 October 2024 an extension of the marketing authorisation.

The MAH applied for a new strength of 300 mg (150 mg/ml) for solution for injection in a pre-filled syringe. The RMP (version 3.0) is updated in accordance.

In addition, the applicant has updated SmPC (Annex I) and Package Leaflet (Annex IIIB) for both 450 mg concentrate for solution for infusion and 150 mg and 300 mg solution for injection in line with the new excipient guideline.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, indent (2), point (c) - Extensions of marketing authorisations.

1.3. Information on Paediatric requirements

Not applicable.

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 did not seek Scientific advice at the CHMP.

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: N/A

CHMP Peer reviewer(s): N/A

The Rapporteur appointed by the PRAC was: Zoubida Amimour

The application was received by the EMA on	11 October 2024
The procedure started on	31 October 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 January 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 January 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 February 2025
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	27 February 2025
The MAH submitted the responses to the CHMP consolidated List of Questions on	11 April 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	16 May 2025
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	19 June 2025

2. Scientific discussion

2.1. Problem statement

In this procedure, the MAH applies for a new strength of 300 mg (150 mg/ml) for solution for injection in a 2 ml pre-filled syringe (2 ml PFS) with a needle safety device (PFS-NSD-2) intended to be used for the prevention of GPP flares. The PFS-NSD-2 is a larger volume syringe filled with the same formulation (150 mg/ml solution for subcutaneous injection) as the previously approved 1 ml syringe (PFS-NSD-1).

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. A GPP flare consists of the acute onset of rapidly disseminating painful skin manifestations, which can be accompanied by systemic symptoms, such as high fever and extreme fatigue, as well as acute phase response (with increased C-reactive protein). GPP flares may 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.

2.1.2. Management

Spesolimab (Spevigo) was first approved in the EU in December 2022 as an intravenous formulation for the treatment of a GPP flare in adults. Subsequently, in September 2024, it was approved as a subcutaneous formulation intended for continuous use for the prevention of GPP flares in adults and adolescents. In addition, the previously approved treatment indication was widened to include also adolescent patients.

Although there is limited evidence of the efficacy and safety for the use of non-targeted immunomodulatory therapies (e.g. methotrexate, ciclosporin, retinoids, systemic corticosteroids) in patients with GPP, spesolimab is currently the only treatment specifically approved for the treatment or prevention of GPP flares.

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.

Spesolimab (Spevigo) has been previously available as 450 mg concentrate for solution for intravenous infusion, intended for treatment of GPP flares, and as a 1 ml prefilled syringe (PFS) containing 150 mg spesolimab as a solution for subcutaneous injection for the prevention of GPP flares.

The previously approved dose regimen for spesolimab for the prevention of GPP flares, in adults and adolescents from 12 years of age and weighing at least 40 kg, is a loading dose of 600 mg (four subcutaneous injections of the 1 ml PFS), followed by a dose of 300 mg (two subcutaneous injections) every 4 weeks (Q4W).

Introduction of the larger volume 2 ml pre-filled syringe is intended to reduce the number of injections per dosing occasion and, thus, the burden to the patient.

Like the 1 ml PFS, the 2 ml PFS can be self-administered by the patient, if the healthcare professional determines that it is appropriate.

The two dose strengths are provided in different pack sizes, with one syringe per pack for the 2ml PFS and two syringes per pack for the one ml PFS.

The indication (prevention of GPP flares) and the recommended dose (600 mg loading dose followed by 300 mg Q4W) of the subcutaneous formulation of spesolimab remain unchanged.

2.3. Type of Application and aspects on development

Clinically, this application is primarily based on pharmacokinetic comparisons between administration of 300 mg subcutaneous spesolimab using the previously approved 1 ml PFS and the new 2 ml PFS. As, according to standard bioequivalence criteria, the overall exposure (AUC) was slightly higher with the new 2 ml PFS compared with the 1 ml PFS, the MAH also provided a discussion of safety data across previous studies with spesolimab.

In summary, the MAH provided the following clinical information in support of the application:

- Results from the pivotal bioavailability trial 1368-0029 comparing 1 mL×2 sites and 2 mL×1 site (hereafter trial 0029).
- The comparison of trough concentrations in patients with Palmoplantar Pustulosis (PPP) who received the same spesolimab dose using the 1-mL PFS (in trial 1368-0016) or the 2-mL PFS in trial 1368-0024 (hereafter trials 0016 and 0024, respectively).
- Safety assessment across clinical trials with spesolimab.
- A complete human factors engineering (HFE)/usability engineering (UE) analysis of the spesolimab PFS-NSD-2.

No scientific advice has been sought for the development of the 2 ml syringe.

2.4. Quality aspects

2.4.1. Introduction

This submission applies for the use of Spevigo (INN: spesolimab) solution for injection in pre-filled syringe 300 mg/syringe (150 mg/mL) equipped with a needle safety device for subcutaneous administration.

The active substance in Spevigo is spesolimab, which is a humanized antagonistic monoclonal IgG1 antibody that binds to IL-36R and blocks human IL-36α-, IL-36β-, and IL-36γ-induced IL-36R activation, as leading to suppressed pro-inflammatory and pro- fibrotic pathways in inflammatory skin diseases.

The currently approved finished products are:

- Spevigo 450 mg concentrate for solution for infusion: Spevigo is indicated for the treatment of generalised pustular psoriasis (GPP) flares in adults and adolescents from 12 years of age as monotherapy.
- Spevigo 150 mg (150 mg/mL) solution for injection in pre-filled syringe: Spevigo is indicated for the prevention of generalised pustular psoriasis (GPP) flares in adults and adolescents from 12 years of age monotherapy.

With this Extension application the Applicant proposes a new strength:

- Spevigo 300 mg (150 mg/mL) solution for injection in pre-filled syringe

The introduction of the new strength is intended to reduce the number of injections per dosing and thus the burden on the patient.

The product is available as Spevigo 300 mg solution for injection in pre-filled syringe and pack size of 1 pre-filled syringe.

This line extension concerns a new strength, Spevigo 300 mg solution for injection in pre-filled syringe (PFS, also referred to as PFS-2 in this report) equipped with a needle safety device (NSD) for subcutaneous (SC) administration. The active substance for manufacture of spesolimab solution for injection 300 mg/PFS (150 mg/mL) remains unchanged as previously approved.

The finished product is presented as solution for injection in pre-filled syringe containing 300 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).

A Notified Body Opinion was issued by the TÜV Süd in Germany as the medicinal product is a single integral product which is intended exclusively for use in the given combination, and which is not reusable (Art 1(9) second subparagraph of Regulation (EU) 2017/745). The Notified Body Opinion is provided in the dossier, Regional Part 3.2.R and it is acceptable.

2.4.2. Active Substance

The active substance used in Spevigo 300 mg solution for injection in pre-filled syringe is identical to the previously authorised active substance used in Spevigo 450 mg concentrate for solution for infusion and Spevigo 150 mg (also referred to as PFS-1 in this report) solution for injection in pre-filled syringe. No changes to the authorised dossier have been introduced with this line extension application.

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 is currently authorised as 150 mg solution for injection in pre-filled syringe and 450 mg concentrate for solution for infusion. The new presentation 300 mg solution for injection in pre-filled syringe retains identical formulation compared to previously approved 150 mg pre-filled syringe. The excipients are unchanged, they are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation.

The fill volume is different in the new presentation (2 mL), as well as the container closure system in terms of size (the pre-filled syringe is changed to a larger 2.25 mL pre-filled syringe) to accommodate the new, larger volume.

The primary packaging is a larger 2mL pre-filled glass syringe assembled with an automatic needle guard, extended finger flange, plunger rod, and plunger stopper (coated butyl rubber, siliconised). The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The described formulation development is aligned with authorised 150 mg 1 mL PFS-1. A formulation robustness study on 300 mg 2 mL PFS-2 was performed with new active substance batches. The presented data is consistent with previous study on approved 150 mg 1 mL PFS-1. The product has no overage, the physiochemical and biological properties are unchanged and described in previously approved product. The formulation development section in the dossier describes and justifies the chosen formulation and is sufficiently comprehensive.

The submitted Notified Body Opinion concludes that relevant General Safety and Performance Requirements of Annex I of Regulation (EU) 2017/745GSPR for the device part of Spevigo 300 mg solution for injection in pre-filled syringe in a needle safety device are fulfilled (provided in section R of the dossier).

The intended purpose, use, user and shelf life have been adequately described and assessed by Notified Body (along with other relevant GSPRs). Adult and adolescent have been included in the human factors / usability studies. This is adequately described.

The design verification study will continue over 36 months, though only 12 months data has been submitted for NBOp. The intended shelf life of the device is covered by accelerated aging data. Real-life aging data is available for 12 months, 24 months testing is ongoing. The presented data is acceptable, the medical device part is a well- established design with well know materials and characteristics thus no potential risks are considered by not covering the whole intended shelf life by real time aging data only by accelerated aging.

In terms of manufacturing process development, the applicant have adapted / developed the filling process for the new syringe and fill volume (300 mg 2 mL PFS-2) and reviewed the process parameters from the previously authorised 150 mg 1 mL PFS-1 process. Volumes are adjusted in the sterile filtration step to the new presentation, with adequate supporting data, whereas filter integrity pressure limit/criterion and duration of filtration are unaltered (same as for approved 150 mg 1 mL PFS-1). The applicant has given attention to filling speed and fill volume among others. Tested filling speeds did not have any impact on critical quality attributes (CQAs) or filling accuracy (data presented). Fill volumes were adequately shown, confirmed by presented data. The exercise established ranges for later verification in process performance qualification (PPQ). Assembly, labelling and packaging and hold time have also been investigated during development. Regarding extractable/leachable, elemental impurities and nitrosamine the applicant has reviewed the respective evaluations and risk assessments with respect to the new presentation PFS-NSD-2 in relation to the already approved PFS-NSD-1. The revisions are minimal, and the conclusions are unaltered compared to already approved PFS-NSD-1: There are no/negligible risks. In all, the process development section is adequately described and found acceptable.

