EU Risk Management Plan for SPEVIGO (Spesolimab)

RMP version to be assessed as part of this application:

RMP version number:	4.1
Data lock point for this RMP:	26 Nov 2024
Date of final sign off:	18 May 2025
Rationale for submitting an updated RMP:	Consolidation of v3.0 (new strength for GPP flare prevention, pre-filled syringe needle device, 300 mg) and v4.0 (Reclassification of 'Systemic hypersensitivity reaction' from an important potential risk to an important identified risk)
Summary of significant changes in this RMP:	V3.0 New strength for GPP flare prevention (prefilled syringe-needle safety device, 300 mg) Update of Parts I and VI to include the new strength; administrative update to Appendix 8 V4.0 *Safety concerns* Reclassification of 'Systemic hypersensitivity reaction' from an important potential risk to an important identified risk (Part II Modules SIV, SVII and SVIII; Parts III, V and VI; Appendix 7) *Other* Update of post-marketing exposure (Part II Module SV) Administrative updates to Part I, Appendices 1 and 8

Other RMP versions under evaluation:	Not applicable
RMP version number:	
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Details of the currently approved RMP:

Version number:	4.0
Approved with procedure:	EMA/VR/0000249137
Date of approval (opinion date):	08 May 2025

QPPV name:	Sven Kohler
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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PART I PRODUCT OVERVIEW

PI.Table 1 Product Overview

Active substance (INN or common name)	Spesolimab (spesolimab)
Pharmacotherapeutic group (ATC code)	Interleukin inhibitor (L04AC22)
Marketing Authorisation Holder	Boehringer Ingelheim International GmbH
Medicinal product to which this RMP refers	1
Invented name in the EEA	Spevigo
Marketing authorisation procedure	Centralised
Brief description of the product	*Chemical class* Monoclonal antibody to IL-36R
	Summary of mode of action Spesolimab is a humanised monoclonal IgG1 antibody to IL-36R. Spesolimab blocks signalling of human IL-36R. Binding of spesolimab to IL-36R is anticipated to prevent the subsequent activation of IL-36R by cognate ligands (IL-36 α, β, and γ) as well as downstream activation of pro-inflammatory and pro-fibrotic pathways.
	Important information about its composition Spesolimab is a humanised monoclonal IgG1 antibody against human IL-36R. Spesolimab is expressed in CHO cells. It is manufactured using standard mammalian cell culture techniques, followed by a series of protein purification steps including several chromatography steps, as well as steps for removal and inactivation of potential viruses. No materials of animal/human origin are used in the manufacturing process.
Hyperlink to the Product Information	Product information

PI.Table 1 (cont'd) Product Overview

Indications in the EEA	*Current* Treatment of generalized pustular psoriasis (GPP) flares in adults and adolescents from 12 years of age as monotherapy Prevention of generalized pustular psoriasis (GPP) flares in adults and adolescents from 12 years of age
	Proposed Not applicable
Dosages in the EEA	*Current* <u>GPP flare treatment</u> *Adults and adolescents from 12 years of age and weighing ≥40 kg* 900 mg (2 vials of 450 mg), single dose for i.v. infusion *Adolescents from 12 years of age and weighing ≥30 and <40 kg* 450 mg (1 vial of 450 mg), single dose for i.v. infusion <u>GPP flare prevention</u> *Adults and adolescents from 12 years of age and weighing ≥40 kg* s.c. loading dose of 600 mg (either four 150 mg injections or two 300 mg injections), followed by 300 mg (either two 150 mg injections or one 300 mg injection) administered s.c. every 4 weeks *Adolescents from 12 years of age and weighing ≥30 and <40 kg* s.c. loading dose of 300 mg (either two 150 mg injections or one 300 mg injection), followed by 150 mg (one 150 mg injection) administered s.c. every 4 weeks)
	Proposed Not applicable
Pharmaceutical forms and strengths	*Current* <u>GPP flare treatment</u> Concentrate for solution for i.v. infusion, 450 mg <u>GPP flare prevention</u> Solution for s.c. injection, 150 mg and 300 mg
	Proposed Not applicable
Is the product subject to additional monitoring in the EU?	Yes

ABBREVIATIONS

ATC	Anatomical therapeutic chemical
CHO	Chinese hamster ovary
EEA	European Economic Area
EU	European Union
GPP	Generalized pustular psoriasis
i.v.	Intravenous
IgG1	Immunoglobulin G1
IL-36R	Interleukin 36 receptor
INN	International non-proprietary name
RMP	Risk Management Plan
s.c.	Subcutaneous

PART II SAFETY SPECIFICATION

MODULE SI EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATIONS

SI.1 GENERALIZED PUSTULAR PSORIASIS

SI.1.1 Incidence

There is currently newly published data on the incidence of GPP. A study was conducted by BI using the NPR in Sweden to determine the incidence of GPP [R22-0363]. Patients were considered as having GPP if they had an ICD-10 diagnosis code L40.1 (“generalised pustular psoriasis”) and no previous code for GPP in the NPR. In 2015, the incidence of GPP was determined to be 0.82 per 100 000 persons in Sweden. The incidence of GPP decreased to 0.42 per 100 000 in Sweden when the case definition required 2 GPP-related visits [R22-0363] A national adjusted incidence was reported as 0.51 to 0.63 per 100 000 based on a Chinese retrospective cohort study using claims databases representing 23 provinces in 2016 [R22-0494]. A Canadian study reported an incidence rate of 1.95 per million over a 5-year period [R22-4073].

SI.1.2 Prevalence

Estimates of the prevalence of GPP are sparse in the literature because of the rarity of the disease. 9 publications R16-2698, R18-1635, R20-1502, R21-3418, R21-3492, R22-0363, R22-0384, R22-0461, R22-4162] showed the prevalence of GPP in the general population and the range of prevalence was between 1.76 per 1 000 000 persons in France [R16-2698] to 46 per 100 000 persons in Germany [R18-1635]. This large variability in the prevalence estimates may be attributed to differences in calculation methodologies. In the French study [R16-2698], the definition of GPP was determined by individual dermatologists as no criteria for diagnosis was specified in the survey. Additional information on the method used to calculate the prevalence, including the size of the denominator, proportion and representativeness of the chosen dermatology clinics, and other relevant information was not provided. Therefore, it cannot be determined if the prevalence reported is a reliable estimation of the true prevalence of GPP in France. GPP is a difficult condition to diagnose and most often diagnosed by a dermatologist, but the prevalence estimate in the German study [R18-1635] was not restricted to claims by dermatologists only. Therefore, it is possible that patients were incorrectly diagnosed as having GPP and the reported prevalence may be an overestimate of the true prevalence.

To better understand the global prevalence of GPP, BI published analyses using administrative claims databases from the US, Japan, Sweden, and China [R21-3418, R22-0363]. In the US, individuals enrolled in either the Truven MarketScan administrative claims database (from 01 Jan 2018 to 31 Dec 2018) with an ICD-10 code: L40.1 “Generalized pustular psoriasis” or the Optum claims database (from 01 Jan 2019 to 31 Dec 2019) were considered GPP patients. The calculated prevalence was 7 per 100 000 persons in the Truven Market Scan database and 9 per 100 000 persons in Optum [R21-3418]. It is possible that the prevalence in the US claims databases can be either an under or overestimate of the true prevalence. Since GPP is difficult to diagnosis, physicians may have incorrectly classified the

patient as GPP and then subsequently ruled out the diagnosis, leading to an overestimate of the prevalence. It is also possible that GPP patients were intentionally classified as psoriasis patients in order to receive treatment, thereby underestimating the true prevalence.

Prevalence of GPP in Japan was explored using the JMDC and MDV claims databases [R21-3418]. Similar to other claims databases, an individual was considered to have GPP if they had an ICD-10 diagnosis code of L40.1. In 2018, the GPP prevalence was 2 per 100 000 persons in MDV and 3 per 100 000 persons in JMDC. Both databases have their limitations that may suggest the calculated prevalence is an underestimate of the true prevalence in Japan. MDV is a hospital-based system and patients outside of the MDV system would not be captured in the database. JMDC is an employer-based health insurance system. Older individuals and those who cannot work are not well represented in JMDC, therefore individuals with a more debilitating course of GPP may not be included in the database.

BI also collaborated with the University of Peking to estimate the prevalence of GPP in China. ICD-10 diagnosis codes plus free text from a claims database was evaluated. The annual prevalence was determined to be 1.108 per 100 000 based on 2010 Census data and the national crude prevalence was 1.403 per 100 000 [R22-0494].

A collaboration with the National Psoriasis Register (PsoReg) and the IHE in Sweden to better understand the prevalence and incidence, natural history and patient reported burden of GPP is ongoing. Using data from the NPR, individuals were considered to have GPP if they had a first or second ICD-10 diagnosis code of L40.1. In 2015, the prevalence of GPP in Sweden was 9 per 100 000 persons. The NPR does not contain primary care data but has comprehensive secondary care data on the entire Swedish population, so it is likely the prevalence estimate is close to the true prevalence of GPP in Sweden [R22-0363].

The prevalence of GPP from the published literature highlight GPP as a rare condition with a prevalence range from 2 per 1 000 000 to 46 per 100 000. Variation across studies can mainly be attributable to variation in methods. Recent studies capturing cases diagnosed over several years, reported estimates between 1.386 and 9 per 100 000 people [R22-0363, R21-3418, R19-1562, R21-2789, R23-0922].

SI.Table 1 Prevalence of GPP

Author	Country	Study years	Population source	GPP case definition	GPP prevalence
Region: Europe					
Augey 2006 [R16-2698]	France	2004	Survey of 121 dermatology clinics	Clinical diagnosis by dermatologist based on non-standardised criteria	17.6 per 100 000 persons (annual)
Feldman 2021 [R21-3418]	Germany	2019-2020	IQVIA German EMR database	Presence of at least 1 diagnosis code of L40.1 in EMR database	14 per 100 000 persons (annual)
Löfvendahl 2022 [R22-0363]	Sweden	2015	NPR	Physician visit with the primary or secondary diagnosis code L40.1	9 per 100 000 persons (point, 12 years)
Schafer 2011 [R18-1635]	Germany	2005	National health insurance claims database	At least 1 ICD-10 code L40.1	46 per 100 000 persons (annual)
Region: Asia					
Miyachi 2022 [R21-2789]	Japan	2010-2019	National Japanese inpatient database	Patients with ICD-10 code L40.1 who received systemic treatment for GPP during hospitalisation	8.178 per 100 000 (point)
Feldman 2021 [R21-3418]	Japan	2018	JMDC claims database	Presence of at least 1 diagnosis code of L40.1 in claims	2 per 100 000 persons (annual)
Feldman 2021 [R21-3418]	Japan	2015-2018	MDV claims database	Presence of at least 1 diagnosis code of L40.1 in claims	3 per 100 000 persons (point, 4 years)
Feng 2023 [R22-0494]	China	2012-2016	Urban Employee Basic Medical Insurance and Urban Resident Basic Medical Insurance	ICD-10: L40.1 and ICD-9: 694.3 and related text of diagnosis	1.108 per 100 000 persons (annual, standardised)
Fujita 2018 [R19-1562]	Japan	2004-2010	Patients registered to receive public financial aid from the Japanese MHLW	Presence of systemic symptoms such as fever, extensive flush, neutrophilic subcorneal pustules	1.386-2.619 per 100 000 persons (point)
Lee 2017 [R20-1502]	South Korea	2015	National Health Institution insurance claims data	Outpatient or inpatient primary diagnosis code of L40.1	12 per 100 000 persons (annual)

SI.Table 1 (cont'd) Prevalence of GPP

Author	Country	Study years	Population source	GPP case definition	GPP prevalence
Region: North America					
Zema 2022 [R23-0922]	US	2016-2019	Optum EHR	Presence of diagnosis code L40.1	31.6 per 1 million (point)
Tarride 2022 [R22-4073]	Canada	2010-2020	Canadian Institute for Health Information	Diagnostic code indicating GPP (ICD-10-CA L40.1).	2.8 per 1 million (point)
Feldman 2021 [R21-3418]	US	2019	Optum claims database	Presence of at least 1 inpatient or outpatient diagnosis code of L40.1 in claims	9 per 100 000 persons (annual)
Feldman 2021 [R21-3418]	US	2018	Truven MarketScan claims database	Presence of at least 1 inpatient or outpatient diagnosis code of L40.1 in claims	7 per 100 000 persons (annual)
Region: South America					
Duarte, 2022 [R22-0384]	Brazil	2018-2020	Public claims database (outpatient [SIA] and inpatient [SIH] information systems)	ICD-10: L40.1; 1 procedure in SIA; GPP proportion was based on all psoriasis phenotypes (L40.0, L40.1, L40.2, L40.3, L40.4, L40.5, L40.8, L40.9)	0.7 to 0.9 per 100 000 persons (point, 2.67 years)

SI.Table 2 Proportion of GPP among individuals with psoriasis

Author	Country	Study years	Population source	GPP case definition	GPP prevalence
Region: Europe					
Dubertret 2006 [R17-3266]	Belgium, Czech Republic, Finland, France, Germany, Italy, the Netherlands	2002	Survey of EUROPSO members	Self-reported diagnosis	4% of the psoriasis population
Iskandar 2015 [R21-0068]	UK/Ireland	2014	BADBIR	Information collected from the patient case report form at enrolment into the registry	1% of the BADBIR population
Perez-Plaza 2017 [R21-0067]	Spain	2015	BIOBADADERM	Information collected from the patient case report form at enrolment into the registry	1% of the BIOBADADERM population
Region: Asia					
Ito 2018 [R18-1635]	Japan	2009-2012	Diagnosis reported by dermatology centre	Annual survey of dermatology centres (response rate not provided; 131 centres contributing 9290 psoriasis patients)	2.3%
Kawada 2003 [R17-3265]	Japan	1982-2001	Diagnosis reported by dermatology centre	Annual survey of dermatology centres (57% response rate; 148 centres contributing 28 628 psoriasis patients)	0.9%
Takahashi 2011 [R17-3264]	Japan	2002-2008	Diagnosis reported by dermatology centre	Annual survey of dermatology centres (96% response rate; 152 centres contributing 11 631 psoriasis patients)	1.3%

SI.1.3 Demographics of the population in the proposed indication – age, gender, and risk factors for the disease

There is limited data describing the demographic profile of patients with GPP. Among adult patients with GPP, there is some published literature suggesting a slightly higher proportion of females compared to males (ranging from 52% to 83%) [R16-0933, R21-2844, R21-2788, R23-4388]. These data are consistent with internal analyses conducted using the US Optum and Truven MarketScan databases. Of the 1175 patients with a GPP diagnosis code identified in Truven MarketScan between October 2015 and September 2018, 63.3% were female [R21-2243]. Similarly, 67.6% of the 1669 GPP patients were female in the Optum database [R21-2244]. However, internal analyses using the Japan claims databases showed a slightly higher proportion of females in the MDV database but a higher proportion of males in the JMDC database (51.6% vs 38.5% female in MDV and JMDC, respectively [R20-3140, R20-3139].