The comparability studies provided in this line extension focus on the comparability of spesolimab 150 mg/mL finished product in pre-filled syringes, 300 mg/syringe (PFS-2), to the already approved spesolimab 60 mg/mL finished product in the vial presentation, 450 mg/vial, as well as to spesolimab 150 mg/mL finished product in pre-filled syringes, 150 mg/syringe (PFS-1).

Comparability has been evaluated in accordance to ICH Q5E, 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.

In general comparability has been sufficiently demonstrated for the comparisons described above, i.e. for the 150 mg/mL finished product in pre-filled syringes (300 mg/syringe) to the already approved 60 mg/mL finished product in the vial presentation (450 mg/vial) as well as to spesolimab 150 mg/mL finished product in pre-filled syringes 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..

The container closure system is adequately described. The differences between clinical and commercial presentation are identified. The addition of the needle safety device on the commercial presentation is concluded not to impact the representativeness of the clinical data. In addition, functionality and performance design control are described as well as design verification and validation, to support Notified Body Opinion. Compatibility with the primary packaging is discussed, with spiking studies with silicon, ethylene oxide and tungsten and selection of worst-case conditions are adequately described and compatibility demonstrated.

Regarding microbiological attributes, the microbial quality measures of the process including bioburden reduction, sterile filtration and filling, and associated testing, including endotoxins and CCIT are described and found acceptable.

2.4.3.2. Manufacture of the product and process controls

The names of manufacturing and testing sites involved in the manufacturing process have been provided together with demonstration of GMP compliance which was found acceptable. These are identical to the ones used for PFS-NSD-1.

Information on manufacturing process and process controls and controls of critical steps and intermediates is adequate and found acceptable. The process is outlined, including tabulated controls, criteria, and justifications. The unit operations in the manufacturing process flow are identical between PFS-NSD-2 and previously approved PFS-NSD-1, as is manufacturing facility and buildings.

Reprocessing procedures are previously approved and unchanged in current line extension. The active substance handling and parameters are basically unchanged from previously approved presentation. The sterile filter area is increased with bulk volume and so is discard volume after filter. This is acceptable. Regarding hold times there are some updates, such as total hold time for the finished product at room temperature and light compared to PFS-1. This is also found acceptable.

The process validation and/or evaluation is adequately described and found acceptable. The process was outlined in a structured manner, including controls, validation strategy and predetermined criteria. Three finished product PPQ batches of filled syringes (PFS-2) and following assembled syringes with needle safety device (PFS-NSD-2) have been produced with different parent active substance batches as well as with a mix of active substance batches. The presented data, process parameters and quality attributes are throughout the process consistent and within the preset criteria. It is noted that the predefined process validation limits (PVL) and process validation acceptance criteria (PVAC) for some of the quality attributes tested are wider than corresponding specified release criteria. The data

demonstrate manufacturing consistency and that the specified release criteria are met. The provided data are found acceptable.

The applicant does not specifically discuss any deviations from the PPQ batches. However, the applicant noted an unexpected high number of class I defects during visual inspection of PPQ 1 batch. The high number of defects was explained The explanation is found acceptable.

All results demonstrate clearly that the aseptic filling process of spesolimab solution for injection in pre-filled syringe 300 mg/syringe in sterile manufacturing delivers consistently a product meeting the pre-defined quality criteria and all results demonstrate clearly that the assembly process of spesolimab PFS-NSD-2 in the commercial manufacturing facility delivers consistently a product meeting the pre-defined quality criteria. The validation is found acceptable.

Media fills are adequately described and found acceptable. The applicant has chosen a bracketing approach clearly describing process parameters, and both the 1 mL and 2.25 mL syringe format are included in the biannual media fill program. The applicant has also analysed worst case conditions, including variations in filling speed, routine, and non-routine interventions. The three most recent routine media fills are presented. The environmental and growth data meet the acceptance criteria. In addition, the filter validation report is included in the dossier and found acceptable. Bacterial retention validation was successful, despite not reaching the target flow. The viscosity of the active substance did not allow for target flow. Bubble points, as well as compatibility were determined. The media fill section and filter validation are found acceptable.

Transport validation is adequately described and found acceptable. The applicant has qualified the transport through product independent and product specific studies. The studies are relevant, quality data and other parameters all met the acceptance criteria. The transport is qualified for worldwide distribution. Transport validation section is found acceptable.

In conclusion, the applicant has adequately described the manufacturing, including controls and validation.

2.4.3.3. Product specification, analytical procedures, batch analysis

The specifications for release and stability of spesolimab solution for injection in pre-filled syringe 300 mg/syringe (150 mg/mL) include tests for: appearance and description, general tests, purity and impurities, heterogeneity, potency, safety, identity, excipients and functionality testing.

Table 1: Finished product release specifications

The specifications for the new strength 300 mg, 2 mL in the new larger syringe (PFS-2 / PFS-NSD-2) have been developed based on the lower strength specifications, the previously approved 150 mg, 1 mL syringe presentation (PFS / PFS-NSD-1). Appearance and description are unchanged from previously presentation (both method and acceptance criteria), as are general tests, identity, quantity, pharmacopeial safety, potency and excipients. CCIT and functional testing methods are changed, adapted to the new presentation. Dose accuracy acceptance criterium is adequately adapted to the new volume in the new presentation.

The applicant has not changed the purity and impurities and heterogeneity methods but adapted some acceptance criteria, compared to the previously approved 150 mg presentation. The revised acceptance criteria and justification is adequate and found acceptable.

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

Analytical methods

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

The applicant has in general used the same methods for 300 mg, 2 mL syringe as for the approved 150 mg, 1 mL syringe. However, container closure integrity test (CCIT) and function testing methods are new to the new presentation. The methods are clearly identified and briefly summarised. Note that extractable volume is omitted and controlled through dose accuracy, this was implemented and approved already in previous submission of the 150 mg 1 mL syringe. The section is adequately described and found acceptable.

Batch analysis

Batch analysis data on 16 batches manufactured at various scale of the active substance were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

Information on the reference standards used for release, in process controls and stability testing of the spesolimab finished product and active substance are identical and found acceptable.

2.4.3.4. Stability of the product

The proposed shelf life for the spesolimab PFS-NSD-2 including 300 mg/syringe (150 mg/mL), is 24 months, rwhen stored at the recommended storage condition at 2-8 °C. In addition, the spesolimab PFS-NSD-2 can be stored at room temperature for up to 14 days prior to use. The 14 days are included in the 24 months.

The applicant has provided stability results at 2-8 °C for up to 36 months for three primary stability batches for the PFS-2 and up to 18 months data for three PPQ batches (PFS-NSD-2). 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 stress studies and 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-2.

All stability results available for the primary stability batches and the PPQ batches stored at 2-8 °C for both the pre-filled syringe/PFS-2 and the PFS-NSD-2 comply with the proposed end-of-shelf-life/stability specification for up to 36 months for the primary stability batches and up to 12 months for the PPQ batches. No significant/very minor changes or trends are seen in any of the attributes tested. Additionally, the attributes included in the functionality testing for the PFS-NSD-2 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-2 at 25 °C-storage.

Furthermore, stability data at 30°C for two weeks after end of storage at 2 – 8°C has been provided demonstrating only slight changes with respect to potency, charge heterogeneity and purity compared to the control samples and all results were well within the acceptance limits. These results are applicable for PFS-NSD-2 and it is accepted that the impact of room temperature on product quality prior to administration is considered negligible for up to 14 days.

Photostability testing has been performed according to ICH Q1B and showed that the spesolimab 150 mg/mL pre-filled syringe/PFS-2 and PFS-NSD-2, 300 mg/syringe, 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.

Compatibility of the spesolimab 150 mg/mL 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.

It can also be noted that a design verification study is ongoing for 36 months and 12 months data has been submitted to date and these data are included and assessed by the Notified Body in the NBOp. The presented data is acceptable, the medical device part is a well-established design with well know materials and characteristics thus no potential risks are considered by not covering the whole intended shelf life by real time aging data only by accelerated aging.

Based on the stability data obtained, the recommended shelf-life for spesolimab pre-filled syringe, 300 mg/syringe (150 mg/mL), is 36 months at refrigerated conditions, 2-8°C. Considering design verification data as provided in Section P.2 and real time stability data, the shelf-life for the PFS-NSD-2, 300 mg/syringe (150 mg/mL), is limited to 24 months. In addition, the spesolimab PFS-NSD-2 can be stored at room temperature for up to 14 days prior to use. The 14 days are included in the 24 months.

The proposed shelf-life for spesolimab PFS-NSD-2, 300 mg/syringe (150 mg/mL), of 24 months at refrigerated conditions, 2-8°C, is found acceptable.

2.4.3.5. Adventitious agents

No changes in the adventitious agents control are introduced compared to approved presentations, which is accepted.

2.4.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and

uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The 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.

2.5. Non-clinical aspects

2.5.1. Introduction

No new non-clinical data are provided with the current submission.

2.5.2. Ecotoxicity/environmental risk assessment

The Applicant has previously submitted a justification for not submitting ERA studies (Spevigo X-06-G). The absence of specific environmental risk study data is justified as spesolimab is a humanised monoclonal antibody (a protein) and 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 which is acceptable. The introduction of the 2 ml PFS does not involve a change in indication or dose regimen for the previously approved subcutaneous formulation of spesolimab. The product is a humanised protein which is not expected to pose a risk to the environment (EMEA/CHMP/SWP/4447/00 Rev. 1 - Corr.).

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

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.

The studies discussed by the MAH, in which the 2 ml PFS was used or which were used for PK comparisons, are listed in the table below:

- **Tabular overview of clinical studies**

Type of Study	Study Identifier (Study No.) [document no.]	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration[1]	Number of Subjects (entered and treated)[1]	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	1368-0029 CTR: [c28472227]	To investigate relative bioavailability, safety, and tolerability after s.c. injection of different doses of spesolimab and different injection sites in healthy male and female subjects	Phase I open-label, matched-group design trial	Study drug: spesolimab: 300 mg s.c. pmbl, 300 mg s.c. pmbl left and right, 300 mg s.c. thigh, 600 mg s.c. pmbl left and right; SD (split over 2 injection sites in some cases); s.c. injection	Total: 48 Spesolimab: 300 mg s.c. pmbl: 12 300 mg s.c. pmbl (l+r): 12 300 mg s.c. thigh: 12 600 mg s.c. pmbl (l+r): 12	Healthy male and female subjects	Single dose	Complete; full CTR
Efficacy	1368-0016 CTR: [c36956347]	To evaluate efficacy and safety of different s.c. doses (dose finding) of spesolimab in patients with moderate to severe PPP	Phase IIb randomized, placebo-controlled, double-blind, parallel-group trial	Study drug: spesolimab: 300 mg, 600 mg control drug: matching placebo; Low dose: spesolimab 300 mg qw (5×), 300 mg q4w (2×), then starting at Week 16 300 mg q8w (5×) Medium-low dose: spesolimab 300 mg qw (5×), 600 mg q4w (12×) Medium-high dose: spesolimab 600 mg qw (5×), 300 mg q4w (12×) High dose: spesolimab 600 mg qw (5×), 600 mg q4w (12×) Placebo qw (5×), q4w (2×), then spesolimab 600 mg q4w (10×); multiple doses qw, q4w, or q8w; s.c. injection	Total: 152 Spesolimab: Low dose s.c.: 22 Medium-low dose s.c.: 21 Medium-high dose s.c.: 22 High dose s.c.: 44 Placebo: 43	Patients with moderate to severe PPP	52 weeks (last dose)	Complete; full CTR
Efficacy	1368-0024 CTR: [c41600493]	To evaluate the long-term efficacy and safety of spesolimab in patients with PPP, who completed previous BI spesolimab trials and qualify for entry in this trial.	Phase II open-label, long-term extension trial	Study drug: Spesolimab: 600 mg; multiple doses q4w; s.c. injection	Total: 108 Spesolimab 600 mg s.c. q4w: 108	Patients with PPP who had a health benefit in and completed previous trial 1368-0016	Planned: 260 weeks (last dose) Trial was prematurely discontinued due to business reasons.	Complete; abbreviated CTR
PK	1368-0043 CTR: [c34783971]	To investigate PK and safety of single s.c. and single i.v. doses of spesolimab in healthy Chinese male and female subjects	Phase I open-label, parallel-group trial	Study drug: spesolimab: 300 mg s.c., 600 mg s.c., 450 mg i.v., 900 mg i.v., 1200 mg i.v.; SD; s.c. injection or i.v. infusion	Total: 50 Spesolimab: 300 mg s.c.: 10 600 mg s.c.: 10 450 mg i.v.: 10 900 mg i.v.: 10 1200 mg i.v.: 10	Healthy Chinese male and female subjects	Single dose	Complete; full CTR
Efficacy	1368-0052 CTR: [c37475396]	To estimate the effect of spesolimab compared with placebo in patients with moderate to severe HS	Phase IIa randomized, placebo-controlled, double-blind, parallel-group trial	Study drug: spesolimab: 1200 mg control drug: matching placebo; multiple doses qw then q2w; s.c. injection and i.v. infusion	Total: 52 Spesolimab: 1200 mg i.v. qw (3×), then 1200 mg s.c. q2w (4×): 35 Placebo: 17	Patients with moderate to severe HS	1 dose qw over 2 weeks (3 doses in total), then 4 doses q2w over 8 weeks (4 doses in total), last dose at Week 10	Complete; full CTR

Efficacy	1368-0067 TFL (in ISS/SCS Appendix): [c39562735] CTP: [c33707086]	To investigate long-term treatment with spesolimab in patients with HS	Phase II open-label, extension trial	Study drug: Spesolimab: Single LD 1200 mg i.v. (for patients in placebo in parent trial) or 600 mg s.c. (for patients on active in parent trial), then 600 mg s.c. q2w Single loading dose then multiple doses q2w; s.c. injection or i.v. infusion	Total: 45[1,5] Spesolimab[1,5]: Single LD 1200 mg i.v./ 600 mg s.c. then 600 mg s.c. q2w: 45	Patients with HS who completed previous trial 1368-0052	Planned[1,5]: 104 weeks (last dose)	Ongoing; no CTR (TFL with interim analysis results)

2.6.1. Clinical pharmacology

2.6.1.1. Pharmacokinetics

The current application concerns a line extension for a new 2 ml pre-filled syringe (PFS-2), with PK bridging to the approved 1 ml PFS (PFS-1) with the same formulation and concentration (150 mg/ml).

The MAH provided the following primary studies in support of the PK bridging in the application:

- Results from the relative bioavailability trial 1368-0029 (hereafter 0029) comparing 1 mL×2 injection sites (PFS-1) and 2 mL×1 injection site (PFS-2).
- The comparison of trough concentrations in patients with Palmoplantar Pustulosis (PPP) who received the same spesolimab dose using the 1-mL PFS (in trial 1368-0016, hereafter 0016) or the 2-mL PFS in trial 1368-0024 (hereafter 0024).

Analytical methods

Assay methodology used to monitor the pharmacokinetic (PK) of spesolimab in the clinical trials has not changed from what was described in the initial MAA where the validation of the method was presented and assessed. Within-study performance for study 0029, 0016 and 0024 were acceptable.

Anti-drug antibody (ADA) assay was assessed and validated in the original MAA for spesolimab. A standard multi-tiered approach was used including screening, confirmatory and titration. Analysis of samples from clinical studies 0029 and 0024 assessed in this application performed acceptably. Drug tolerance for the ADA assay was acceptable with no samples with spesolimab concentration above the established drug tolerance levels at 100 ng/mL PC.

For the target population GPP, there are no ADA/nAb data available for the 2 ml, and thus no new information for the current application.

Neutralising antibody (nAb) assay was performed for study 0016 and 0024 in the PPP population. The drug tolerance was very low, with 12.5 ug/ml spesolimab at MPC (0.900 ug/ml) and <6.00 ug/ml spesolimab at the lowest PC (0.507 ug/ml).

Absorption/Bioavailability

In the comparative bioavailability study 1368-0029, standard non-compartmental analysis was performed (in PKS) for estimation of pharmacokinetic parameters. $AUC_{o\text{-}tz}$ and C_{max}, were primary PK parameters, and $AUC_{o\text{-}inf}$ secondary parameter.

Healthy volunteers were administered a single dose of 300 mg spesolimab either as 1 ml x 2 injections (PFS-1, n=12) (Reference: R) or the new 2 ml x 1 injection (PFS-2, n=12) in the periumbilical region (Treatment group: T1).

PFS-2 was also administered at the thigh (Treatment group: T2) and at a higher dose (600 mg) periumbilically with two injections (left and right) (T3). See table 7 below for a summary of these treatment groups. For this application, the reference (1 ml PFS) is compared with treatment group T1 (2 ml PFS), seen in table 7 in bold.

Table 7: Relevant treatment groups receiving 300 mg 1 ml or 2 ml injections in study 0029.

Treatment group	*Total dose*	*Route of administration*	*Concentration*	*Application volume*	*Injection site*
R	**300 mg**	**SC**	**150 mg/ml**	**2 x 1 ml**	**Periumbilical (left and right)**
T1	**300 mg**	**SC**	**150 mg/ml**	**1 x 2 ml**	**Periumbilical**
T2	300 mg	SC	150 mg/ml	1 x 2 ml	Thigh
T3	600 mg	SC	150 mg/ml	1 x 2 ml	Periumbilical (left and right)

The time-concentration profiles for 300 mg periumbilical, 300 mg periumbilical (left+right), 600 mg periumbilical (left+right) and 300 mg thigh administration, can be seen in Figure 1. Estimated PK parameters can be seen in Table 8.