Various factors may precipitate flares of GPP. The use of and withdrawal of systemic corticosteroids, other drug-specific allergic reactions, pregnancy, infection and stress are all reported triggers of GPP [R20-1248, R18-1887, R17-3458]. The most comprehensive data on potential risk factors for GPP was reported from a case series of 102 patients with GPP in Malaysia [R16-0933]. The most commonly reported risk factor was a history of psoriasis (77.5% of patients). This was followed by the use of any medical treatment (56.9% of patients reporting either traditional or Western medical treatment preceding their GPP episode). Importantly, this was driven by the use of corticosteroids specifically, which was reported among 44% of all cases. Preceding infection was reported among 19.6% of patients with GPP and pregnancy was reported as a precipitating factor among 25% of female patients.

SI.1.4 The main existing treatment options

Therapeutic intervention in GPP is a major challenge. As of 01 Sep 2022, Spevigo injection was approved by the US FDA to treat GPP flares in adults. Spevigo blocks the activation of the IL-36R which is important to signalling the pathway within the immune system related to the cause of GPP. Conditional approval for Spevigo injection occurred in Europe and other approvals may occur. There is limited evidence on the efficacy and safety for the use of non-targeted immunomodulatory therapies (e.g. methotrexate, cyclosporine, retinoids, systemic corticosteroids) for the treatment of GPP flares. Most of these therapies used in clinical practice are associated with toxicities that make them inappropriate for continued use [R17-3600, R19-1562]. Side effects, such as hair loss, excessive hair growth, and teratogenicity particularly limit the use of these treatments in women, who may be disproportionately affected. Additionally, many of these treatments do not fully alleviate the symptoms of GPP. According to experienced clinicians attending BI-sponsored advisory boards, one third of patients with acute GPP treated with acitretin still have chronic ill-defined erythema and plaques affecting 30% to 50% of the BSA.

The limitation in efficacy and safety data also applies to the use of biologic treatment options in GPP, including TNF inhibitors (adalimumab, infliximab, and certolizumab pegol), IL-17 inhibitors (secukinumab, brodalumab, and ixekizumab), and IL-23 inhibitors (risankizumab and guselkumab). The approval of these biologics in Japan for the treatment of GPP is based

on evidence from endpoints assessing any improvement (without the need for complete pustular clearance) at late time points (e.g. 12 to 16 weeks) in small (<12 patients), open-label, single-arm trials only [R16-1462, R17-3596, R17-3604, R18-2718, R18-2719, R18-2720]. As the trials investigated GPP prevention only, there is a lack of data on the impact of these biologics on flare treatment (e.g. time to flare resolution and sustainability of response).

Based on the limitations described above, current therapeutic options such as cyclosporine, methotrexate, retinoids, and biologics have not been investigated in well-controlled CTs, are administered off-label and accordingly not suitable for long-term treatment and do not provide sustained responses in most patients.

SI.1.5 Natural history of the indicated condition in the population, including mortality and morbidity

The published literature on the natural history of GPP flares comes from a few studies looking at a small number of GPP patients. Flare frequency was evaluated in a study of 27 patients with juvenile onset GPP in Malaysia [R17-3458], 48% (n=13) experienced 1 pustular episode over a 6-month period, 33% (n=9) experienced 2 to 5 episodes, and 19% (n=5) experienced 5 or more episodes. A similar distribution of pustular episodes was observed in a study of 102 patients with adult onset GPP in Malaysia [R16-0933]. From 1989 to 2011, 58% of patients (n=59) experienced 1 pustular flare (covering >30% BSA), 29% (n=30) experienced 2 to 5 flares, and 13% (n=13) experienced 5 or more flares. Finally, in the study in France [R16-2960], 19 flares were reported among 11 patients with GPP, resulting in a mean of 1.7 (SD=0.9) flares per patient; however, the study period and length of follow-up were not reported for this study.

Flare duration was evaluated in the study of 102 patients with adult onset GPP in Malaysia [R16-0933] and found a mean duration of 16 days, with a range from 7 to 60 days. In the study of 11 patients with GPP in France [R16-2960], 7/11 patients (64%) experienced clearance of their pustules for 1 of their flares within 7 days, whilst 4/11 patients (36%) achieved pustule clearance for 1 of their flares within 8 to 28 days. In the 3 publications on Chinese GPP patients treated with retinoids [R20-3869, R20-3870, R20-3871], it took on average ≥2 weeks for complete clearing of the pustules. Based on the limited information provided for the time to clearance of the other types of skin lesions of GPP [R20-3871], clearance of these seemed to take much longer, i.e. an average of around 1 month for the clearance of erythema.

To better understand the natural course of flares in GPP, a survey of HCPs enrolled in the CorEvitas (formerly Corrona) Psoriasis Registry was conducted. To participate in the HCP survey, dermatologists in the CorEvitas Psoriasis Registry who had treated adult (aged ≥18 years) patients with GPP within the past 5 years were eligible. The survey included 28 multiple choice questions exploring acute GPP flare onset and diagnosis, flare frequency and duration, treatment of flares, treatment of residual disease, and physicians' overall experience of managing patients with GPP. Most respondents (69%) estimated that their patients had an average of 0-1 flare per year, and 28% estimated 2-3 per year. Over half of respondents (55%) reported that flares typically last 2-4 weeks, and 41% reported flare duration of 1-3 months. The majority (52%) of dermatologists believe that skin lesions take

the shortest time to resolve (2-4 weeks), whilst pustules and erythema require 1-3 months for resolution, according to 48% and 59% of respondents [R21-0751].

A similar survey of patients was conducted to better understand their experiences living with and managing GPP. This survey was done in collaboration with Healthivibe. Of the 66 respondents, 41% experienced 2-3 flares per year, and 46% experienced ≥4 flares in a 12 month period. More than three-quarters (76%) of respondents indicated their flares were severe in a nature, and almost a quarter (23%) of patients surveyed visited an emergency department because of their GPP flare. Even after the flares have resolved, 77% of respondents still expected some residual symptoms when their condition is “under control” [R22-0478].

A retrospective study using the SNDS administrative database in France was conducted to identify flares in patients with GPP [R21-1156]. Acute GPP flares were characterised from patient data between 2010-2018 using the following algorithm: treatment for GPP, with ICD-10 code L40.1 as the primary diagnosis in a medical, surgical, or obstetric inpatient setting, and hospitalisation for ≥3 days. Overall, 1842 unique incident patients with GPP were identified. Of these patients, 30.9% (569) had ≥1 flare and 6.2% (115) had ≥2 flares during the study period, with patients experiencing an overall mean 1.4 (SD 1.14) flares, with 1.26 (SD 0.82) flares per person-year. All-cause mortality for these patients was estimated. Mortality within the first 4 weeks after the last flare was 2.5%, and the median time to death for these patients was 15.64 days (SD 7.97). Throughout the entire study period, all-cause mortality was calculated to be 24.4%.

A Delphi panel provided a clinical characterisation of GPP flare frequency. The Delphi panel study had 6 clinical experts from Germany who observed that on average, patients experience 1.5 flares, with 60% of flares lasting less than 4 weeks. In addition, the experts noted that an estimated 46% of patients with GPP exhibit a moderate disease course, 33% exhibit a mild course, and 21% exhibit a severe course [R22-4489].

This retrospective cohort study of 1535 incident GPP patients from 01 Jul 2015 to 20 Jun 2020 used Optum electronic health records to evaluate disease burden, acute care and burden on emergency departments [R21-3430]. Of those 1535 patients related to the presence of flare, 271 patients had 513 documented flares during a specific follow-up period following the incident diagnosis. Flares were commonly diagnosed in outpatient settings (53%, 271/513), in the hospital (36%, 186/513), or in the emergency room (9%, 48/513).

Though mortality related to GPP is difficult to estimate at a population level due to inconsistent and incomplete follow-up, 7 GPP mortality estimates have been published in the last 25 years. The reported mortality due to GPP or associated treatment ranged between 2% and 7% [R16-2698, R16-0933, R16-1463, R17-3456, R17-3605, R21-0384, R21-2789]. Deaths were directly attributable to GPP or associated treatment, especially with the use of systemic corticosteroids [R16-0933, R17-3456, R16-1463]. Life-threatening complications of GPP include sepsis and renal, hepatic, respiratory, and cardiac failure [R16-0933]. Sepsis was a common cause of death [R16-0933, R16-1463, R17-3605].

SI.1.6 Important co-morbidities

Co-morbidities occurring more frequently in GPP patients than in patients with plaque psoriasis and the general population in US claims data sources [R20-3323, R20-3324] include the following:

- Hyperlipidaemia
- Psoriatic arthritis
- Type 2 diabetes
- Obesity
- COPD
- Asthma
- Anxiety
- Depression

In Japanese claims databases, co-morbidities diagnosed more frequently in patients with GPP compared to patients with plaque psoriasis included the following:

- Psoriatic arthritis
- Other forms of psoriasis
- Peptic ulcer disease
- Osteoporosis
- Interstitial pneumonia [R20-3139]

In Swedish registries [R22-4143], co-morbidities identified among patients with GPP were compared to patients with psoriasis vulgaris and population-based controls included the following:

- Hypertension
- Psoriatic arthritis
- Diabetes, Type 2
- Diabetes, Type 1
- Hyperlipidaemia
- Asthma
- Depression
- COPD
- Obesity
- Stroke
- Myocardial Infarction
- Other malignant skin neoplasms

- Conjunctivitis
- Anxiety
- Chronic renal failure
- Peptic ulcer disease
- Diverticular disease of the intestine

SI.2 REFERENCES

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SI.2.2 Unpublished references

Not applicable.

ABBREVIATIONS

BADBIR	Biologics and Immunomodulators Register
BI	Boehringer Ingelheim
BIOBADADERM	Spanish Registry of Adverse Events Associated With Biologic Drugs in Dermatology
BSA	Body surface area
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
EMR	Electronic medical records
EU	European Union
EUROPSO	European Federation of Psoriasis Patient Associations
FDA	US health agency; Food and Drug Administration
GEK	Gmuender Ersatzkasse; a German public health insurance
GP	General practitioner
GPP	Generalized pustular psoriasis
HCP	Health care professional
ICD	International Classification of Diseases
IHE	Institute for Health Economics
IL-36R	Interleukin 36 receptor
IQVIA	Global clinical research provider
JMDC	Japan Medical Data Center Company
MDV	Medical Data Vision
MHLW	Ministry of Health, Labor and Welfare
NPR	National Patient Register

PPP	Palmoplantar pustulosis
PsoReg	Swedish National Register for Systemic Treatment of Psoriasis
READ	Clinical Terminology System (UK)
SD	Standard deviation
SNDS	French Administrative Health Care Database
TNF	Tumour necrosis factor
UK	United Kingdom
US	United States
vs.	Versus

MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

SII.1 KEY SAFETY FINDINGS FROM NON-CLINICAL STUDIES AND RELEVANCE TO HUMAN USAGE

SII.1.1 Toxicity

As spesolimab does not demonstrate adequate pharmacological activity in common toxicology species, a surrogate antibody (BI 674304) specific for mouse IL-36R was developed and used for toxicology assessments. In intravenous toxicity studies of up to 26 weeks in duration in mice, no adverse effects of IL-36R antagonism were seen at a dose that was 5-fold higher than the dose that was protective in an experimental mouse colonic inflammation model. These preclinical data suggest spesolimab can safely be administered chronically to humans. In addition, a recent characterisation of individuals with homozygous IL-36R loss-of-function mutations revealed that normal immune function was broadly preserved and that the medical history of these individuals showed no increased risk of infections or malignancies. These data suggest that IL-36 signalling pathway inhibition may not substantially compromise host defences [R17-3632].

SII.1.1.1 Reproductive and developmental toxicity

There was no evidence of effects on fertility or development in mice after administration of 50 mg/kg/dose of BI 674304 in directed fertility, and embryonic, and pre- and post-natal development studies [n00243849-01, n00254965-01, n00271726-01].

SII.1.1.2 Carcinogenicity

As spesolimab is not pharmacologically active in rodents, traditional carcinogenicity studies were not performed. Based on a review of the scientific literature, the mechanism of action of spesolimab is not expected to be carcinogenic or to increase the risk of cancer. To date, no evidence of carcinogenic potential has arisen in either non-clinical IL-36R knock-out mouse phenotypic assessments, in repeat dose toxicology studies using the surrogate antibody BI 674304, or in clinical trials using spesolimab [n00232540-01, n00234384-01, n00235413-01, n00243876-01, n00257882-01, n00265831-02].

SII.1.2 Safety pharmacology

As spesolimab is not pharmacologically active in common toxicology species, safety pharmacology assessments were not conducted.

SII.1.3 Other toxicity-related information or data

Immunohistochemistry techniques were used to assess the binding of spesolimab to human tissues. In this assay, spesolimab stained the membrane of epithelium cells in a variety of tissues which is consistent with the known expression of IL-36R [n00239291-01].

SII.2 REFERENCES

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SII.2.2 Unpublished references

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n00243876-01 BI 674304: A 13-week (twice weekly) intravenous injection study in mice with a 4-week recovery period. 01 Jun 2016

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n00265831-02 BI 655130: Carcinogenicity Risk Assessment. 17 June 2021

n00271726-01 An intravenous injection pre and postnatal developmental toxicity study of BI 674304 in the mouse. 06 Dec 2019

ABBREVIATIONS

BI	Boehringer Ingelheim
IL-36R	Interleukin 36 receptor

MODULE SIII CLINICAL TRIAL EXPOSURE

GPP flare prevention (DLP 13 Jan 2023, Spevigo EU-RMP v2.0)
For exposure calculations, the safety analysis set including all patients with GPP and who received at least 1 dose of spesolimab s.c. for GPP flare prevention (SAF-ISS3p) was considered. Exposure for SAF-ISS3p is presented in Section SIII.1.

GPP flare treatment (DLP 08 Jan 2021, Spevigo EU-RMP v1.0)
For exposure calculations, the safety analysis set including all patients with GPP and who received at least 1 dose of spesolimab i.v. for GPP flare treatment (SAF-ISS3) was considered. Exposure for SAF-ISS3 is presented in Section SIII.2.

Pooled exposure (DLP 13 Jan 2023, Spevigo EU-RMP v2.0)
Pooled exposure across GPP indications is presented in Section SIII.3.

Additional exposure analyses SAF-ISS0p (healthy volunteers), SAF-ISS1p (patients from all randomised placebo-controlled trials that are completed/have a completed primary analysis period), and SAF-ISS2p (patients from controlled and uncontrolled trials are provided in Appendix 7. An high-level overview on exposure per additional poolings is provided in SIII.Table 2.

SIII.Table 1 Overview of poolings for exposure analyses

SAF	Description	Trials included
GPP flare prevention		
SAF-ISS3p	This pool includes patients with GPP treated with spesolimab i.v. and/or s.c. (for a comprehensive approach of safety analyses of GPP patients). For exposure in GPP flare prevention, the treatment group spesolimab s.c. only is presented.	1368-0011, 1368-0013, 1368-0025, 1368-0027
GPP flare treatment		
SAF-ISS3	Exposure to placebo or spesolimab 900 mg i.v. in patients from all ongoing or completed GPP trials where at least 1 dose was administered to treat patients with a GPP flare	1368-0013, 1368-0025, 1368-0027
Pooled GPP indications		
SAF-ISS3p	Patients with GPP treated with spesolimab i.v. and/or s.c. (treatment group spesolimab overall)	1368-0011, 1368-0013, 1368-0025, 1368-0027

Data source: ISS3: SAP for RMP for spesolimab (GPP indication) [c35174241-01], Table 4.2.1: 1; ISS3p: SAP for RMP for spesolimab GPP flare prevention [c40265480-01], Table 5.1.2:1

SIII.Table 2 Overview exposure per pooling for exposure analyses

	Placebo N/mean time at risk [months]	Spesolimab s.c. only N/mean time at risk [months]	Spesolimab overall N/mean time at risk [months]	Overall N/mean time at risk [months]
GPP flare prevention				
SAF-ISS3p	48/4.668	109/12.480	181/16.200	183/17.239
GPP flare treatment				
SAF-ISS3	18/0.596	--	57/3.482	59/3.545
Additional poolings for exposure analyses[1]				
SAF-ISS0p	38/3.014	--	246/3.402	284/3.350
SAF-ISS1p	185/3.819	--	445/4.369	630/4.208
SAF-ISS2p	185/4.187	--	589/15.733	645/15.561

[1] Refer to Appendix 7, Section 1 for further details on additional exposure poolings and exposure data.

Data source: data on file, analyses for EU-RMP v1.0, SAF-ISS3, Table A.1.1.1: 1; rmp-output-tlf-gpp-flare-prevention [c41549498], SAF-ISS0p, Table A.1.1.1: 1; SAF-ISS1p, Table A.1.2.1: 1; SAF-ISS2p; Table A.1.3.1: 1; SAF-ISS3p, Table A.1.4.1: 1

SIII.1 INDICATION GPP - FLARE PREVENTION

SAF-ISS3p comprised 48 patients receiving placebo and 109 patients receiving spesolimab s.c. only (rmp-output-tlf-gpp-flare-prevention [c41549498], ISS3p, Table A.1.4.1: 1). Both treatment groups comprised fewer male than female patients. Most patients in both treatment groups were younger than 50 years. 1 patient in the spesolimab s.c. only group was 75 years or older. 2 patients in the placebo group and 7 patients in the spesolimab s.c. only group were younger than 18 years (rmp-output-tlf-gpp-flare-prevention [c41549498], ISS3p, Table A.1.4.2: 5). More Asian than White patients were included. Further details are given in the following tables.

SIII.Table 3 Duration of exposure (SAF-ISS3p) - spesolimab s.c. - Safety set

	Spesolimab s.c. only **N (%)**
Total	109 (100.0)
Cumulative total dose [mg]	
>0	109 (100.0)
≥900	82 (75.2)
≥1800	53 (48.6)
≥2700	34 (31.2)
≥3600	23 (21.1)
Cumulative number of doses administered	
≥1	109 (100.0)
≥2	93 (85.3)
≥5	78 (71.6)
≥8	72 (66.1)
≥11	64 (58.7)
≥14	41 (37.6)
≥20	2 (1.8)
Cumulative time at risk [months]	
≥1 day	109 (100.0)
≥3	89 (81.7)
≥6	77 (70.6)
≥9	73 (67.0)
≥12	65 (59.6)
≥18	24 (22.0)
≥24	11 (10.1)
≥36	1 (0.9)

Data source: rmp-output-tlf-gpp-flare-prevention [c41549498], SAF-ISS3p, Table A.1.4.1: 1

SIII.Table 4 Age group and gender (SAF-ISS3p) - spesolimab s.c. - Safety set

Gender / age group [years]	Spesolimab s.c. only N
Male	
<50	27
50 to <65	6
65 to <75	5
≥75	1
Female	
<50	51
50 to <65	17
65 to <75	2

Data source: rmp-output-tlf-gpp-flare-prevention [c41549498], SAF-ISS3p, Table A.1.4.2: 3

SIII.Table 5 Ethnic origin (SAF-ISS3p) - spesolimab s.c. - Safety set

Race	Spesolimab s.c. only N
White	38
Asian	71

Data source: rmp-output-tlf-gpp-flare-prevention [c41549498], SAF-ISS3p, Table A.1.4.2: 6

SIII.Table 6 BMI (SAF-ISS3p) - spesolimab s.c. - Safety set

BMI class [kg/m^2]	Spesolimab s.c. only N
<25	52
25 to <30	26
≥30	31

Data source: rmp-output-tlf-gpp-flare-prevention [c41549498], SAF-ISS3p, Table A.1.4.2: 7

SIII.Table 7 Weight (SAF-ISS3p) - spesolimab s.c. - Safety set

	Spesolimab s.c. only
Weight class [kg]	**N**
<53.8	22
≥53.8 to <91	68
≥90	19

Data source: rmp-output-tlf-gpp-flare-prevention [c41549498], SAF-ISS3p, Table A.1.4.2: 8

SIII.2 INDICATION GPP - FLARE TREATMENT

SAF-ISS3 comprised 18 patients receiving placebo and 57 patients receiving spesolimab i.v.. Both treatment groups comprised fewer male than female patients. Most patients in both treatment groups were younger than 50 years. There were no patients 75 years or older. More Asian than White patients were included. Further details are given in the following tables.

SIII.Table 8 Duration of exposure (SAF-ISS3) – Safety set

	Placebo **N (%)**	**Spesolimab 900 mg i.v.** **N (%)**	**Overall** **N (%)**
Total	18 (100.0)	57 (100.0)[1]	59 (100.0)
Cumulative total dose [mg]			
>0	0	57 (100.0)[2]	NC
≥900	0	56 (98.2)	NC
≥1800	0	20 (35.1)	NC
≥2700	0	7 (12.3)	NC
Cumulative number of doses administered			
≥1	18 (100.0)	57 (100.0)	59 (100.0)
≥2	0	22 (38.6)	34 (57.6)
Cumulative time at risk [months]			
>0	18 (100.0)	57 (100.0)	59 (100.0)
≥3	0	34 (59.6)	37 (62.7)
≥6	0	6 (10.5)	6 (10.2)

Overall = spesolimab 900 mg i.v. + placebo

[1] Includes patients randomised to placebo who received open-label spesolimab later on

[2] Note: 1 patient in trial 1368-0013 stopped the infusion prematurely (due to worsening of GPP presenting as severe chills, cyanosis, oxygen saturation decreased, hypertension, tachycardia, and fever) and received less than 900 mg i.v. (80% of the spesolimab infusion volume [720 mg] administered).

Data source: data on file, analyses for EU-RMP v1.0, SAF-ISS3, Table A.1.1.1: 1

SIII.Table 9 Age group and gender (SAF-ISS3) – Safety set

	Placebo	Spesolimab 900 mg i.v.	Overall
Age group [years]	**N**	**N**	**N**
Male			
<50	3	12	12
50 to <65	0	4	4
65 to <75	0	1	1
Female			
<50	11	31	32
50 to <65	4	8	9
65 to <75	0	1	1

Overall = spesolimab 900 mg i.v. + placebo

Data source: data on file, analyses for EU-RMP v1.0, SAF-ISS3, Table A.1.1.2: 3

SIII.Table 10 Ethnic origin (SAF-ISS3) – Safety set

	Placebo	Spesolimab 900 mg i.v.	Overall
Race	**N**	**N**	**N**
White	5	25	25
Asian	13	32	34

Overall = spesolimab 900 mg i.v. + placebo

Data source: data on file, analyses for EU-RMP v1.0, SAF-ISS3, Table A.1.1.2: 4

SIII.3 POOLED GPP INDICATIONS

SAF-ISS3p comprised 48 patients receiving placebo and 181 patients receiving spesolimab overall only (rmp-output-tlf-gpp-flare-prevention [c41549498], ISS3p, Table A.1.4.1: 1). Both treatment groups comprised fewer male than female patients. Most patients in both treatment groups were younger than 50 years. 1 patient in the spesolimab overall group was 75 years or older. 2 patients in the placebo group and 7 patients in the spesolimab overall group were younger than 18 years (rmp-output-tlf-gpp-flare-prevention [c41549498], ISS3p, Table A.1.4.2: 5). More Asian than White patients were included. Further details are given in the following tables.

SIII.Table 11 Duration of exposure (SAF-ISS3p) - all GPP trials/any formulations – Safety set

	Spesolimab overall **N (%)**
Total	181 (100.0)
Cumulative total dose [mg]	
>0	NC
Cumulative number of doses administered	
≥1	181 (100.0)
≥2	158 (87.3)
≥5	130 (71.8)
≥8	118 (65.2)
≥11	104 (57.5)
≥14	69 (38.1)
≥20	18 (9.9)
≥30	1 (0.6)
Cumulative time at risk [months]	
≥1 day	181 (100.0)
≥3	170 (93.9)
≥6	138 (76.2)
≥9	125 (69.1)
≥12	113 (62.4)
≥18	60 (33.1)
≥24	45 (24.9)
≥36	18 (9.9)

NC = not calculated

Data source: rmp-output-tlf-gpp-flare-prevention [c41549498], SAF-ISS3p, Table A.1.4.1: 1

SIII.Table 12 Age group and gender (SAF-ISS3p) - all GPP trials/any formulations – Safety set

	Spesolimab overall
Age group [years]	**N**
Male	
<50	47
50 to <65	12
65 to <75	6
≥ 75	1
Female	
<50	83
50 to <65	29
65 to <75	3

Data source: rmp-output-tlf-gpp-flare-prevention [c41549498], SAF-ISS3p, Table A.1.4.2: 3

SIII.Table 13 Ethnic origin (SAF-ISS3p) - all GPP trials/any formulations – Safety set

	Spesolimab overall
Race	**N**
White	69
Asian	111
Not reported	1

Data source: rmp-output-tlf-gpp-flare-prevention [c41549498], SAF-ISS3p, Table A.1.4.2: 6

SIII.1 REFERENCES

SIII.1.1 Published references

Not applicable.

SIII.1.2 Unpublished references

c35174241-01 Statistical analysis plan for risk management plans (EU and core) for the submission of spesolimab to treat acute flares in patients with GPP. 11 Mar 2021

c40265480-01 Statistical analysis plan for the risk management plans (EU and core) for the submission of Spesolimab for flare prevention in patients with GPP. 07 Sep 2022

c41549498 rmp-output-tlf-gpp-flare-prevention (analyses for EU-RMP v2.0)

ABBREVIATIONS

BMI	Body mass index
DLP	Datalock point
EU	European Union
GPP	Generalized pustular psoriasis
i.v.	Intravenous
ISS	Integrated Summary of Safety
NC	Not calculated
RMP	Risk Management Plan
s.c.	Subcutaneous
SAF	Safety analysis set
SAP	Statistical analysis plan

MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL TRIALS WITHIN THE DEVELOPMENT PROGRAMME

GPP flare prevention	
Patients with body weight <40 kg	
Reason for exclusion	Patients with body weight <40 kg were excluded from trial 1368-0027, as a higher exposure was anticipated in these patients with the proposed spesolimab doses. The weight cut-off was chosen as 40 kg (median weight of a 12-year-old subject) and not 30 kg (3rd percentile for a 12-year-old subject) because the probability of exceeding the maximum observed concentration was calculated as 0.5% for subjects weighing 40 kg while the probability of exceeding the maximum observed concentration was 4.4% for subjects weighing 30 kg.
Is it considered to be included as missing information?	Yes
Rationale	Limited experience is available from clinical trial data; post-marketing data is not yet available. Use of spesolimab in this subpopulation is expected (especially in adolescents). 'Use in patients with body weight <40 kg' is considered missing information.
GPP flare treatment	
History of allergy/hypersensitivity to a systemically administered trial medication agent or its excipients	
Reason for exclusion	Patients with known hypersensitivity reactions to the active substance or to any of the excipients are excluded from clinical trials for safety reasons, to safeguard the wellbeing of susceptible patients.
Is it considered to be included as missing information?	No
Rationale	Severe or life-threatening hypersensitivity to the active substance or to any of the excipients is covered in the SmPC under the "Contraindications" section (including further references to the "List of excipients" and "Special Warnings and Precautions" sections). Hypersensitivity may include immediate reactions such as anaphylaxis and delayed reactions such as DRESS and is covered in the SmPC ("Special Warnings and Precautions" and "Undesirable effects" [immediate systemic hypersensitivity reactions only]). Systemic hypersensitivity reaction is defined as an important identified risk.