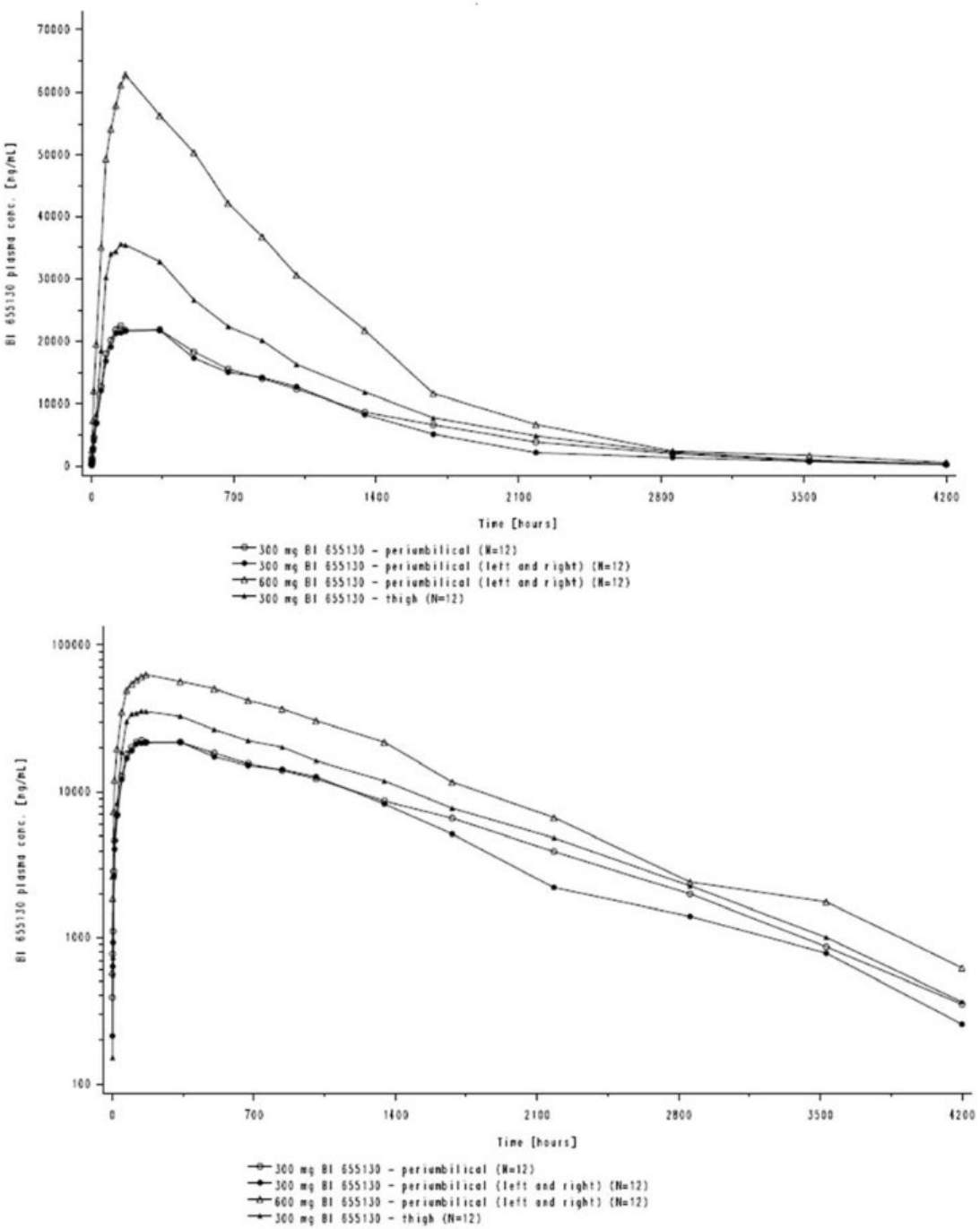

Figure 1: Plasma concentrations of spesolimab vs time for all groups, with linear and log-scale y-axis.

Table 8. Pharmacokinetic parameters for treatment group R, T1, T2 and T3 (**N.B reversed groups, R = 2 ml, T1 = 1 ml**).

	300 mg pmbl R N = 12		300 mg pmbl (l+r) T1 N = 12		300 mg thigh T2 N = 12		600 mg pmbl (l+r) T3 N = 12	
	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
$AUC_{0\text{-}tz}$ [day·µg/mL]	1230	17.7	1150	38.0	1720	16.9	2990	31.3
$AUC_{0\text{-}tz,\ norm}$ [day·g/mL/kg]	4.09	17.7	3.83	38.0	5.73	16.9	4.99	31.3
$AUC_{0\text{-}\infty}$ [day·µg/mL]	1240	18.2	1160	38.8	1740	17.5	3020	31.6
$AUC_{0\text{-}\infty,norm}$ [day·µg/mL/mg]	4.14	18.2	3.88	38.8	5.79	17.5	5.03	31.6
C_{max} [µg/mL]	24.6	14.5	24.4	28.1	38.4	19.3	68.0	35.5
$C_{max,\ norm}$ [µg/mL/mg]	0.0819	14.5	0.0812	28.1	0.128	19.3	0.113	35.5
t_{max} [day][1]	6.48	5.00-14.1	5.50	4.00-15.9	6.50	3.92-14.0	7.03	4.01-21.0
$t_{½}$ [day]	21.9	26.8	17.9	59.0	21.3	33.9	19.4	46.3
CL/F [L/day]	0.241	18.2	0.258	38.8	0.173	17.5	0.199	31.6
V_z/F [L]	7.64	24.9	6.67	40.7	5.30	25.8	5.56	47.1

[1]Median and range (minimum-maximum) are displayed instead of gMean and %gCV.

Bioavailability comparisons between treatment groups (T1, T2, T3) and reference was performed with a standard statistical analysis on log-transformed PK parameters using ANOVA. The following comparisons were made; T1/R, T2/R and T3/R. Point estimates and 2-sided 90% CI were provided. An acceptance range for the 90% CI was not pre-specified, but the standard BE limits of 80.00%-125.00% were used as a reference point.

C_{max} for T1/R met the standard BE criteria (2 ml/1 ml administration), while $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ exceeded the upper 80.00-125.00% interval slightly (point estimates and 90% CI: 106.76% [89.45%-127.42%] and 106.86% [89.20%-128.02%] respectively). Thus, total exposure was slightly higher after 2 ml administration compared with 1 ml administration (See table 9).

Table 9. Relative bioavailability between subcutaneous (SC) injections of 150mg/ml spesolimab with PFS-1 and PFS-2.

	Adjusted gMean (gSE)				90% CI		
Pharmacokinetic parameter	300 mg spesolimab pmbl T1 N = 12	300 mg spesolimab pmbl (l+r) R N = 12	Ratio T1/R [%]	gSE	Lower limit [%]	Upper limit [%]	gCV [%]
Primary endpoints							
C_{max} [µg/mL]	24.56 (1.08)	24.35 (1.08)	100.84	1.10	85.19	119.37	24.8
$AUC_{0\text{-}tz}$ [day·µg/mL]	1227.91 (1.08)	1150.18 (1.08)	106.76	1.11	89.45	127.42	26.0
Secondary endpoint							
$AUC_{0\text{-}\infty}$ [day·µg/mL]	1243.29 (1.08)	1163.47 (1.08)	106.86	1.11	89.20	128.02	26.6

Study 0016 and 0024

In study 0016 and 0024, pharmacokinetic analysis was not performed. Spesolimab plasma trough concentrations (adjusted gMean) at the last sampling time (52 weeks) in 0016 were compared with the C_{trough} at first steady state dosing at 16 weeks in study 0024 using ANOVA. The standard BE limits of 80.00%-125.00% were used as a reference point.

The ratio between 2ml/1ml were 90.69% (90%CI: 81.34%-101.12%) for the high dose group (Speso High) and 94.11% (90%CI: 81.44%-108.75%) for the medium-low dose group (Speso Medium-low). Thus, C_{trough} met standard BE criteria.

Table 10. Comparison of C_{trough} values in plasma after 600 mg q4w SC in study 1368-0016 (PFS-1) and 1368-0024 (PFS-2).

Patients originating from ***treatment arm*** *in 1368-0016*	Adjusted gMean (gSE)	Ratio PFS-2/PFS-1 [%]	gSE	90% CI Lower limit	90% CI Upper limit	gCV[1] [%]
Speso High *(N = 29)*						
1368-0016 (PFS-1)	64 666.69 (1.10)					
1368-0024 (PFS-2)	58 649.06 (1.10)	90.69	1.07	81.34	101.12	24.3
Speso Medium-low *(N=16)*						
1368-0016 (PFS-1)	61 179.10 (1.16)					
1368-0024 (PFS-2)	57 573.95 (1.16)	94.11	1.09	81.44	108.75	23.7

ANOVA model included treatment as fixed effect and subject as random effect.
1 Intra-individual SD

Distribution

No new data on distribution of spesolimab has been submitted in this application. Due to the size of spesolimab (~150 kDa), the distribution is expected to be limited to blood and interstitial fluids, and a smaller portion to tissues.

Elimination

In study 0029, the half-life, $t_{1/2}$, was estimated to 21.9 days for 2 ml x 1 injection and 17.9 days for 1 ml x 2 injections, which is within the expected range for spesolimab.

Dose proportionality

In line with previous data, following SC administration, spesolimab exposure increases slightly more than dose-proportionally due to slightly increased bioavailability at higher SC doses.

Time dependency (Immunogenicity)

ADA has previously been shown to influence spesolimab PK in an individual and time-dependent manner. In GPP patients, ADA affected PK at high titers, but there was no clinically relevant impact on efficacy and safety.

Immunogenicity in study 1368-0029

ADA
Antidrug-antibodies (ADA) were screened for in all 48 subjects, and in total 17 subjects (35.4%) were ADA-positive. This is in a similar range as in other studies of spesolimab (range 7.38%-48.1%, mean 30.0%). ADA was most prevalent in the high dose group (600 mg) found in 8/12 subjects (66.7%), followed by the thigh-administered 300 mg group with 4/12 subjects (33%), the 300 mg PFS-1 group with 3/12 subjects (25%) and the fewest ADA-positive subjects was found in the PFS-2 with 2/12 subjects (16.7%).