Pregnant or breast-feeding women	
Reason for exclusion	Clinical trials in pregnant or breast-feeding women cannot be conducted for ethical reasons.
Is it considered to be included as missing information?	Yes
Rationale	Limited experience is available from clinical trial data; post-marketing data is not yet available. There was no evidence of effects on fertility or embryonic development in mice after administration of 50 mg/kg/dose of spesolimab in directed fertility, and embryonic, and pre- and post-natal development studies. Due to the negative outcome of the completed teratogenicity study a double barrier method of contraception is not required. This topic is considered missing information.
Patient with relevant acute or chronic infections, including HIV, or viral hepatitis	
Reason for exclusion	Patients with relevant acute or chronic infections are excluded from clinical trials for safety reasons, to safeguard the wellbeing of susceptible patients and to improve interpretability of data by reducing confounding factors like pre-existing infections
Is it considered to be included as missing information?	No
Rationale	Very limited experience is available from clinical trial data; post-marketing data is not yet available. Instructions for patients with a chronic infection or a history of recurrent infection is given in the SmPC (“Special Warnings and Precautions”). This topic is addressed under the important potential risk ‘Serious or opportunistic infections’.

Patient with active tuberculosis	
Reason for exclusion	Patients with active tuberculosis are excluded from clinical trials for safety reasons, to safeguard the wellbeing of susceptible patients and to improve interpretability of data by reducing confounding factors like pre-existing infections
Is it considered to be included as missing information?	No
Rationale	Evaluation of tuberculosis status prior to initiation of treatment with spesolimab and anti-tuberculosis therapy prior to treatment with spesolimab in patients with tuberculosis or a history of tuberculosis is covered in the SmPC ("Special Warnings and Precautions"). This topic is addressed under the important potential risk 'Serious or opportunistic infections'.
Patient with any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix	
Reason for exclusion	Patients with active or suspected malignancy or a history of malignancy are excluded from clinical trials for safety reasons and to improve interpretability of data by reducing interfering factors like pre-existing or relapsing malignancies.
Is it considered to be included as missing information?	No
Rationale	No experience is available from clinical trial data; post-marketing data is not yet available. Patients with malignancies have been excluded from the clinical trials conducted with spesolimab. Therefore, the safety and efficacy of spesolimab has not been studied in this population. This topic is addressed under the important potential risk 'Malignancy'.

Children and adolescents <18 years of age	
Reason for exclusion	Clinical development programmes routinely start with clinical trials in adults. Adolescents ≥12 years of age were included in trial 1368-0027. Dedicated paediatric development plans for the different indications for spesolimab are under preparation.
Is it considered to be included as missing information?	No
Rationale	Patients <18 years are investigated in dedicated paediatric development programmes. In patients with GPP, adolescents ≥12 years are in addition allowed for inclusion in parts of the adult development programme.
Elderly patients >75 years of age	
Reason for exclusion	At the current stage of development, most clinical trials with spesolimab limit the inclusion of adults to an age up to 75 years. Nevertheless, open-label extension trials do not contain an age-related criterion.
Is it considered to be included as missing information?	No
Rationale	There is no indication that the safety profile of spesolimab may change with increasing age. Elderly patients per se might be at a higher risk of infection.
Administration of live virus vaccination from 6 weeks prior and during spesolimab treatment	
Reason for exclusion	Administration of live virus vaccination is excluded from 6 weeks prior to start until the end of spesolimab treatment for safety reasons.
Is it considered to be included as missing information?	No
Rationale	No specific studies have been conducted in patients who have recently received live viral or live bacterial vaccines. The possibilities to further characterise the topic are expected to be very limited; no clinical trial data will address the risk. Risk minimisation measures for this topic are in place as a warning in the SmPC. Spontaneous post-marketing reporting on this topic will likely be very limited.

Concomitant treatment with other biologicals	
Reason for exclusion	Concomitant treatment with other approved or non-approved investigational biologicals was excluded in most spesolimab clinical trials as part of the standardisation to improve interpretability of safety and efficacy data.
Is it considered to be included as missing information?	No
Rationale	Experience from concomitant use of spesolimab and other GPP treatments (e.g. such as biologics) is limited. The use of spesolimab as monotherapy is added to the SmPC of spesolimab i.v. for GPP flare treatment.
Major surgical procedure within 12 weeks prior to or planned for during spesolimab treatment	
Reason for exclusion	Standard criterion related to subject compliance during a trial. This criterion limits any potential bias on the efficacy and safety results in a trial.
Is it considered to be included as missing information?	No
Rationale	Standard exclusion criterion for clinical trials. There is no evidence to suggest that the efficacy or safety of spesolimab is affected by major surgical procedure within 12 weeks prior to or planned for during spesolimab treatment.
Chronic drug or alcohol abuse or any other condition that may interfere with the protocol requirements and the participant's compliance	
Reason for exclusion	Standard criterion related to subject compliance during a trial in order to maintain the integrity of the trials.
Is it considered to be included as missing information?	No
Rationale	Standard exclusion criterion for clinical trials. Further, there is no evidence to suggest that the efficacy or safety of spesolimab is affected by concurrent abuse of recreational drugs or alcohol.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

SIV.Table 1 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure	
	Number	Person-time
Pregnant women	N=6 (all spesolimab)[1]	
Breastfeeding women	Not included in the clinical development programme	
Patients with relevant co-morbidities		
• Patients with hepatic impairment	Not included in the clinical development programme	
• Patients with renal impairment	Not included in the clinical development programme	
• Patients with cardiovascular impairment	Not included in the clinical development programme	
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme	
Population with relevant different ethnic origin	See SIII.Table 13 for information on ethnic origin.	
Subpopulations carrying relevant genetic polymorphisms	Presence of potential pathogenic IL-36RN variation (with amino acid substitution) was shown for 14 patients overall (spesolimab: 8 patients, placebo: 6 patients).[2]	
Other	Not included in the clinical development programme	

Data source: [1] GSP and data on file, 1368_pregnancy_DSUR_LL; [2] Biomarker report 1 for trial 1368-0013 [c34018597-01], Table 6

SIV.4 REFERENCES

SIV.4.1 Published references

Not applicable.

SIV.4.2 Unpublished references

c34018597-01 Biomarker report 1 for trial 1368-0013. Effisayil™ 1: Multi-center, double-blind, randomized, placebo-controlled, Phase II study to evaluate efficacy, safety and tolerability of a single intravenous dose of BI 655130 in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity. 30 Jul 2021

ABBREVIATIONS

DRESS	Drug reaction with eosinophilia and systemic symptoms
GPP	Generalized pustular psoriasis
GSP	Global safety platform
HIV	Human immunodeficiency virus
i.v.	Intravenous
IL-36RN	Natural interleukin 36 receptor antagonist
SmPC	Summary of Product Characteristics

MODULE SV POST-AUTHORISATION EXPERIENCE

SV.1 METHOD USED TO CALCULATE EXPOSURE

Spevigo i.v. infusion (single dose)
Ex-factory (commercial) sales numbers for Spevigo as the basis for the estimation of the post-authorisation (non-clinical trial) exposure are only available for complete months, from the beginning of September 2022.

The method used to estimate the patient exposure to the marketed drug is based on the number of bulk units (mL) sold (ex-factory sales). It is assumed that all bulk units were used by the patients and that each patient was treated with 15 mL (2 vials with 7.5 mL each, i.e. the recommended single dose), i.e. a single dose of 900 mg (15 mL) is equivalent to 1 patient, even though in some instances a second dose may have been administered. The number of patients treated is calculated by dividing the bulk units (mL) sold (ex-factory sales) by the defined single dose.

Spevigo s.c. administration (multiple doses)
Ex-factory (commercial) sales numbers for Spevigo as the basis for the estimation of the post-authorisation (non-clinical trial) exposure are only available for completed months, beginning in April 2024.

The method used to estimate the patient exposure to the marketed drug is based on the number of bulk units (mL) sold (ex-factory sales). It is assumed that all bulk units were used by the patients. Each patient receives an initial s.c. loading dose of 4 injections (4 mL) followed by 2 injections (2 mL) 4 weeks later and every 4 weeks thereafter. The assumption for calculation of the average dose is 50% new patients receiving the initial dose and 50% of patients on maintenance dose. The number of PY is calculated by dividing the bulk units (mL) sold (ex-factory sales) by the average dose.

SV.2 EXPOSURE

Calculated cumulative exposure figures by region/countries are presented in the tables below. Exposure data by gender and age are not available for Spevigo.

Spevigo i.v. infusion (single dose)

SV.Table 1 Cumulative patient exposure from marketing experience by region/countries for Spevigo i.v. (September 2022 to August 2024)

	Units sold [mL][1]	Exposed patients [n][1]
[redacted]	[redacted]	[redacted]
Total	**45 090**	**3006**

[1] All numbers are rounded to the nearest integer.

Data source: data on file, ER-026 Spevigo IV (2024 08)

SV.Table 2 Cumulative exposure from marketing experience by EU/EEA country for Spevigo i.v. (September 2022 to August 2024)

EU/EEA country	Units sold [mL][1]	Exposed patients [n][1]
[redacted]	[redacted]	[redacted]
Total	**3450**	**230**

[1] All numbers are rounded to the nearest integer.

Data source: data on file, ER-026 Spevigo exposure (2024 08)

Spevigo s.c. administration (multiple doses)

SV.Table 3 Cumulative patient exposure from marketing experience by region/countries for Spevigo s.c. (April 2024 to August 2024)

	Units sold [mL][1]	Patient exposure[1] [PY]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Total	**860**	**32**

[1] All numbers are rounded to the nearest integer.

Data source: data on file, ER-038 Spevigo SC exposure (2024 08)

Data on use in the EU/EEA are not yet available.

SV.3 REFERENCES

Not applicable.

ABBREVIATIONS

EEA	European Economic Area
EU	European Union
i.v.	Intravenous
PY	Patient-year
s.c.	Subcutaneous
US	United States

MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Spesolimab is available as prescription medicine only and administered in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases. Pharmacological properties, non-clinical, and clinical data do not indicate an impact on the central nervous system suggestive for stimulant, depressant, hallucinogenic, or mood-elevating effects, or other effects that might lead to dependency. Abuse for illegal purpose is not expected with spesolimab.

SVI.2 REFERENCES

Not applicable.

ABBREVIATIONS

EU	European Union

MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:
The following risks are ADRs that require no further characterisation and are followed up via routine pharmacovigilance (signal detection, adverse reaction reporting):

- Fatigue
- Pruritis
- Upper respiratory tract infection
- Urinary tract infection
- Injection site reactions

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

The patient population for the RMP analyses are patients with GPP who experience an acute flare with supplemental data being provided based on trials of spesolimab in healthy volunteers, GPP patients on maintenance treatment, and trials of spesolimab in other diseases, including PPP, UC, and AtD; see Section SVII.3 for further details.

Based on all available data, there are no important identified risks for spesolimab.

SVII.1.2.1 Important potential risk: Serious or opportunistic infections

Risk-benefit impact:
A theoretical risk of serious and opportunistic infections exists for all immune-modulating biologic medications. Risk of infection is due to potential alteration of the immune response to pathogens [R20-3252, R20-3223, R20-3221].

There was no signal for infections in non-clinical trials (see Module SII). Further, a recent published analysis of 12 human subjects with IL-36R KO mutations showed no evidence of history of recurrent infections and all showed normal leukocyte counts [R17-3632].

In the clinical development programme of spesolimab to date, a higher proportion of patients with infections was noted after spesolimab than placebo treatment. Nevertheless, infections were mild to moderate and non-serious. There was no indication for a higher proportion of

patients with serious or opportunistic infections (SCS spesolimab [c32483404-01], Section 2.1.7.2).

Therefore, serious or opportunistic infections are considered an important potential risk for spesolimab. A potential impact on individual health and on individual benefit-risk cannot be excluded.

For further details on seriousness, frequency, and severity refer to Section SVII.3.1.2.3.

SVII.1.2.2 Important potential risk: Systemic hypersensitivity reaction

Risk-benefit impact:
A theoretical risk of systemic immediate or delayed (including DRESS) hypersensitivity reaction exists for all immune-modulating biologic medications. In principle, hypersensitivity reactions (including infusion-related reactions, anaphylactic reactions, and DRESS) are possible with any foreign substance, particularly protein-based therapeutics [R20-3220].

Based on the safety data collected in clinical trials with spesolimab, injection site reactions (including injection site erythema, injection site swelling, injection site pain, injection site induration, and injection site warmth) were identified as ADRs for spesolimab in the treatment of GPP flares (SCS spesolimab [c32483404-01], Section 2.6). However, these were limited, if observed, to localised symptoms such as erythema, swelling and pain at the injection site.

No signal of systemic hypersensitivity including infusion reaction and anaphylactic reaction was identified.

The potential immunogenicity of spesolimab is low [c35356518-01]. The likelihood of an immune reaction in response to spesolimab was found to be similar to that obtained for therapeutic monoclonal antibodies associated with relatively low levels of clinical immunogenicity. However, predicted CD4 T-cell epitopes were identified in both the variable heavy and light chain sequences of spesolimab, which raises the possibility that administration could induce a T-cell dependent humoral immune response.

Symptoms observed in 2 patients receiving spesolimab in a trial in patients with GPP flares were reported as DRESS (with RegiSCAR scores 1 and 3) [P14-06207], and in close temporal relationship to the reported GPP flares, which was 2 days after start of treatment with spesolimab in 1 case. Both patients received concomitant medication at the time of the DRESS, which included cefuroxime, cefepime, spiramycin, and paracetamol. The rapid occurrence of symptoms after spesolimab administration in 1 case makes a causal relationship between spesolimab and DRESS implausible. In the other case, similar cutaneous symptoms re-occurred after re-administration with spiramycin, suggesting spiramycin as an alternative explanation.

No cases of DRESS were reported in any other trial conducted with spesolimab in other diseases including inflammatory bowel disease, AtD, or PPP.

Systemic hypersensitivity reaction, including DRESS, is considered an important potential risk for spesolimab. A potential impact on individual health and on individual benefit-risk cannot be excluded.

For further details on seriousness, frequency, and severity refer to Section SVII.3.1.1.3.

SVII.1.2.3 Important potential risk: Malignancy

Risk-benefit impact:
To date, no evidence of carcinogenic potential has arisen in either non-clinical IL-36R KO mouse phenotypic assessments, or in repeat dose toxicology studies using the surrogate antibody BI 674304, or in clinical trials using spesolimab. Since rodent non-clinical carcinogenicity studies using the clinical candidate spesolimab are not feasible owing to lack of pharmacological relevance of the rodent, no additional non-clinical studies are planned as they would not add value to the current assessment [n00265831-02].

Meta-analyses of cancer incidence among patients that have received immune suppression therapy (e.g. TNFs, methotrexate) have not yielded clear correlation between tumour incidence and therapies not intended to completely ablate immune function [n00265831-02].

A theoretical risk of malignancy exists for all immune-modulating biologic medications including spesolimab. The risk of malignancy is potentially increased due to impaired immune defences [R20-3218]. Malignancy is considered an important potential risk for spesolimab. A potential impact on individual health and on individual benefit-risk cannot be excluded.

For further details on seriousness, frequency, and severity refer to Section SVII.3.1.3.3.

SVII.1.2.4 Important potential risk: Peripheral neuropathy

Risk-benefit impact:
The potential for peripheral neuropathy with spesolimab is unknown. In preclinical toxicity studies with the surrogate antibody BI 674304, no histopathological changes were noted in the nervous system. There is no indication from the literature, that the inhibition of the IL-36 pathway is linked to an increased risk of treatment-emergent peripheral neuropathy.

Cases of peripheral neuropathy were reported in clinical trials with spesolimab (investigator reporting). However, the reported cases showed a heterogenous clinical pattern and a causal association with spesolimab for any of the reported cases was assessed to be unlikely as per independent external expert adjudication.

Peripheral neuropathy is considered an important potential risk for spesolimab. A potential impact on individual health and on individual benefit-risk cannot be excluded.

For further details on the reported cases refer to Section SVII.3.1.4.

SVII.1.2.5 Missing information: Pregnant or breast-feeding women

Risk-benefit impact:
There are limited data from the use of spesolimab in pregnant women. Pre-clinical studies using a surrogate, mouse specific anti-IL-36R monoclonal antibody do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is recommended to avoid the use of spesolimab in pregnancy, unless the expected clinical benefit clearly outweighs the potential risks.

Very limited experience is available from clinical trial data; post-marketing data is not yet available. The risk for the unborn or breastfed child is not known, but cannot be excluded. Therefore, this topic is considered missing information.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Reclassification of 'Systemic hypersensitivity reaction' from an important potential risk to an important identified risk

There is a general risk for biologics to cause hypersensitivity reactions, and systemic hypersensitivity has been considered an important potential risk for spesolimab for this reason. *In vitro* data for spesolimab have shown that it has a low potential to cause cytokine release, and the relative immunogenic potential is similar to monoclonal antibodies with relatively low clinical immunogenicity.

Systemic hypersensitivity had not been identified previously as an ADR due to the data from completed clinical trials. Review of these data showed that within placebo-controlled periods across indications and dosing regimens, the frequency of potential hypersensitivity events was generally balanced across placebo and spesolimab treatment groups. None of the events appeared to reflect systemic hypersensitivity events caused by spesolimab.

Within ongoing open-label clinical trials, 2 infusion-related reactions, one of which triggered the initiation of a signal assessment for events of systemic hypersensitivity, included clinical descriptions and laboratory evidence to suggest acute systemic hypersensitivity events to spesolimab. Within the post-marketing database, 3 cases of varying involvement (reported as urticaria, anaphylaxis, and anaphylactic shock) suggested acute systemic hypersensitivity events. There was no evidence for delayed systemic hypersensitivity events.

No publications describing hypersensitivity events with spesolimab or IL-36R antagonists were identified in the literature.

In conclusion, while there is not a preponderance of evidence definitively identifying systemic hypersensitivity reactions after spesolimab administration, given the biologic plausibility and new accumulation of cases, with some including confirmatory laboratory data, the signal was confirmed. Hence, hypersensitivity is considered an ADR for spesolimab.

With the adoption of systemic hypersensitivity as an ADR, the MAH proposes to reclassify it in the RMP from an important potential risk to an important identified risk. Given the limited number of cases that were identified as representing systemic hypersensitivity to spesolimab, the risk is not fully characterised. However, the PASS 1368-0128 already includes systemic hypersensitivity as a safety event of interest, and no additional changes are proposed for the safety monitoring strategy.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

Note: information on the indication GPP flare prevention is newly added in the following (DLP 13 Jan 2023). Information on the indication GPP flare treatment (DLP 08 Jan 2021) from the initial submission (EU-RMP v1.0) is not updated. Additional data from clinical trials conducted in other diseases is provided in Appendix 7.

GPP flare prevention (DLP 13 Jan 2023, Spevigo EU-RMP v2.0)
For analysis of safety concerns, the safety analysis set including all patients with GPP and who received at least 1 dose of spesolimab (i.v. and/or s.c.) was considered (SAF-ISS3p). In addition, data from trial 1368-0027 (pivotal trial in GPP flare prevention) are presented. Supportive data from randomised, placebo-controlled, clinical trials conducted in other diseases is provided in Appendix 7.

SVII.Table 1 Overview of safety analysis sets/trials

SAF/trial	Description	Trials included	MedDRA version
SAF-ISS3p	This pool includes patients with GPP treated with spesolimab i.v. and/or s.c. (for a comprehensive approach of safety analyses of GPP patients). For safety in GPP flare prevention, the treatment group overall is presented[1].	1368-0011, 1368-0013, 1368-0025, 1368-0027	25.1
Trial 1368-0027	Randomised, placebo-controlled, clinical trial in patients with GPP (randomised treatment period [placebo-controlled] and overall spesolimab treatment [including open-label phases])	1368-0027	25.1

[1] No placebo comparison is available due to the variability in duration of the randomised periods among GPP trials, posing a limitation to the placebo comparison.

Note: information on trial 1368-0027 was already provided in the initial submission for GPP flare treatment (DLP 08 Jan 2021, EU-RMP v1.0). Updated information on this trial is provided for the indication GPP flare prevention.

Data source: SAP for RMP for spesolimab GPP flare prevention [c40265480-01], Table 5.1.2:1

GPP flare treatment (DLP 08 Jan 2021, Spevigo EU-RMP v1.0)
Data from all completed or ongoing clinical trials were considered for the analysis of safety concerns. The primary focus of the analysis is on the GPP trials in patients receiving

spesolimab 900 mg i.v. or placebo i.v. (1368-0013, 1368-0025, and 1368-0027). Supportive data from trial 1368-0011 (GPP indication) and placebo-controlled, randomised clinical trials conducted in other diseases (UC [1368-0005, 1368-0010], PPP [1368-0015, 1368-0016], and AtD [1368-0032]) is provided in Appendix 7. Additional long-term data will be available from the ongoing extension trial 1368-0025 (trial duration 5 years) and trial 1368-0027 (trial duration 1 year).

Due to the heterogeneity of the clinical trials in the spesolimab clinical development programme regarding trial characteristics, indication, dosing and route of administration, the characterisation of risks is based on data from individual trials rather than on pooled data.

For the GPP trials in patients receiving spesolimab 900 mg i.v. or placebo i.v., the following treatment periods are analysed and presented:

SVII.Table 2 Overview of analysed treatment periods for GPP trials in patients receiving spesolimab 900 mg i.v. or placebo i.v.

Trial	Analysis period	Description
1368-0013	Up to week 1	From date of first dose of randomised trial medication (day 1) through the first week of treatment (i.e. up to day 8).
	Up to week 12[1]	From date of first dose of randomised trial medication (day 1) through the first 12 weeks of treatment (i.e. up to day 85); only the spesolimab treatment arm is shown (as the corresponding placebo comparison is not available for nearly all patients after week 1).
	By treatment period of spesolimab use including REP[2] of any randomised treatment or non-randomised spesolimab[3]	Overall period post use of spesolimab: From first use of any spesolimab to the minimum of the day of last spesolimab in the trial +112 or the last contact date per EoS page if patient did not roll over or the day prior to first dose in the extension trial if patient rolled over.
1368-0025	Entire treatment period	All maintenance treatment periods and all flare rescue treatment periods were pooled and analysed by per patient analysis.
1368-0027	Open-label overall period	From date/time of start of the first rescue treatment to earliest of: date of any trial treatment +112 days for patients with flare, the day of EoS if patients did not roll over, the day before first dose in open-label trial if patients rolled over or the cut-off date of interim analysis, if applicable.

[1] Data after intake of (optional) open-label spesolimab on day 8 or rescue medication with spesolimab for treatment of a GPP flare were censored for reporting.

[2] For the RMP analyses, the definition of the REP was harmonised to 16 weeks across all trials.

[3] Patients received 1 to 3 doses of randomised and/or non-randomised spesolimab. Number of doses administered in trial 1368-0013: 1 dose of 900 mg i.v. in the up to week 1 and 12 analysis periods; up to 3 doses of 900 mg i.v. in REP (data on file, MQRM_5_1_4_L-EXP_1_L-speso-exposure_1368-0013).

Data source: SAP for RMP for spesolimab (GPP indication) [c35174241-01], Table 4.3: 1

SVII.3.1 Presentation of important identified risks and important potential risks

SVII.3.1.1 Important identified risk: Systemic hypersensitivity reaction

SVII.3.1.1.1 Potential mechanisms

Spesolimab is a humanised monoclonal IgG1 antibody. The presence of modified proteins in the human blood may result in a certain risk for the occurrence of allergic reactions. The potential immunogenicity of spesolimab is low, as described in Section SVII.1.2.2.

SVII.3.1.1.2 Evidence source(s) and strength of evidence

There is a general risk for proteins to cause hypersensitivity reactions. Humanisation of the parental murine monoclonal antibody has reduced relative intrinsic immunogenic potential, as assessed by *in silico* prediction of CD4 T-cell epitopes, to a level consistent with that of therapeutic monoclonal antibodies associated with low to negligible levels of clinically impactful immunogenicity. However, predicted CD4 T-cell epitopes were identified in both the variable heavy and light chain sequences of spesolimab, which raises the possibility that administration of spesolimab could induce a T-cell dependent humoral immune response (data on file, prospective IRA Appendix 6, Section 2.4).

In many cases of hypersensitivity events observed in clinical trials, alternative risk factors were present; however, contribution of spesolimab to these events cannot be fully excluded. Post-approval, clinical trial and post-marketing cases triggered a signal assessment report. The signal was confirmed, and systemic hypersensitivity (specified as hypersensitivity comprising immediate systemic hypersensitivity reactions, including anaphylactic reaction) is considered an ADR.

No additional risk minimisation measures for the important identified risk ‘systemic hypersensitivity reactions’ are planned.

A PASS (1368-0128) for which the protocol is endorsed by the PRAC is in preparation, to further investigate this important identified risk.

SVII.3.1.1.3 Characterisation of the risk

Search strategy

Cases of potential systemic hypersensitivity reaction were analysed using a combined search of the narrow SMQs ‘Anaphylactic reaction’, ‘Angioedema’, and ‘Hypersensitivity’ (indication GPP flare prevention: MedDRA version 25.1 [DLP 13 Jan 2023, Spevigo EU-RMP v2.0]; indication GPP flare treatment: MedDRA version 23.1 [DLP 08 Jan 2021, Spevigo EU-RMP v1.0]).

Cases of DRESS were analysed using the narrow SMQ ‘Drug reaction with eosinophilia and systemic symptoms syndrome’, defined using an algorithmic approach (as defined in the SAP [c40265480-01] (indication GPP flare prevention: MedDRA version 25.1 [DLP 13 Jan 2023,

Spevigo EU-RMP v2.0]; indication GPP flare treatment: MedDRA version 23.1 [DLP 08 Jan 2021, Spevigo EU-RMP v1.0]).

Indication GPP flare prevention (DLP 13 Jan 2023, Spevigo EU-RMP v2.0)

Summary

The reported events potentially reflective of hypersensitivity in the pooled GPP trials (SAF-ISS3p) and in trial 1368-0027 were mainly non-serious, of mild to moderate intensity, and the majority of patients had recovered from the events. There were 2 patients reported with DRESS (trial 1368-0013, reported previously in the initial submission [EU-RMP v1.0], see Appendix 7 for details).

Refer to Appendix 7, Section 2.1 for summary of results from clinical trial data from other diseases.

Based on the analyses of the frequency of injection site reactions in clinical trials at the time of the marketing authorisation application, there was no evidence for spesolimab to induce clinically relevant hypersensitivity. The observed injections site reactions were non-serious and of mild intensity and rather local tolerability.
Post-approval, clinical trial and post-marketing cases triggered a signal assessment report. The signal was confirmed, and systemic hypersensitivity (specified as hypersensitivity comprising immediate systemic hypersensitivity reactions, including anaphylactic reaction) is considered an ADR.

SAF-ISS3p

42 patients (23.2%) in the spesolimab overall group were reported with events potentially reflective of hypersensitivity (spesolimab overall), including 2 patients (1.1%) reported with DRESS. There were 5 patients (2.8%) with serious events, mainly requiring/prolonging hospitalisation. The events were mainly of moderate intensity, and most patients had recovered from the event. Further details are given in the table below.

SVII.Table 3 Overview of potential systemic hypersensitivity reaction – SAF-ISS3p

	Spesolimab overall
Number of patients treated, N (%)	181 (100.0)
Total overall time at risk (PY)	244.3
Patients with potential systemic hypersensitivity reaction, N (%)	42 (23.2)
Rate per 100 PY	20.5
Seriousness, N (%)	5 (2.8)
Life-threatening	1 (0.6)
Requiring/prolonging hospitalisation	4 (2.2)
Other	1 (0.6)
Outcome, N (%)	
Recovered/resolved	35 (19.3)
Not recovered/not resolved	7 (3.9)
Intensity, N (%)	
Mild	17 (9.4)
Moderate	23 (12.7)
Severe	2 (1.1)

A subject may have serious AE(s) with multiple seriousness criteria.

A subject with more than one AE will be counted once according to worst intensity, outcome or RCTC grade.

Data source: rmp-output-tlf-gpp-flare-prevention [c41549498], Tables A.2.1.1: 1, A.2.1.1: 2 'Hypersensitivity ALL'

Trial 1368-0027

Randomised treatment period

3 patients (10.0%) in the placebo SC group and 17 patients (18.3%) receiving spesolimab (3 patients [10%] in the spesolimab SC high group) were reported with events potentially reflective of hypersensitivity. There were no patients reported with DRESS (rmp-output-tlf-gpp-flare-prevention [c41549498], Table A.2.5.3: 1 'DRESS narrow'). The events in either treatment group were mainly of mild intensity. Most patients in either treatment group recovered from the event. Further details are given in the table below. 2 patients (2.2%) in the spesolimab SC low group had serious events:

- Drug eruption: reported in a female patient (age 30-40 years), reported as reaction to COVID-19 vaccination with erythematous rash, tachycardia, and palpitations 2 hours after vaccination. The event was treated with chlorpheniramine and dexamethasone. No previous history of hypersensitivity to vaccines was reported. Trial medication was continued.
- Angioedema: reported in a female (age 30-40 years), the time to onset was 6 days. Reported as angioedema of both eyes. The event was reported in association with worsening of GPP, fever, and fatigue. No previous history of angioedema, urticaria or other allergic symptoms, or hereditary angioedema was reported. The patient

recovered from the angioedema without treatment. The patient received rescue spesolimab i.v. dose 1 day after angioedema.