Table 11. Summary of ADA positivity in study 0029 (**N.B: reversed groups**, R = 2 ml and T1 = 1 ml).

	BI 655130				
	300 mg pmbl R N (%)	300 mg pmbl (l+r) T1 N (%)	300 mg thigh T2 N (%)	600 mg pmbl (l+r) T3 N (%)	Total on-treatment N (%)
Frequency of treatment-induced ADA positive subjects					
Number of subjects	12 (100)	12 (100)	12 (100)	12 (100)	48 (100)
Subjects with negative ADA status at baseline	12 (100)	12 (100)	12 (100)	12 (100)	48 (100)
Treatment-induced ADA-positive	2 (16.7)	3 (25.0)	4 (33.3)	8 (66.7)	17 (35.4)
Transient induced ADA response[1]	1 (8.3)	0	1 (8.3)	0	2 (4.2)
Persistent induced ADA response[2]	0	2 (16.7)	1 (8.3)	4 (33.3)	7 (14.6)
Potentially persistent induced ADA response[3]	1 (8.3)	1 (8.3)	2 (16.7)	4 (33.3)	8 (16.7)
Range of individual ADA titer values	360-2880	720-46 080	360-21 600	180-57 600	180-57 600

[1] Treatment-emergent ADA-positive subjects with 1 or more ADA positive sample where the time period between first and last positive sample is <16 weeks AND the subject was ADA negative for a time period of at least 16 weeks after the last ADA positive sample

[2] Treatment-emergent ADA-positive subjects with at least 2 ADA positive samples where the time period between first and last positive sample is ≥16 weeks

[3] Treatment-emergent ADA-positive subjects whose immunogenic response cannot be classified unambiguously as either transient or persistent

Elimination by ADA status

Spesolimab exposure (AUC and C_{max}) was similar in the ADA positive subjects compared with the ADA negative subjects. The $t_{1/2}$ was on average lower in the ADA-positive subjects, in all treatment groups. ADA positive subjects in the 2-ml group displayed a higher $t_{1/2}$ gMean of 18.4 days, while the 1-ml group displayed a gMean $t_{1/2}$ of 12.8 days. In contrast, ADA-negative subjects in the 2-ml group and 1-ml displayed similar gMean $t_{1/2}$ of 23.5 days and 22.7 days respectively. CL showed a similar trend and tended to be higher in the ADA-positive group.

Overall, ADA incidence was in a similar range as in other studies of spesolimab (35.4%). The ADA incidence was similar between 1 ml and 2 ml periumbilical administration (3 vs 2 subject, respectively).

Study 0016 and 0024

There is no data of ADA after 2 ml administration in the target population, GPP. In PPP, the ADA incidence overall was 48% (68/143) for study 0016 and 51% (55/107) for subjects continued in the OLE trial 0024. This indicates a similar incidence of ADA after multiple dosing of PFS-1 or PFS-2 in PPP patients.

NAbs were not measured in study 0029, and the assay suffered from low drug tolerance yielding most results inconclusive in PPP patients.

Special populations

Special populations were not specifically investigated in the clinical studies relevant to this application and have been previously addressed in MAAs for approved formulations of Spevigo.

Pharmacokinetic interaction studies

There is no new data or literature submitted on interactions for spesolimab.

Pharmacodynamics

N/A

Mechanism of action

N/A

Primary and Secondary pharmacology

N/A

2.6.2. Discussion on clinical pharmacology

This line extension applications concerns a new 2 ml prefilled syringe (PFS), with the same concentration (150 mg/ml) and formulation of spesolimab as the previously approved 1 ml PFS.

Bioanalytical methods

Bioanalytical methods for PK, ADA and nAb have been validated and assessed in previous applications. Overall, the bioanalytical methods were in-study validated and performed in line with current guidelines and were adequate for their purpose.

As raised in a previous assessment (EMEA/H/C/005874/X/0006/G), the nAb assay had insufficient drug tolerance in the PPP population. This is however, not pursued here as the current application is for the indication GPP. However, this issue needs to be addressed in any future application including the indication PPP.

For the target population GPP, there are no ADA/nAb data available for the 2 ml, and thus no new information for the current application.

Bioavailability/Comparability

The primary study submitted in support of this application was a comparative bioavailability study in healthy volunteers (0029) and a secondary comparative analysis of spesolimab trough concentrations (C_{trough}) after 1 ml and 2 ml PFS administration in PPP patients.

In study 0029, the absorption phase was similar between PFS-1 (1 ml x 2 injection sites) and PFS-2 (2 ml x 1 injection site), indicating that the SC administration of 1 ml or 2 ml does not impact the absorption/bioavailability of spesolimab. The ANOVA analysis of PK parameters, C_{max}, AUC_{0-tz} and AUC_{0-inf}, indicated comparable exposure between 1 ml and 2 ml spesolimab administration.

For AUC_{0-tz} and AUC_{0-inf}, the lower limit of the 90% CI was within the bioequivalence (BE) criteria (80% to 125%) but the upper limit was slightly above the upper bound of the BE criteria of 125% (127.42 and 128.02, respectively). This is considered acceptable, as safety and efficacy are not expected to be of concern at a slightly higher exposure. Furthermore, the 1 ml PFS-1 is previously approved, hence efficiency and safety for the (lower) exposure already assessed. See Clinical safety section for more information on potential safety risks.

Moreover, the C_{trough} comparison between study 0016 and 0024 was within standard BE criteria, 80.00%-125.00% 90% CI, indicating that through concentrations are comparable after multiple dosing

of 1 ml and 2 ml administration, at least in the PPP population. Of note, this study is considered secondary, but supportive to study 0029.

The formulation and concentration of spesolimab is not changed between PFS-1 and PFS-2. See Quality AR for further information.

Overall, the submitted comparative BA study 0029 and C_{trough} data from study 0016 vs 0024 are deemed sufficient to bridge PK for PFS-2.

Immunogenicity

ADA has previously been shown to influence spesolimab PK in an individual and time-dependent manner. In GPP patients, ADA affected PK at high titres, but there was no clinically relevant impact on efficacy and safety.

Changing injection volume from 1 ml to 2 ml is not expected to impact ADA incidence significantly. Available data support this, with similar incidence of ADA both after 1 ml and 2 ml spesolimab in healthy volunteers and PPP.

In study 0029, ADA incidence was in a similar range as in other studies of spesolimab (35.4%). ADA positive subjects generally displayed a lower $t_{1/2}$ compared with ADA negative subjects. The ADA incidence was similar between 1 ml and 2 ml periumbilical administration (3 vs 2 subjects). Due to the small sample size, it is difficult to draw any conclusions regarding the impact of ADA on PK for 1 ml vs 2 ml, but injection volume is not expected to affect ADA occurrence significantly.

There is no data of ADA after 2 ml administration in the target population, GPP. In PPP, the ADA incidence overall was 48% (68/143) for study 0016 and 51% (55/107) for subjects continued in the OLE trial 0024. This indicates a similar incidence of ADA after multiple dosing of PFS-1 or PFS-2 in PPP patients.

NAbs were not measured in study 0029. This would have been expected but is acceptable due to the small size of the study and low number of subjects that were ADA positive. For PPP, the nAb assay suffered from low drug tolerance yielding most results inconclusive. However, the level of nAbs are not expected to differ between 1 ml and 2 ml administration, therefore this is not further pursued.

In conclusion, ADA levels were similar after 1 ml and 2 ml injections, and ADA and nAb is not expected to differ at the same dose because of injection volumes. Furthermore, ADA and nAb are not expected to result in clinically significant changes in PK of spesolimab.

Target population

PFS-2 has not been studied in the target population, GPP. This is acceptable, as PK for healthy volunteers and GPP has been assessed in the original MAA and there is no expected difference of clinical relevance between 1 ml and 2 ml administration of spesolimab.

Overall, the submitted comparative BA study 0029 and C_{trough} data from study 0016 vs 0024 are deemed sufficient to bridge PK for PFS-2.

2.6.3. Conclusions on clinical pharmacology

The PK bridging of spesolimab following subcutaneous administration with PFS-2 is supported. Comparable bioavailability can be concluded between PFS-1 and PFS-2. The proposed changes by the MAH to the SmPC (sections 4.2 and 5.2) are endorsed.

2.6.4. Clinical efficacy

No new efficacy data for the 300 mg formulation has been provided.

2.6.1. Discussion on clinical efficacy

No new efficacy data for the 300 mg formulation has been provided. Based on the PK results of trial 0029 comparing the 1 ml and the 2 ml syringe, C_{max} is bioequivalent, and $AUC_{0\text{-}tz}$ slightly exceeds the BE criteria (point estimate 1.07, 90% confidence interval 0.89-1.27). No relevant impact on the efficacy of spesolimab by switching from 1-mL to 2-mL injection is expected.

2.6.2. Conclusion on the clinical efficacy

No efficacy data have been submitted and this is acceptable in the context of this application.

2.6.3. Clinical safety

No new clinical safety studies were performed to specifically support the current application.

In the relative bioavailability study, Trial 0029, after periumbilical administration of a 300 mg dose, a slightly higher than bioequivalent exposure ($AUC_{o\text{-}tz}$) after administration of 2 mL×1 site compared with 1 mL×2 sites was observed, with a mean ratio (1x 2ml / 2x 1ml) of 106.76% and a confidence interval of 89.45 - 127.42%.