Overall spesolimab treatment

21 patients (19.6%) in the overall spesolimab group were reported with events potentially reflective of hypersensitivity. There were no patients reported with DRESS. 2 patients (1.9%) had serious events (described above). The events were mainly of mild or moderate intensity. Most patients recovered from the event (rmp-output-tlf-gpp-flare-prevention [c41549498], Table A.2.5.4: 1 ‘Hypersensitivity ALL’, ‘DRESS narrow’).

SVII.Table 4 Overview of potential systemic hypersensitivity reaction – Trial 1368-0027 (randomised treatment period)

	Placebo SC	Spesolimab SC low	Spesolimab SC medium	Spesolimab SC high	Spesolimab total
Number of patients treated, N (%)	30 (100.0)	32 (100.0)	31 (100.0)	30 (100.0)	93 (100.0)
Total overall time at risk (PY)	17.7	25.1	22.8	23.9	71.8
Patients with potential systemic hypersensitivity reaction, N (%)	3 (10.0)	8 (25.0)	6 (19.4)	3 (10.0)	17 (18.3)
Rate per 100 PY	18.9	39.8	30.8	13.0	27.1
Incidence rate ratio[1] (95% CI)	--	--	--	--	1.4 (0.5, 4.2)
Incidence rate difference[1] (95% CI)	--	--	--	--	8.3 (-19.5, 36.0)
Risk ratio[1] (95% CI)	--	--	--	--	1.8 (0.6, 10.8)
Risk difference[1] (95% CI)	--	--	--	--	8.3 (-10.0 20.8)
Seriousness, N (%)	0	2 (6.3)	0	0	2 (2.2)
Requiring/ prolonging hospitalisation	0	1 (3.1)	0	0	1 (1.1)
Other	0	1 (3.1)	0	0	1 (1.1)
Outcome, N (%)					
Recovered/ resolved	2 (6.7)	7 (21.9)	6 (19.4)	1 (3.3)	14 (15.1)
Not recovered/ not resolved	1 (3.3)	1 (3.1)	0	2 (6.7)	3 (3.2)
Intensity, N (%)					
Mild	2 (6.7)	2 (6.3)	5 (16.1)	2 (6.7)	9 (9.7)
Moderate	1 (3.3)	5 (15.6)	1 (3.2)	1 (3.3)	7 (7.5)
Severe	0	1 (3.1)	0	0	1 (1.1)

[1] Active treatment vs. placebo.

A subject may have serious AE(s) with multiple seriousness criteria.

A subject with more than one AE will be counted once according to worst intensity, outcome or RCTC grade.

Data source: rmp-output-tlf-gpp-flare-prevention [c41549498], Tables A.2.5.3: 1, A.2.5.3: 2, A.2.5.3: 3, A.2.5.3: 4 'Hypersensitivity ALL'

Indication GPP flare treatment (DLP 08 Jan 2021, Spevigo EU-RMP v1.0)

Summary (indication GPP and other diseases)

The number of patients with systemic hypersensitivity reaction in the GPP trials in patients receiving spesolimab 900 mg i.v. or placebo i.v. was low (5 patients in trial 1368-0013, originally including 2 cases reported as DRESS of which 1 was life-threatening, and 4 patients in trial 1368-0025). In line with the supportive data from other diseases (UC, PPP, AtD; see Appendix 7), the reported hypersensitivity events were mainly non-serious, of mild to moderate intensity, and the majority of patients recovered. There was 1 life-threatening hypersensitivity event (trial 1368-0005, PT 'Infusion related reaction', see Appendix 7 for details).

Based on the analyses of the frequency of injection site reactions in clinical trials, at the time of the marketing authorisation application, there was no evidence for spesolimab to induce clinically relevant hypersensitivity. The observed injections site reactions were non-serious and of mild intensity and rather local tolerability.
Post-approval, clinical trial and post-marketing cases triggered a signal assessment report. The signal was confirmed, and systemic hypersensitivity (specified as hypersensitivity comprising immediate systemic hypersensitivity reactions, including anaphylactic reaction) is considered an ADR.

GPP trials in patients receiving spesolimab 900 mg i.v. or placebo i.v.

Trial 1368-0013

Up to week 1

1 patient (5.6%) in the placebo group and 3 patients (8.6%) in the spesolimab 900 mg i.v. group were reported with hypersensitivity reactions. There was 1 serious event (DRESS, reported by 1 patient in the spesolimab 900 mg i.v. group; the event required/prolonged hospitalisation, was of moderate intensity, and the patient recovered). Except for the event of DRESS, all remaining events were of mild intensity. All patients recovered. Further detail is given in the table below.

SVII.Table 5 Overview of systemic hypersensitivity reaction – Trial 1368-0013 (week 1)

	Placebo	**Spesolimab 900 mg i.v.**
Number of patients treated, N (%)	18 (100.0)	35 (100.0)
Total overall time at risk (PY)	0.3	0.7
Patients with systemic hypersensitivity reaction, N (%)	1 (5.6)	3 (8.6)
Rate per 100 PY	289.9	478.5
Reported PTs[1]	Dermatitis allergic	Drug reaction with eosinophilia and systemic symptoms, Eye oedema, Urticaria
Incidence rate ratio[2] (95% CI)	--	1.7 (0.2, 15.7)
Incidence rate difference[2] (95% CI)	--	188.6 (-1151.2, 1121.9)
Risk ratio[2] (95% CI)	--	1.5 (0.2, 13.8)
Risk difference[2] (95% CI)	--	3.0 (-18.0, 17.6)
Seriousness[3], N (%)	0	1 (2.9)
Requires/prolongs hospitalisation	0	1 (2.9)
Outcome, N (%)		
Recovered/resolved	1 (5.6)	3 (8.6)
Intensity[4], N (%)		
Mild	1 (5.6)	2 (5.7)
Moderate	0	1 (2.9)

Patients with systemic hypersensitivity reaction were identified using a combined search of the narrow SMQs 'Anaphylactic reaction', 'Angioedema', and 'Hypersensitivity' (MedDRA version 23.1).

[1] A patient can be reported with more than 1 PT.

[2] Respective active treatment vs. placebo.

[3] Patients can be counted in more than 1 seriousness category.

[4] Intensity was collected with mild/moderate/severe categories for trial 1368-0011 and derived from RCTC grading for all other remaining trials.

A patient with more than 1 AE was counted once according to worst intensity or outcome.

Data source: data on file, analyses for EU-RMP v1.0, 'hypersensitivity all' Tables A.2.1.2: 1, A.2.1.2: 2, A.2.1.2: 3, and A.2.1.2: 4

Up to week 12

1 additional patient with DRESS was reported (spesolimab 900 mg i.v.). The event was serious (life-threatening, requiring/prolonging hospitalisation), of severe intensity, and the patient recovered. Further detail is given in the table below.

For 1 of the 2 cases reported as DRESS (RegiSCAR score 1, i.e. no DRESS), the rapid occurrence of symptoms after spesolimab administration makes a causal relationship between spesolimab and DRESS implausible. For the other case (RegiSCAR score 3), similar cutaneous symptoms reoccurred after re-administration with spiramycin, suggesting

spiramycin as an alternative explanation. Further detail on the 2 DRESS cases is given in Appendix 7.

SVII.Table 6 Overview of systemic hypersensitivity reaction – Trial 1368-0013 (week 12)

	Spesolimab 900 mg i.v.
Number of patients treated, N (%)	35 (100.0)
Total overall time at risk (PY)	5.0
Patients with systemic hypersensitivity reaction, N (%)	4 (11.4)
Rate per 100 PY	87.9
Reported PTs[1]	Drug reaction with eosinophilia and systemic symptoms, Urticaria, Dermatitis, Eye oedema
Incidence rate ratio[2] (95% CI)	0.6 (0.1, 5.2)
Incidence rate difference[2] (95% CI)	-63.7 (-758.9, 121.9)
Risk ratio[2] (95% CI)	2.1 (0.2, 17.1)
Risk difference[2] (95% CI)	5.9 (-15.5, 21.1)
Seriousness[3], N (%)	2 (5.7)
Life-threatening	1 (2.9)
Requires/prolongs hospitalisation	2 (5.7)
Outcome, N (%)	
Recovered/resolved	4 (11.4)
Intensity[4], N (%)	
Mild	2 (5.7)
Moderate	1 (2.9)
Severe	1 (2.9)

Patients with systemic hypersensitivity reaction were identified using a combined search of the narrow SMQs 'Anaphylactic reaction', 'Angioedema', and 'Hypersensitivity' (MedDRA version 23.1).

Note: incidence rate ratio and risk ratio are <1 and <0, respectively, as the exposure time is longer in the spesolimab group.

[1] A patient can be reported with more than 1 PT.

[2] Respective active treatment vs. placebo.

[3] Patients can be counted in more than 1 seriousness category.

[4] Intensity was collected with mild/moderate/severe categories for trial 1368-0011 and derived from RCTC grading for all other remaining trials.

A patient with more than 1 AE was counted once according to worst intensity or outcome.

Data source: data on file, analyses for EU-RMP v1.0, 'hypersensitivity all' Tables A.2.1.1: 1, A.2.1.1: 2, A.2.1.1: 3, and A.2.1.1: 4

By treatment period of spesolimab use (including REP of any randomised treatment or non-randomised spesolimab)/overall period post use

1 additional patient with 'Urticaria' was reported. The event was not serious, of moderate intensity, and the patient recovered. Further detail is given in the table below.

SVII.Table 7 Overview of systemic hypersensitivity reaction – Trial 1368-0013 (by treatment period of spesolimab use including REP of any randomised treatment) - pooled arms

	Post Speso Total
Number of patients treated, N (%)	51 (100.0)
Total overall time at risk (PY)	13.0
Patients with systemic hypersensitivity reaction, N (%)	5 (9.8)
Rate per 100 PY	42.3
Reported PTs[1]	Drug reaction with eosinophilia and systemic symptoms, Urticaria, Dermatitis, Eye oedema
Seriousness[2], N (%)	2 (5.7)
Life-threatening	1 (2.9)
Requires/prolongs hospitalisation	2 (5.7)
Outcome, N (%)	
Recovered/resolved	5 (14.3)
Intensity[3], N (%)	
Mild	2 (5.7)
Moderate	2 (5.7)
Severe	1 (2.9)

Patients with systemic hypersensitivity reaction were identified using a combined search of the narrow SMQs 'Anaphylactic reaction', 'Angioedema', and 'Hypersensitivity' (MedDRA version 23.1).

[1] A patient can be reported with more than 1 PT.

[2] Patients can be counted in more than 1 seriousness category.

[3] Intensity was collected with mild/moderate/severe categories for trial 1368-0011 and derived from RCTC grading for all other remaining trials.

A patient with more than 1 AE was counted once according to worst intensity or outcome.

Data source: data on file, analyses for EU-RMP v1.0, 'hypersensitivity all'/Randomised dose at Day 1: pooled arms, Tables A.2.1.3: 1 and A.2.1.3: 2

Trial 1368-0025 (entire treatment period)

Trial 1368-0025 was a single-arm spesolimab trial, therefore all events occurred in patients receiving spesolimab. 4 patients (10.3%) with hypersensitivity reaction were reported (1 patient with the PTs 'Application site urticaria' and 'Injection site urticaria', 2 patients with 'Rhinitis allergic', and 1 patient with 'Rash'). All events were non-serious, of mild or moderate intensity, and all patients recovered. There were no patients with DRESS (data on file, analyses for EU-RMP v1.0, 'hypersensitivity all' and 'DRESS' Table A.2.3.1: 1, and 1368-0025-16207-adverse-event-listings-final-20210310).

Trial 1368-0027 (open-label overall period)

There were no patients with hypersensitivity reaction or DRESS (data on file, analyses for EU-RMP v1.0, 'hypersensitivity all' and 'DRESS' Table A.2.4.1: 1).

SVII.3.1.1.4 Risk factors and risk groups

Risk groups or risk factors are unknown. There is a general risk for proteins to cause hypersensitivity reactions, with a potential intrinsic risk for spesolimab to induce a T-cell humoral immune response (see Section SVII.3.1.1.2).

SVII.3.1.1.5 Preventability

The preventability is unknown.

SVII.3.1.1.6 Impact on the risk-benefit balance of the product

There is a risk of a hypersensitivity reaction to spesolimab. Treatment with spesolimab should be administered in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases.

Currently, hypersensitivity is considered to have no impact on the risk-benefit balance of the product.

SVII.3.1.1.7 Public health impact

No impact on public health is expected.

SVII.3.1.2 Important potential risk: Serious or opportunistic infections

SVII.3.1.2.1 Potential mechanisms

Like all immune modulating agents, spesolimab may have the potential to alter the immune response resulting in a potential risk of infection. A recent characterisation of individuals with homozygous IL-36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL-36 signalling pathway inhibition does not compromise host defences [R17-3632].

SVII.3.1.2.2 Evidence source(s) and strength of evidence

There was no indication for an increased occurrence of serious or opportunistic infections in clinical trials with spesolimab.

A PASS (1368-0128) for which the protocol is endorsed by the PRAC is in preparation, to further investigate this important potential risk.

SVII.3.1.2.3 Characterisation of the risk

Search strategy
Cases of serious or opportunistic infections were analysed using the following searches (indication GPP flare prevention: MedDRA version 25.1 [DLP 13 Jan 2023, Spevigo EU-RMP v2.0]; indication GPP flare treatment: MedDRA version 23.1 [DLP 08 Jan 2021, Spevigo EU-RMP v1.0]):

- All serious events in the SOC 'Infections and infestations'
- All events in the SOC 'Infections and infestations' of at least severe RCTC grade
- Narrow SMQ 'Opportunistic infections'
- BIcMQ 'Infections', narrow sub-search 8.2 'Tuberculosis related terms' (see Appendix 7 for a list of PTs in included in the BIcMQ)

In all GPP trials, according to the CTPs, tuberculosis testing was to be performed as part of the routine testing at screening and at the end of study (except for trial 1368-0011). In the long-term extension trial 1368-0025, routine tuberculosis testing was to be repeated every 48 weeks.
In the non-GPP trials, these cases were observed upon routine TB testing according to the CTPs and were not followed by findings or AEs indicative of a TB reactivation.

Indication GPP flare prevention (DLP 13 Jan 2023, Spevigo EU-RMP v2.0)
Summary
The number of patients with serious or opportunistic infections in the pooled GPP trials (SAF-ISS3p) and in trial 1368-0027 was low. No event of reactivation of tuberculosis was reported.

- SAF-ISS3p: 12 patients (spesolimab overall group), including 2 patients with non-serious events of latent tuberculosis (PT 'Latent tuberculosis').
- Trial 1368-0027: 3 patients receiving spesolimab during the randomised treatment period (PTs 'Pneumonia', 'Latent tuberculosis', 'Encephalitis viral' [reported as differential diagnosis to the condition of hypertensive encephalopathy, and without diagnostic confirmation of viral encephalitis]), and 6 patients during overall spesolimab treatment (PTs 'Pneumonia [2 patients]', 'Septic shock', 'Urinary tract infection', 'Cellulitis', 'Skin bacterial infection', 'Latent tuberculosis', and 'Encephalitis viral'; 'Skin bacterial infection' was reported in connection with a skin breakdown due to GPP flare in 1 patient who developed 'Septic shock' on the following day and a few days later 'Pneumonia').

Refer to Appendix 7, Section 2.2 for summary of results from clinical trial data from other diseases.

Like all immune modulating agents, spesolimab may have the potential to alter the immune response resulting in a potential risk of infection. However, effective treatment options for serious or opportunistic infections are available and potential infections are not expected to have a relevant impact on the overall risk-benefit assessment.

SAF-ISS3p
12 patients (6.6%) in the spesolimab overall group were reported with serious or opportunistic infections (spesolimab overall), including 10 patients with serious infections (requiring/prolonging hospitalisation) and 2 patients with opportunistic infections (PT 'Latent tuberculosis', both events were non-serious). No event of reactivation of tuberculosis was

reported. 6 patients (3.3%) had events of severe intensity. Most patients recovered from the event. Further details are given in the table below.

SVII.Table 8 Overview of serious or opportunistic infections – SAF-ISS3p

	Spesolimab overall
Number of patients treated, N (%)	181 (100.0)
Total overall time at risk (PY)	244.3
Patients with serious or opportunistic infections, N (%)	12 (6.6)
Rate per 100 PY	5.3
Seriousness, N (%)	10 (5.5)
Requiring/prolonging hospitalisation	10 (5.5)
Outcome, N (%)	
Recovered/resolved	10 (5.5)
Not recovered/not resolved	2 (1.1)
Intensity, N (%)	
Mild	2 (1.1)
Moderate	4 (2.2)
Severe	6 (3.3)

A subject may have serious AE(s) with multiple seriousness criteria.

A subject with more than one AE will be counted once according to worst intensity, outcome or RCTC grade.

Data source: rmp-output-tlf-gpp-flare-prevention [c41549498], Tables A.2.1.1: 1, A.2.1.1: 2 'Infections ALL'

Trial 1368-0027

Randomised treatment period

3 patients (3.2%) receiving spesolimab were reported with serious or opportunistic infections (see table below); none of the infections was reported in the spesolimab high group. This includes 1 patient with non-serious latent tuberculosis (PT 'Latent tuberculosis) and 2 patients with serious infection requiring/prolonging hospitalisation (PTs 'Pneumonia', 'Encephalitis viral' [reported as differential diagnosis to the condition of hypertensive encephalopathy, and without diagnostic confirmation of viral encephalitis; see below for further details] (rmp-output-tlf-gpp-flare-prevention [c41549498], Table A.2.5.3: 1 'Infections ALL', 'Tuberculosis infections'; and BI GSP).

- Community-acquired pneumonia: reported in a female adolescent, started 207 days after the first dose of spesolimab s.c. (i.e. on Day 208); no pathogen was identified; the event was treated with antibiotics, and the patient recovered without complications.
- Viral encephalitis: reported in a female patient (age 50-60 years at screening) with a history of untreated hypertension, started 73 days after the first dose of spesolimab s.c. (i.e. on Day 74). The patient was hospitalised due to elevated blood pressure (229/109 mmHg). According to the investigator, headache and altered sensorium could rather be explained by the hypertensive emergency and were additionally reported as an SAE of 'Hypertensive encephalopathy'. The lack of nuchal rigidity and

photophobia, normal CSF results, except for a slightly elevated protein, normal brain CT, and negative CSF culture for tuberculosis do not seem to support an infectious encephalopathy (either viral or bacterial).

Overall spesolimab treatment

6 patients (5.6%) in the overall spesolimab group were reported with serious or opportunistic infections. This includes 1 patient with non-serious latent tuberculosis (PT 'Latent tuberculosis') and 5 patients with serious infections (PTs 'Pneumonia' [there were 2 patients with pneumonia, one patient with the community-acquired pneumonia is described above; the other patient with pneumonia is described below], 'Septic shock', 'Urinary tract infection', 'Cellulitis', 'Skin bacterial infection', and 'Encephalitis viral' [described above]), requiring/prolonging hospitalisation. 'Skin bacterial infection' was reported in connection with a skin breakdown due to GPP flare occurring 30 days after the first spesolimab dose in 1 patient who developed 'Septic shock' on the following day and a few days later 'Pneumonia'). 5 patients (4.7%) had events of severe intensity. All patients with a serious infection recovered from the event, the patient with latent tuberculosis had not yet recovered (rmp-output-tlf-gpp-flare-prevention [c41549498], Tables A.2.5.4: 1, A.2.5.4: 2 'Infections ALL', 'Tuberculosis infections'; and BI GSP).

- Septic shock, skin bacterial infection: septic shock was reported in a female patient (age 20-30 years at screening), with skin bacterial infection. During hospitalisation for GPP flare, the patient developed septic shock, treated with ceftriaxone and norepinephrine. The event was considered secondary to cutaneous infection. 12 days into hospitalisation the patient developed pneumonia, with no other apparent risk factors. The skin bacterial infection occurred secondary to a GPP flare (suspected to be triggered by administration of COVID-19 vaccine) that led to skin breakdown.
- Urinary tract infection: reported a female patient (age 40-50 years), started 210 days after the 1st spesolimab dose. The patient had a GPP flare, developed fever, dysuria, cough but no sputum and dyspnoea for 4 days, oxygen saturation (room air) 88%. Urine culture showed *K. Pneumonia*. The event was treated with ceftriaxone and clindamycin for 7 days. No history of recurrent UTIs, pulmonary disease, or sick contacts. Poorly controlled diabetic with persistent glucosuria, which the investigator considered as one potential cause of UTI.
- Cellulitis: reported in a female patient (age 40-50 years); the time to onset was 76 days; 1 day after treatment with spesolimab i.v. for GPP flare, both of the patient's lower limbs became more swollen, red and painful. Unknown exposure. No pathogen identified. Diabetes mellitus was considered a risk factor. Treated with cefuroxime.

SVII.Table 9 Overview of serious or opportunistic infections – Trial 1368-0027 (randomised treatment period)

	Placebo SC	Spesolimab SC low	Spesolimab SC medium	Spesolimab SC high	Spesolimab total
Number of patients treated, N (%)	30 (100.0)	32 (100.0)	31 (100.0)	30 (100.0)	93 (100.0)
Total overall time at risk (PY)	17.7	25.1	22.8	23.9	71.8
Patients with serious or opportunistic infections, N (%)	0	2 (6.3)	1 (3.2)	0	3 (3.2)
Rate per 100 PY	0	8.4	4.4	0	4.3
Incidence rate ratio[1] (95% CI)	--	--	--	--	--
Incidence rate difference[1] (95% CI)	--	--	--	--	4.3 (-5.4, 13.9)
Risk ratio[1] (95% CI)	--	--	--	--	--
Risk difference[1] (95% CI)	--	--	--	--	3.2 (-9.3, 9.6)
Seriousness, N (%)	0	2 (6.3)	0	0	2 (2.2)
Requiring/ prolonging hospitalisation	0	2 (6.3)	0	0	2 (2.2)
Outcome, N (%)					
Recovered/ resolved	0	2 (6.3)	0	0	2 (2.2)
Not recovered/ not resolved	0	0	1 (3.2)	0	1 (1.1)
Intensity, N (%)					
Mild	0	0	1 (3.2)	0	1 (1.1)
Moderate	0	0	0	0	0
Severe	0	2 (6.3)	0	0	2 (2.2)

[1] Active treatment vs. placebo.

A subject may have serious AE(s) with multiple seriousness criteria.

A subject with more than one AE will be counted once according to worst intensity, outcome or RCTC grade.

Data source: rmp-output-tlf-gpp-flare-prevention [c41549498], Tables A.2.5.3: 1, A.2.5.3: 2, A.2.5.3: 3, A.2.5.3: 4 'Infections ALL'

Indication GPP flare treatment (DLP 08 Jan 2021, Spevigo EU-RMP v1.0)

Summary (indication GPP and other diseases)

There were 4 patients with serious, severe, or opportunistic infections in the GPP trials in patients receiving spesolimab 900 mg i.v. or placebo i.v.:

- Trial 1368-0013: 3 patients (1 patient in the placebo group following open-label spesolimab infusion [i.e. after 1 spesolimab dose] and 2 in the spesolimab group [1 each before and after open-label spesolimab infusion]). The reported PTs were 'Urinary tract infection', 'Influenza', and 'Latent tuberculosis'.
- Trial 1368-0025: 1 patient (PT 'Pneumonia')

There were no patients with serious, severe, or opportunistic infections in the remaining GPP, PPP, or AtD trials. There were 2 patients with a serious infection in the UC trials (both placebo):

- Trial 1368-0005: 1 patient (PT 'Clostridium difficile colitis')
- Trial 1368-0010: 1 patient (PT 'Rectal abscess')

Like all immune modulating agents, spesolimab may have the potential to alter the immune response resulting in a potential risk of infection. However, effective treatment options for serious or opportunistic infections are available and potential infections are not expected to have a relevant impact on the overall risk-benefit assessment.

GPP trials in patients receiving spesolimab 900 mg i.v. or placebo i.v.
Trial 1368-0013
Up to week 1
There was 1 patient with a serious infection (PT 'Urinary tract infection') in the spesolimab 900 mg i.v. group. The patient had fever, drowsiness, hypocalcaemia, and hypokalaemia as baseline conditions, prompting suspicion of sepsis in addition to GPP flare; serious UTI was diagnosed on day 3. Co-medications at baseline (started before UTI diagnosis) included cefuroxime, potassium chloride, paracetamol, cefepime and calcium carbonate. The event required/prolonged hospitalisation, was of moderate intensity, and the patient recovered (data on file, analyses for EU-RMP v1.0, 'serious infections' Tables A.2.1.2: 1 and A.2.1.2: 2; and CTR 1368-0013, Section 12.1.2.6.3 [c31523813-01]).

Up to week 12
There were no patients with serious, severe, or opportunistic infections up to week 12 (data on file, analyses for EU-RMP v1.0, 'serious infections', 'severe infections', 'opportunistic infections', 'tuberculosis infections' Table A.2.1.1: 1).

By treatment period of spesolimab use (including REP of any randomised treatment or non-randomised spesolimab)/overall period post use
There were 2 additional patients in this analysis period:

- 1 patient with a serious infection (PT 'Influenza') (post open-label spesolimab day 8). The event required/prolonged hospitalisation, was of moderate intensity, and the patient recovered. The event developed in winter, a month after the investigator had recommended influenza vaccination (due to risk factors), but the vaccination was not performed. In addition, a bacterial superinfection was reported. The bacteriological analysis revealed moderately rich flora of oro-pharyngeal type. At day+1, result was $1x10^7$ CFU/mL (or g), confirming flora of oro-pharyngeal type, and the antigen tests for Streptococcus pneumoniae interstitial cystitis and Legionella pneumophila

interstitial cystitis were negative (data on file, analyses for EU-RMP v1.0, 'serious infections' Tables A.2.1.3: 1 and A.2.1.3: 2; and CTR 1368-0013, Section 12.1.2.6.3 [c31523813-01]).

- 1 patient with latent tuberculosis (placebo group, receiving post open-label spesolimab at day 8):

  A Quantiferon tuberculosis test was scheduled for each patient at screening and at week 12; unscheduled tests could be done if required. 3 patients had a positive tuberculosis result at week 12, after testing negative at screening. This comprised 2 patients in the placebo group and 1 patient in the spesolimab group (CTR 1368-0013 [c31523813-01], Section 12.3.5). 1 patient (placebo group) was reported with latent tuberculosis after receiving open-label spesolimab at day 8. The AE was non-serious and of mild intensity (data on file, analyses for EU-RMP v1.0, 'tuberculosis infections' Tables A.2.1.3: 1 and A.2.1.3: 2). No relevant history or baseline conditions were reported for this patient. As the patient had no respiratory symptoms or abnormalities on pulmonary function tests and chest X-ray was normal, active tuberculosis was excluded. The patient was treated with isoniazid and successfully rolled over into the open-label extension trial. The remaining 2 patients (1 placebo, 1 spesolimab) had a negative re-test at screening for the open-label extension trial 1368-0025 (CTR 1368-0013 [c31523813-01], Sections 12.3.5 and 12.12.6.3).

  Furthermore, 2 patients (1 placebo, 1 spesolimab) converted from a negative baseline to an indeterminate tuberculosis test at or after week 12, but both re-tested negative at screening for the open-label extension trial 1368-0025. 1 patient in the spesolimab group had an indeterminate Quantiferon test at baseline with 3 subsequent (unscheduled) negative tests. Moreover, 1 patient in the spesolimab group with a history of active tuberculosis tested Quantiferon positive at baseline. After ruling out active disease, this patient completed trial treatment with an expected positive Quantiferon test at week 12 and at an unscheduled follow-up visit (at week 16) (CTR 1368-0013 [c31523813-01], Section 12.3.5).

Trial 1368-0025 (entire treatment period)
There was 1 patient with serious infection (PT 'Pneumonia'). The event was pneumonia of probable bacterial origin. Sputum cytobacteriological examination analysed poor flora of buccopharyngeal origin without predominance. Legionella and pneumococcus testing was negative. The event required/prolonged hospitalisation, was of severe intensity, and the patient recovered (data on file, analyses for EU-RMP v1.0, 'serious infections' Tables A.2.3.1: 1 and A.2.3.1: 2).