Therefore, the MAH discussed the potential for safety concerns with the additional/new presentation with 2 mL volume based on the following:

- Safety data from the single-dose bioavailability Trial 1368-0029
- Safety data from other trials in healthy volunteers (HVs):
    - 1368-0002, a multiple rising dose trial, IV administration
    - trial 1368-0003, a Phase I study in Caucasian healthy volunteers, IV and SC administration
    - trial 1368-0009, a Phase I study Japanese healthy volunteers, IV and SC administration
    - trial 1368-0043, a Phase I study Chinese healthy volunteers, IV and SC administration
- Safety data from trials in HVs or patients with Hidradenitis suppurativa (HS) that used the 2 mL PFS (PFS-2):
    - trial 1368-0043 in healthy volunteers
    - trial 1368-0024 in patients with palmoplantar pustolosis (PPP)
    - trial 1368-0052 in patients with hidradenditis suppurativa (HS)
    - 1368-0067 (ongoing) in patients with HS
- Safety and PK exposure-response data for safety from the GPP flare prevention trial 1368-0027
- Safety data from all completed clinical trials and open-label data from ongoing clinical trials with spesolimab up to the sBLA submission date of 18 May 2023 for GPP flare prevention indication.

In addition, the MAH has performed a new human factors engineering (HFE)/usability engineering (UE) analysis of the 2 ml PFS.

All the safety data reviewed by the MAH for the current submission, except the pivotal relative bioavailability study and the new HFE/UE analysis, have been previously discussed within the marketing authorisation application procedures for the approved formulations of Spevigo, and are not described in detail here.

2.6.3.1. Safety results from trial 1368-0029

Trial 0029 was a single dose, relative bioavailability study in healthy volunteers (n=12 per treatment group). The safety of spesolimab was generally comparable after administration of 300 mg SC as either 1 mL×2 sites or 2 mL×1 site. In particular, adverse events (AEs) related to injection site reactions were similar between SC administration of 1 mL×2 sites and 2 mL×1 site:

- 1 mL×2 sites: 3 patients with injection site erythema (all mild)
- 2 mL×1 site: 3 patients with injection site erythema, 1 patient with injection site swelling (all mild).

2.6.3.2. Safety results from other trials in healthy volunteers

Trials discussed:

- 1368-0002, a multiple rising dose trial
- trial 1368-0003, a Phase I study in Caucasian healthy volunteers
- trial 1368-0009, a Phase I study Japanese healthy volunteers
- trial 1368-0043, a Phase I study Chinese healthy volunteers

In Trial 0002, healthy subjects received multiple (4×q1w) IV doses of up to 20 mg/kg body weight (mean body weight was 75.55 kg; approximately equivalent to 1500 mg). The overall incidence of subjects with treatment-emergent AEs was similar for the placebo group and the spesolimab treatment groups, and no dose-dependency was observed. Drug-related AEs were reported in 13 of the 24 subjects (54.2%) who received spesolimab and 4 of the 8 subjects (50.0%) who received placebo. The only drug-related AE with an apparent dose-dependent increase in incidence was headache.

Trials 0003, 0009 and 0043 compared pharmacokinetics and safety after different IV and SC doses. In Trial 0003, injection site oedema was the only local reaction reported as an AE and was reported in 1/12 subjects in each of the two subcutaneous dose groups (150 mg and 300 mg). In Trial 0009, no AEs were reported after a 300 mg SC dose administered as 1x2 ml to 6 subjects. In Trial 0043 subjects received a single SC dose of either 300 mg or 600 mg, using a 2 ml syringe. No local reactions at the administration site were reported as AEs in this study.

2.6.3.3. Safety results from trials that used the 2 ml prefilled syringe (PFS-2)

Trials discussed:

- trial 1368-0043 in healthy volunteers
- trial 1368-0024 in patients with palmoplantar pustolosis (PPP)
- trial 1368-0052 in patients with hidradenitis suppurativa (HS)
- 1368-0067 (ongoing) in patients with HS

Trial 0043

No local reactions at the administration site were reported as AEs in the study.

Trial 0024

This was an extension trial in which patients with PPP rolling over from the parent trial (Trial 0016) received SC doses of 600 mg spesolimab Q4W using the 2 ml syringe. The study was prematurely discontinued due to the sponsor's decision to terminate the clinical program for spesolimab in PPP. The MAH confirms that this decision was not based on any safety finding in the clinical trials.

Overall, 108 patients were treated with spesolimab leading to a time at risk of 193 pt-yrs.

The most frequently reported AEs (≥5%) are shown in Table 12. The most common AEs were reported in the SOC infections and infestations with the PTs COVID-19 and nasopharyngitis. The study was performed between 08 Sep 2020 and 15 May 2023; thus, partly during the COVID-19 pandemic. All except one AE of COVID-19 were assessed as not related to spesolimab administration by the investigator.

The majority of AEs judged as drug-related by the investigator were related to injection site reactions, similarly to the parent trial 1368-0016 (using the 1 ml syringe).

Most of the injection site reactions were of mild severity, i.e. Rheumatology Common Toxicity Criteria (RCTC) Grade 1. There were two reports of Grade 2 injection site erythema and one report each of Grade 2 injection site swelling, injection site pain, injection site induration, injection site pruritus, and injection site warmth. There were no injection site reactions of RCTC Grade 3 or higher.

Table 12. Adverse events reported for more than 5% of patients on the preferred term level in Trial 1368-0024.

System organ class/ Preferred term	600 mg spesolimab s.c. q4w			
	N	%	Time at risk [pt-yrs]	Rate/100 pt-yrs
Number of patients	108	100.0	193	
Total with AEs	96	88.9	52.6	182.6
Infections and infestations	71	65.7	115.2	61.6
COVID−19	31	28.7	169.4	18.3
Nasopharyngitis	16	14.8	173.2	9.2
Upper respiratory tract infection	6	5.6	187.2	3.2
Nervous system disorders	21	19.4	169.4	12.4
Headache	8	7.4	182.9	4.4
Skin and subcutaneous tissue disorders	47	43.5	141.3	33.3
Eczema	9	8.3	182.0	4.9
Palmoplantar pustulosis	8	7.4	188.7	4.2
Dermatitis contact	7	6.5	184.9	3.8
Musculoskeletal and connective tissue disorders	35	32.4	150.4	23.3
Arthralgia	12	11.1	179.6	6.7
Back pain	11	10.2	182.0	6.0
General disorders and administration site conditions	41	38.0	133.5	30.7
Injection site erythema	20	18.5	160.9	12.4
Pyrexia	14	13.0	174.0	8.0
Injection site swelling	12	11.1	174.5	6.9
Injection site pain	9	8.3	178.1	5.1
Injection site induration	6	5.6	185.2	3.2
Injection site pruritus	6	5.6	183.7	3.3
Injection site warmth	6	5.6	184.0	3.3
Injury, poisoning and procedural complications	29	26.9	161.7	17.9
Fall	6	5.6	186.0	3.2

pt-yrs = patient years; q4w = every four weeks
Patients with AE: Time at risk = start of first AE − start of treatment + 1 day.
Patients without AE: time at risk = end of time at risk − start of treatment + 1 day.
Incidence rates were calculated using number of patients with the respective events per treatment divided by time at risk expressed as [100 pt-yrs].

Trial 0052

This was a placebo-controlled study of spesolimab in patients with moderate to severe hidradenitis suppurativa. The study consisted of a 12-week treatment phase. A total of 36 patients received three weekly IV loading doses of 1200 mg each, for a total loading dose of 3600 mg, followed by subcutaneous doses of 1200 mg every 2 weeks, at weeks 4, 6, 8 and 10. After treatment evaluation by week 12, there was a 16-week safety follow-up period. The placebo group included 12 patients.

The proportions and incidence rates of patients with any AE were comparable between the placebo and the spesolimab treatment group. The incidence rate of drug-related AEs was higher in the spesolimab treatment group (15 patients, 41.7%) than in the placebo treatment group (3 patients, 18.8%), largely due to injection site reactions.

AEs reported for at least 2 patients in any of the groups are displayed in Table 13.

All AEs, reported in this trial, were classified as mild (RCTC grade 1) or moderate (RCTC grade 2) intensity. No patients were reported with AEs of severe (RCTC grade 3) or a life-threatening (RCTC grade 4) intensity across the entire treatment period.

All administration site reactions were of RCTC grade 1 in this trial.

Table 13. AEs reported for at least 2 patients in Overall Total on the PT level in trial 1368-0052 (HS).

MedDRA SOC PT	Placebo N (%)	Spesolimab N (%)	Overall Total N (%)
Number of patients	16[1] (100.0)	36[1] (100.0)	52 (100.0)
Total with any AE	14 (87.5)	28 (77.8)	42 (80.8)
Infections and infestations	5 (31.3)	14 (38.9)	19 (36.5)
Nasopharyngitis	3 (18.8)	3 (8.3)	6 (11.5)
COVID-19	1 (6.3)	1 (2.8)	2 (3.8)
Upper respiratory tract infection	0	2 (5.6)	2 (3.8)
Urinary tract infection	0	2 (5.6)	2 (3.8)
Psychiatric disorders	2 (12.5)	4 (11.1)	6 (11.5)
Anxiety	1 (6.3)	2 (5.6)	3 (5.8)
Nervous system disorders	4 (25.0)	8 (22.2)	12 (23.1)
Headache	3 (18.8)	4 (11.1)	7 (13.5)
Dizziness	1 (6.3)	1 (2.8)	2 (3.8)
Sciatica	0	2 (5.6)	2 (3.8)
Tremor	1 (6.3)	1 (2.8)	2 (3.8)
Respiratory, thoracic and mediastinal disorders	3 (18.8)	3 (8.3)	6 (11.5)
Cough	1 (6.3)	1 (2.8)	2 (3.8)
Gastrointestinal disorders	1 (6.3)	6 (16.7)	7 (13.5)
Nausea	0	4 (11.1)	4 (7.7)
Diarrhoea	0	2 (5.6)	2 (3.8)
Skin and subcutaneous tissue disorders	3 (18.8)	10 (27.8)	13 (25.0)
Hidradenitis	2 (12.5)	1 (2.8)	3 (5.8)
Pruritus	1 (6.3)	2 (5.6)	3 (5.8)
Acne	0	2 (5.6)	2 (3.8)
Intertrigo	1 (6.3)	1 (2.8)	2 (3.8)
Musculoskeletal and connective tissue disorders	1 (6.3)	5 (13.9)	6 (11.5)
Back pain	1 (6.3)	2 (5.6)	3 (5.8)
Pain in extremity	1 (6.3)	1 (2.8)	2 (3.8)
Renal and urinary disorders	1 (6.3)	2 (5.6)	3 (5.8)
Dysuria	1 (6.3)	1 (2.8)	2 (3.8)
Reproductive system and breast disorders	2 (12.5)	1 (2.8)	3 (5.8)
Intermenstrual bleeding	1 (6.3)	1 (2.8)	2 (3.8)
General disorders and administration site conditions	2 (12.5)	12 (33.3)	14 (26.9)
Fatigue	0	4 (11.1)	4 (7.7)
Injection site erythema	0	4 (11.1)	4 (7.7)
Injection site pain	1 (6.3)	3 (8.3)	4 (7.7)
Investigations	2 (12.5)	2 (5.6)	4 (7.7)
Bacterial test positive	1 (6.3)	1 (2.8)	2 (3.8)

Trial 0067

This is an ongoing long-term (2-year) extension trial of spesolimab treatment in adult patients with Hidradenitis Suppurativa (HS). The study aims at assessing the long-term safety of spesolimab in patients with HS who have completed the 1368-0052. The trial included 45 patients with HS. Patients from the placebo arm of the 1368-0052 trial were given an initial 1200 mg IV loading dose of

spesolimab, followed by 600 mg spesolimab SC every two weeks. Patients from the active arm of the 1368-0052 trial were given a loading dose of placebo followed by 600 mg spesolimab SC every two weeks.

A study report for this trial is not yet available. AEs reported for at least 5% of patients up to a cut-off date of 1 Dec 2022 were summarised in the Summary of Clinical Safety submitted with variation EMEA/H/C/005874/X/0006/G and are shown in Table 14.

Table 14. AEs reported for at least 5% of patients on the PT level in trial 1368-0067 (HS).

SOC PT	N (%)
Number of patients	45 (100.0)
Patients with any AE	41 (91.1)
Infections and infestations	27 (60.0)
COVID-19	12 (26.7)
Nasopharyngitis	6 (13.3)
Skin and subcutaneous tissue disorders	18 (40.0)
Hidradenitis	8 (17.8)
Musculoskeletal and connective tissue disorders	15 (33.3)
Back pain	4 (8.9)
Myalgia	4 (8.9)
Arthralgia	3 (6.7)
Pain in extremity	3 (6.7)
General disorders and administration site conditions	13 (28.9)
Pyrexia	3 (6.7)
Gastrointestinal disorders	11 (24.4)
Diarrhoea	4 (8.9)
Respiratory, thoracic and mediastinal disorders	8 (17.8)
Oropharyngeal pain	4 (8.9)
Cough	3 (6.7)
Nervous system disorders	8 (17.8)
Headache	3 (6.7)

Events up to a cut-off date of 01 Dec 2022 are included.

2.6.3.4. Safety results from the GPP flare prevention trial 1368-0027

This trial was described and discussed in detail within variation EMEA/H/C/005874/X/0006/G.

Three subcutaneous dose regimens of spesolimab were evaluated in the trial, all administered using the 1 ml PFS. The highest dose, a loading dose of 600 mg followed by Q4W doses of 300 mg, was the one proposed and approved for the GPP flare prevention indication (EMEA/H/C/005874/X/0006/G).

The safety analysis did not identify any clear dose dependency of the AEs observed in this study.

2.6.3.5. Trials with higher plasma levels

In the Clinical Overview Statement submitted with the current application, the MAH discusses in particular trials with IV administration of spesolimab, which leads to higher peak plasma concentrations (C_{max}) than after administration of spesolimab via the SC route. In summary, safety results from the trials with IV administration were consistent with the overall safety results.

2.6.3.6. Human factors engineering/usability engineering study

The MAH has conducted a complete human factors engineering (HFE)/usability engineering (UE) analysis of the spesolimab PFS-NSD-2 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-2 implemented solutions to the problems. Four 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-2 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.

The MAH analysed use events and non-safety related findings associated with the completed studies. The risk of each use event, safety and non-safety, was analysed. All safety relevant findings including use difficulties, test administrator assistance, and close calls were described and potential root causes discussed – please see below the discussion on clinical safety.

2.6.3.7. Potential for medication errors and planned risk minimisation measures

The introduction of the PFS-NSD-2 formulation is planned to be supported by the following routine risk minimisation measures that support an uneventful introduction of this new strength and avoid potential medication errors:

- Clear guidance in the local product information (mainly in the sections Handling instructions / IFU and Dosage and Administration) to ensure that the correct dose is used;
- Packaging and labelling - artwork to support adequate differentiation, e.g. use of different colours and device images on the carton;
- Different pack sizes, with one syringe per pack for PFS-NSD-2 and two syringes per pack for PFS-NSD-1;
- Training material for patients and HCPs are planned to be prepared for the introduction of the PFS-NSD-2 addressing differences of the devices;
- Dosage and administration section of the product information recommends that 'Spevigo treatment be initiated and supervised by physicians experienced in the management of patients with inflammatory skin diseases'.

If, despite these measures, the two strengths are interchanged unintentionally, this medication error would most likely result in administration of a wrong dose, either by:

- Use of PFS-NSD-1 instead of PFS-NSD-2 leading to administration of a lower/sub-therapeutic dose (halving of the dose)
- Use of PFS-NSD-2 instead of PFS-NSD-1 leading to administration of a higher than the recommended dose (doubling of the dose).

See below the discussion on safety.

2.6.4. Discussion on clinical safety

The current application concerns a new prefilled syringe (PFS) of spesolimab 150 mg/ml, with a greater volume (2 ml as compared with the previously approved 1 ml syringe), which reduces the number of

injections per dosing occasion. There is no change in dose or indication (prevention of GPP flares) for the subcutaneous formulation of spesolimab.

A relative bioavailability study in healthy volunteers indicated that the total exposure ($AUC_{0\text{-}tz}$) may be slightly higher following administration of 300 mg dose of spesolimab using the 2 ml PFS (1 injection) compared with the 1 ml PFS (2 injections), with a mean ratio for AUC (1 injection/2 injections) of 1.07.

The most relevant safety aspects to consider for this application are:

- Potential differences in local reactions at the administration site with administration of 1 x 2 ml compared with 2 x 1 ml of the spesolimab 150 mg/ml solution for subcutaneous injection;
- Potential safety issues with a slightly higher exposure to spesolimab following use of the 2 ml PFS than in the pivotal study supporting the original approval of GPP flare prevention indication (in which the 1 ml PFS was used);
- The potential risk for misuse/dosing errors.

The MAH provided a short Clinical Overview statement, discussing safety data from previously submitted studies with spesolimab at different doses and indications, including GPP, PPP, and HS. All these studies have been previously submitted and discussed within the original MAA for spesolimab and/or in the extension application for the 1 ml PFS.

In addition, the MAH has performed a new Human factors engineering (HFE)/usability engineering (UE) analysis and discussed risk minimisation measures for the 2 ml PFS.

Injection site reactions

In the relative bioavailability study, which was a single-dose, parallel group trial in healthy volunteers (n=12 per treatment group), there were no relevant differences between the two treatment groups (SC administration of 300 mg spesolimab as 1 x 2ml and 2 x 1ml, respectively) in terms of local reactions at the injection site. There were 3 subjects with injection site erythema (all mild) in the 2 x 1 ml group and 3 subjects with injection site erythema + 1 patient with injection site swelling (all mild) in the 1 x 2 ml group. Of note, injection site pain, which could be expected to be more frequent with a larger injection volume, was not reported by the investigator in either treatment group.

Also in other completed studies using the 2 ml PFS in healthy volunteers or in patients with PPP or HS, the rate of injection site adverse reactions was relatively low, and most reactions were of mild severity, i.e. Rheumatology Common Toxicity Criteria (RCTC) Grade 1. A few cases of Grade 2 reactions were reported, while there were no injection site reactions of Grade 3 or higher. Therefore, the higher injection volume of the new 2 ml PFS does not give raise to safety concerns regarding local reactions that would outweigh the benefit of a reduced number of injections per dosing occasion.

Other adverse events

During the original MAA and the subsequent variation application (EMEA/H/C/005874/X/0006/G) for spesolimab for the treatment and prevention of GPP flares, respectively, it was concluded that in placebo-controlled trials with spesolimab in different indications, there were few notable differences in adverse event profiles between treatment groups. In terms of systemic adverse events, the exception was infections, which in some studies were more commonly reported in spesolimab-treated patients than in the placebo group. In addition, in studies with subcutaneous administration of spesolimab, a higher rate of injection site reactions were seen in spesolimab-treated groups than in placebo groups.

The data included in the previous applications further showed that the safety profile of spesolimab was largely similar and manageable across studies, indications and dose regimens. This included studies

with intravenous administration, leading to high C_{max} levels as compared with subcutaneous administration, and studies with higher doses of subcutaneous maintenance treatment than that recommended for prevention of GPP flares. The adverse events that differed between the different patient populations could mainly be attributed to the disease studied, rather than to spesolimab. The reported SAEs were few and of various nature and were generally assessed as unrelated to spesolimab. Altogether, the previous safety assessment did not give raise to any major safety concerns and did not indicate a clear dose dependency of adverse events.

Therefore, the somewhat higher exposure (on average about 7% higher AUC) that, based on the relative bioavailability study, may be obtained with the 2 ml PFS as compared with the 1 ml PFS, is not likely to constitute a higher risk for adverse drug reactions than what has been previously observed in the GPP flare prevention studies.

Risk for misuse/dosing errors

A human factors engineering (HFE)/usability engineering (UE) analysis of the pre-filled syringe was previously discussed within the extension application for the 1 ml PFS (EMEA/H/C/005874/X/0006/G). The MAH provided a new HFE/UE analysis with the current variation. The MAH suggests that any residual risk that remains after usability testing would not be further reduced by modifications of design of the user interface (including any accessories and the instructions for use [IFU]) and is outweighed by the benefits that may be derived from the device's use. Therefore, the PFS-NSD-2 has shown to be safe and effective for the intended users, intended uses, and in the intended use environments. This is accepted.

Apart from the differences in injection volume, the 1 ml PFS and the 2 ml PFS are similar, and are similarly handled. The main added device-associated risk with introduction of the new 2 ml PFS is therefore the risk of administration of the wrong dose, either if the 1 ml syringe is used for a single injection, or the 2 ml syringe is used for two injections, leading to a too low or a too high dose, respectively.

The MAH suggests that since spesolimab has a relatively wide therapeutic window in GPP patients, both in terms of efficacy and safety, administration of a too low or a too high dose will not have unacceptable consequences. This can be accepted, at least for single occasions of administering the wrong dose. In the long-term, lack of efficacy may be a greater risk than administration of a too high dose, as a GPP flare can be life-threatening, and given that a statistically significant effect in reducing the number of GPP flares was only shown for the highest spesolimab dose in the pivotal GPP flare prevention study (variation EMEA/H/C/005874/X/0006/G).

The MAH proposes a number of risk minimisation measures to avoid erroneous use of the two PFS strengths, including clear instructions for use, labelling, colour coding, and training materials. The SmPC recommends that self-administration is advisable only "if the healthcare professional determines that it is appropriate". In addition, the pack sizes differ, with one syringe per pack for the new 2 ml PFS and two syringes per pack for the previously approved 1 ml PFS. These measures seem adequate to mitigate the risk of mix-up between the two strengths. Any reports of dosing errors are expected to be routinely described and discussed in future PSURs.

2.6.5. Conclusions on clinical safety

From a safety perspective there are no objections to the approval of the new spesolimab 2 ml PFS.

2.7. Risk management plan

2.7.1. Safety concerns

Summary of safety concerns

Important identified risks	Systemic hypersensitivity reaction
Important potential risks	Serious or opportunistic infections
	Malignancy
	Peripheral neuropathy
Missing information	Pregnant or breast-feeding women
	Use in patients with body weight <40 kg

2.7.2. Pharmacovigilance plan

Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones/Due dates
PASS 1368-0128 (Cat. 3) 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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks Systemic hypersensitivity reaction	*Routine risk minimisation measures* EU-SmPC sections 4.3, 4.4, 4.8 PL sections 2, 4 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)
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 *Additional pharmacovigilance activities* PASS 1368-0128 (final report 31 Dec 2031)
Important potential risks 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)

Important potential risks 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)
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
Missing information Use in patients with body weight <40 kg	*Routine risk minimisation measures* EU-SmPC section 4.2 PL section 3 Prescription only medicine Reduced dosing regimen for adolescents weighing ≥30 and <40 kg 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 4.1 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the 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

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Spevigo (Spesolimab) is included in the additional monitoring list as

- it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and
- 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 assessment

3.1. Therapeutic Context

The present application concerns a new 2 ml prefilled syringe (PFS) with a needle safety device (PFS-NSD-2), intended to be used for prevention of GPP flares. The PFS-NSD-2 is a larger volume syringe filled with the same formulation (150 mg/ml solution for subcutaneous injection) as the previously approved 1 ml syringe (PFS-NSD-1).

The indication (prevention of GPP flares) and the recommended dose (600 mg loading dose followed by 300 mg Q4W) of the subcutaneous formulation of spesolimab remain unchanged.

3.1.1. Disease or condition

Spesolimab for subcutaneous administration is intended for the prevention of generalised pustular psoriasis (GPP) flares in adults and adolescents from 12 years of age.

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. A GPP flare consists of the acute onset of rapidly disseminating painful skin manifestations, which can be accompanied by systemic symptoms, such as high fever and extreme fatigue, as well as acute phase response (with increased C-reactive protein). GPP flares may 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.

3.1.2. Main clinical studies

The application is primarily based on the results of a comparative bioavailability trial, no 1368-0029, which was previously submitted with the original MAA. The study compared the pharmacokinetics and safety of a single dose of subcutaneous spesolimab following administration of 300 mg using the previously approved 1 ml PFS and using the new 2 ml PFS to healthy volunteers.

3.2. Favourable effects

In trial 1368-0029, comparative exposure was demonstrated after administration of 300 mg spesolimab subcutaneously, using the new 2 ml PFS and the previously approved 1 ml PFS, respectively, with an $AUC_{0\text{-}tz}$ mean ratio (1x2ml / 2x1ml) of 106.76% (90% confidence interval: 89.45 - 127.42%).

No new efficacy data have been provided. The expected benefit of the new 2 ml PFS, compared with the 1 ml PFS, is a reduced number of injections per dosing occasion, and thereby a reduced burden for the patient.

3.3. Uncertainties and limitations about favourable effects

Like the 1 ml PFS, the 2 ml PFS can be self-administered by the patient, if the healthcare professional determines that it is appropriate. The main risk with the introduction of a 2 ml PFS is considered the risk of mix-up between syringes and in particular the administration of a too low dose if only 1 x 1 ml (150 mg) is administered. If this would go on for a longer timer period, it could potentially lead to an increased risk of the patient having a GPP flare. However, the MAH's proposed risk minimisation measures, e.g. the different pack sizes, are expected to mitigate the risk.

3.4. Unfavourable effects

No new safety data have been provided.

Across previously submitted studies with subcutaneously administered spesolimab, in different indications and at different dose regimens, the injection site reactions have mostly been mild to moderate. The safety data from the comparative bioavailability study did not indicate an increased risk for injection site reactions with the 2 ml PFS, as compared with the 1 ml PFS. Altogether, there were 3/12 subjects with injection site erythema (all mild) in the 2 x 1 ml group and 3/12 subjects with injection site erythema + 1 patient with injection site swelling (all mild) in the 1 x 2 ml group. Also,

between-study comparisons of previously submitted studies indicated no increase in the frequency or severity of injections site reactions with the 2 ml PFS, as compared with the 1 ml PFS.

3.5. Uncertainties and limitations about unfavourable effects

The results of the comparative bioavailability study indicated a slightly higher exposure, with a mean ratio for AUC of 1.07, and upper confidence interval limit not entirely meeting standard bioequivalence (BE) criteria, following administration of 300 mg spesolimab using the 2 ml PFS as compared with the 1 ml PFS. The deviation from BE was minor. Based on previously available safety data, where no clear dose-dependency in the frequency or severity of adverse events could be detected, a potentially slightly higher exposure with the 2 ml PFS is not expected to lead to an increased risk of adverse drug reactions.

There may be a potential risk of administering a too high dose if there is a mix-up between the 1 ml and the 2 ml PFS. Due to the lack of dose dependency for adverse events across studies, occasional administration of a too high dose is not of concern. The MAH's proposed risk minimisation measures are expected to mitigate the risk of mix-up between the two strengths.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The information on the finished product is satisfactory and this application is recommended for approval from a quality point of view.

With the new 2 ml PFS, the complete dose can be administered with one injection, instead of two injections, reducing the burden for the patient, which is a relevant benefit.

A potentially slightly higher exposure to spesolimab using the 2 ml PFS is not expected to lead to an increased risk of systemic adverse drug reactions as, across studies, no apparent dose dependency in adverse drug reactions of spesolimab has been observed. Further, safety data from spesolimab studies using the 2 ml PFS does not give raise to concern regarding a potentially increased risk for injection site reactions as compared with the 1 ml PFS.

The MAH's proposed risk minimisation measures are expected to mitigate the risk of dosing errors due to mix-up between the two syringes.

3.6.2. Balance of benefits and risks

A reduced number of injections per dosing occasion is considered a benefit for the patient. The potential risk of erroneous use of the 1 ml instead of the 2 ml syringe is expected to be mitigated with the MAH's proposed risk minimisation measures, and this potential risk does not outweigh the benefit of a reduced dosing burden.

3.7. Conclusions

The overall benefit /risk balance of Spesolimab solution for injection in pre-filled syringe 300 mg is positive subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety, the CHMP considers by consensus that the benefit-risk balance of, Spevigo new strength of 300 mg (150 mg/ml) for solution for injection is favourable in the following indication:

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 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.