Trial 1368-0027 (open-label overall period)
There were no patients with serious, severe, or opportunistic infections (data on file, analyses for EU-RMP v1.0, 'serious infections', 'severe infections', 'opportunistic infections', 'tuberculosis infections' Table A.2.4.1: 1).

SVII.3.1.2.4 Risk factors and risk groups

Risk factors for infection may include in general increased age, impaired immune function, presence of comorbidities, and duration of exposure to and the number of concomitant immunosuppressive therapies. For patients with GPP, there is very limited epidemiological data and no clear indication for an increased risk of serious or opportunistic infections [R16-0933].

SVII.3.1.2.5 Preventability

Exposure to patients with active or latent mycobacterium tuberculosis infections and relevant chronic or acute infections including HIV and viral hepatitis is limited. Therefore, preventability of serious or opportunistic infections in the context of spesolimab use is not known.

Evaluation of tuberculosis status prior to initiation of treatment with spesolimab and anti-tuberculosis therapy prior to treatment with spesolimab in patients with tuberculosis or a history of tuberculosis is covered in the SmPC. Spesolimab is contraindicated to patients with active tuberculosis infection.

SVII.3.1.2.6 Impact on the risk-benefit balance of the product

GPP is regarded to represent a severe, potentially life-threatening disease. GPP flares can be fatal. Serious or opportunistic infections can potentially lead to hospitalisations, and can be fatal or life-threatening. In general, effective treatment options are available. Overall, infections are not expected to have a relevant impact on the overall risk-benefit assessment.

SVII.3.1.2.7 Public health impact

A potential impact on public health is not expected.

SVII.3.1.3 Important potential risk: Malignancy

SVII.3.1.3.1 Potential mechanisms

While there is evidence that supraphysiological levels of IL-36 can reduce tumour growth in mice, there is no evidence that normal levels of IL-36 are protective against cancer. Nor is there any evidence that IL-36 antagonism results in increased tumour growth. Finally, meta-analyses of cancer incidence among patients that have received immune suppression therapy have not yielded a clear correlation between tumour incidence and therapies not intended to completely ablate immune function [n00265831-02].

SVII.3.1.3.2 Evidence source(s) and strength of evidence

Clinical data on malignancy associated with IL-36R inhibition is limited by both duration and number of treated individuals. In related mechanisms, meta-analyses of cancer incidence among patients that have received immune suppression therapy (e.g. TNFs, methotrexate)

have not yielded clear correlation between tumour incidence and therapies not intended to completely ablate immune function [n00265831-02].

Like all immune modulating agents, spesolimab may have the potential to alter the immune response resulting in a potential risk of malignancy. A recent characterisation of individuals with homozygous IL-36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL-36 signalling pathway inhibition does not compromise host defences; none of the individuals had cancer [R17-3632].
The role of IL-36 in tumour immunity is not well established at this time, but a theoretical risk of cancer from an IL-36R antagonist, though considered small, cannot be excluded.

A carcinogenicity risk assessment was performed. In summary, review of the scientific literature has not indicated that inhibition of IL-36R signalling increases the risk of cancer although the limited data available has indicated that increasing IL-36 signalling can be protective against cancer. To date, no evidence of carcinogenic potential has arisen in either non-clinical IL-36R KO mouse phenotypic assessments, or in repeat dose toxicology studies using the surrogate antibody BI 674304, or in clinical trials using BI 655130 [n00265831-02], see also Module SII.1.1.2.

A PASS (1368-0128) for which the protocol is endorsed by the PRAC is in preparation, to further investigate this important potential risk.

SVII.3.1.3.3 Characterisation of the risk

Search strategy
Cases of malignancy were analysed using the following searches (indication GPP flare prevention: MedDRA version 25.1 [DLP 13 Jan 2023, Spevigo EU-RMP v2.0]; indication GPP flare treatment: MedDRA version 23.1 [DLP 08 Jan 2021, Spevigo EU-RMP v1.0]):

- Malignant tumours:
    - Narrow sub-SMQ ‘Malignant tumours’:
        - Narrow sub-SMQ ‘Haematological malignant tumours’
        - Narrow sub-SMQ ‘Non-Haematological malignant tumours’
- Malignant skin tumours:
    - Broad sub-SMQ ‘Skin malignant tumours’
- Skin melanomas:
    - HLT ‘Skin melanomas (excluding ocular)’
- Non-melanoma skin cancer:
    - Broad sub-SMQ ‘Skin malignant tumours’ excluding HLT ‘Skin melanomas (excluding ocular)’
- Malignancies excluding NMSC:
    - Sub-SMQ ‘Malignant tumours’ excluding NMSC

Indication GPP flare prevention (DLP 13 Jan 2023, Spevigo EU-RMP v2.0)

Summary

Clinical data on malignancy is limited both by duration of the observational period and the number of patients. The occurrence of malignancies is rare and may only be diagnosed after years. Across the complete duration of individual trials, no pattern regarding malignancies was observed that could indicate a causal association with spesolimab treatment and in most of the patients concerned underlying risk factors were present.

The number of patients with malignancies in the pooled GPP trials (SAF-ISS3p) and in trial 1368-0027 was low:

- SAF-ISS3p: 5 patients (spesolimab overall group) had malignant tumours (PTs 'Basal cell carcinoma' (2 patients), 'Adenocarcinoma', 'Breast cancer', and 'Squamous cell carcinoma of skin').
- Trial 1368-0027: 1 patient in the spesolimab SC high group (randomised treatment period) had a malignant tumour (PT 'Breast cancer'). During the overall spesolimab treatment, 1 additional patient with a NMSC (PT 'Basal cell carcinoma') was reported.

Refer to Appendix 7, Section 2.3 for summary of results from clinical trial data from other diseases.

SAF-ISS3p

5 patients (2.8%) in the spesolimab overall group had malignant tumours (PTs 'Basal cell carcinoma' (2 patients), 'Squamous cell carcinoma of skin', 'Adenocarcinoma', and 'Breast cancer'; details are given below). All events were serious, with no clear pattern regarding intensity discernible. Most patients recovered from the event. Further details are given in the table below. None of the malignant skin tumours was a melanoma.

- Basal cell carcinoma: reported in a female patient (age 60-70 years). The time to onset was 323 days. The SAE was reported during the open-label maintenance treatment period (trial 1368-0027), in a patient initially randomised and treated with speso SC medium dose. 8 mm diameter lesion at the left side of the nose at the nasal wing, which was excised by the dermatologist. No known risk factors were reported.
- Basal cell carcinoma: SAE reported in a female patient (age 40-50 years), who rolled over from trial 1368-0013 to the open-label extension trial 1368-0025. The SAE 'Basal cell carcinoma' was reported in trial 1368-0025. The time to onset was 751 days from the first dose in the OLE trial 1368-0025 and 841 days from the first dose of spesolimab in the preceding trial 1368-0013. The event was reported as superficial baso-cellular carcinoma on the right lateral aspect of the right thigh (1.1 cm x 1 cm). The patient was also diagnosed with histiocytofibroma. The patient underwent complete excision of the lesion on the day that it was diagnosed (recovered from the event on Day 752 of the trial 1368-0025). The patient had no known risk factors. Trial medication was continued. Causality was reported as related, although the investigator considered it unlikely, and other previous treatments more attributable (e.g. cyclosporin).

- Squamous cell carcinoma of skin: SAE reported in a male patient (age 50-60 years) from trial 1368-0013 (reported in previous EU-RMP v1.0). The patient was diagnosed a with a well-differentiated SCC of the left thumb 71 days after starting trial medication. The patient was in the 900 mg spesolimab i.v. treatment group. He underwent surgical excision. The event was reported as resolved on the day of surgery and was considered unrelated to trial medication. The SCC may have been a result of the patient's long-standing lesion of acrodermatitis continua of hallopeau. Trial medication was continued, and the patient transitioned into the long-term extension trial 1368-0025.
- Adenocarcinoma: SAE reported in a male patient (age 30-40 years) who rolled over from trial 1368-0013 to the open-label extension trial 1368-0025, and SAE reported in trial 1368-0025 (reported in previous EU-RMP v1.0). The time to onset was 31 days from the first dose in the OLE trial 1368-0025, and 131 days from the first dose of spesolimab in the preceding trial 1368-0013. The patient was diagnosed with a microinvasive adenocarcinoma of the lung (left upper lobe). The lesion was already detected prior to this patient's enrolment in the trial (and also prior to enrolment in the parent trial, 1368-0013), but increased in size over time, which led to additional diagnostic procedures. The patient had a past history of smoking and a grandfather that died of lung cancer (smoker). The patient underwent anterior segmentectomy of the left upper lobe through video-assisted thoracoscopic surgery. The event was considered unrelated to trial medication. Trial medication was discontinued.
- Breast cancer: reported in a female patient (age 50-60 years) in trial 1368-0027. The SAE occurred in the open-label maintenance treatment period with SC speso, in a patient initially randomised and treated with Speso SC High. The time to onset was 200 days. No known risk factors were reported. The patient discontinued medication and underwent chemotherapy and unilateral mastectomy.

SVII.Table 10 Overview of malignancy – SAF-ISS3p

	Spesolimab overall		
	Malignant tumours	**Malignant skin tumours**	**Malignancies excluding NMSC**
Number of patients treated, N (%)	181 (100.0)	181 (100.0)	181 (100.0)
Total overall time at risk (PY)	244.3	244.3	244.3
Patients with malignancy, N (%)	5 (2.8)	3 (1.7)	2 (1.1)
Rate per 100 PY	2.1	1.2	0.8
Seriousness, N (%)	5 (2.8)	3 (1.7)	2 (1.1)
Requiring/prolonging hospitalisation	2 (1.1)	0 (0.0)	2 (1.1)
Other	3 (1.7)	3 (1.7)	0 (0.0)
Outcome, N (%)			
Recovered/resolved	4 (2.2)	3 (1.7)	1 (0.6)
Not recovered/not resolved	1 (0.6)	0 (0.0)	1 (0.6)
Intensity, N (%)			
Mild	2 (1.1)	1 (0.6)	1 (0.6)
Moderate	1 (0.6)	1 (0.6)	0 (0.0)
Severe	2 (1.1)	1 (0.6)	1 (0.6)

A subject may have serious AE(s) with multiple seriousness criteria.

A subject with more than one AE will be counted once according to worst intensity, outcome or RCTC grade.

Data source: rmp-output-tlf-gpp-flare-prevention [c41549498], Tables A.2.1.1: 1, A.2.1.1: 2 ‘Malignant tumours’, ‘Malignancies excluding NMSC’, ‘Malignant skin tumours’

Trial 1368-0027

Randomised treatment period

1 patient (3.3%) in the spesolimab SC high group had a malignant tumour (PT ‘Breast cancer’, details are given above, under SAF-ISS3p). The event was serious (requiring/prolonging hospitalisation), of severe intensity, and the patient had not yet recovered from the event (rmp-output-tlf-gpp-flare-prevention [c41549498], Tables A.2.5.3: 1, A.2.5.3: 2 ‘Malignant tumour, ‘Malignancies excluding NMSC’).

Overall spesolimab treatment

There were 2 patients (1.9%) in the overall spesolimab group with malignancies: 1 patient had a malignant tumour (PT ‘Breast cancer’). The patient is described above (randomised treatment period). The other patient had a NMSC (PT ‘Basal cell carcinoma’, details are given above under SAF-ISS3p). The event was serious (other medically important serious event), of moderate intensity, and the patient recovered from the event (rmp-output-tlf-gpp-flare-prevention [c41549498], Tables A.2.5.4: 1, A.2.5.4: 2 ‘Malignant tumour, ‘Malignancies excluding NMSC’, ‘Malignant skin tumours’, ‘NMSC’).

Indication GPP flare treatment (DLP 08 Jan 2021, Spevigo EU-RMP v1.0)

Summary (indication GPP and other diseases)

Clinical data on malignancy is limited both by duration of the observational period and the number of patients. The occurrence of malignancies is rare and may only be diagnosed after years. In the open-label periods, no pattern regarding malignancies indicating a causal association with spesolimab treatment and underlying risk factors was observed in the patients concerned.

There were 2 patients with malignancies: 1 patient had a NMSC (PT 'Squamous cell carcinoma of skin') in trial 1368-0013, and 1 patient had a malignant tumour (PT 'Adenocarcinoma') in trial 1368-0025. This patient had rolled over from trial 1368-0013 and had a pre-treatment AE of enlarging pulmonary mass in trial 1368-0013.

In the supportive GPP and AtD trials (see Appendix 7), there were no patients with malignancies. In the UC trials, there was 1 patient with a malignant tumour (PT 'Adenocarcinoma of colon') in trial 1368-0010. In the PPP trials, there was 1 patient in the placebo group with a malignant tumour (PT 'Prostate cancer') in trial 1368-0016.

GPP trials in patients receiving spesolimab 900 mg i.v. or placebo i.v.

Trial 1368-0013

Up to week 1 and up to week 12

There were no patients with malignancies up to week 1 and up to week 12 (data on file, analyses for EU-RMP v1.0, 'malignant tumours', 'malignant skin tumours', 'skin melanomas', 'non-melanoma skin cancer', 'malignancies excluding NMSC' Tables A.2.1.1: 1 and A.2.1.2: 1).

By treatment period of spesolimab use (including REP of any randomised treatment or non-randomised spesolimab)/overall period post use

1 patient had a NMSC (PT 'Squamous cell carcinoma of skin'), following open-label spesolimab administration (i.e. after 2 doses of spesolimab). The event was serious (other medically important serious event), of severe intensity, and the patient recovered (data on file, analyses for EU-RMP v1.0, 'malignant tumours' Tables A.2.1.3: 1 and A.2.1.3: 2, pooled arms).

Trial 1368-0025 (entire treatment period)

1 patient had a malignant tumour (PT 'Adenocarcinoma') in the lung. The event was serious (requiring/prolonging hospitalisation), of mild intensity, and the patient recovered. This patient had rolled over from trial 1368-0013 and had a pre-treatment AE of enlarging pulmonary mass in trial 1368-0013 (data on file, analyses for EU-RMP v1.0, 'malignant tumours' Tables A.2.3.1: 1 and A.2.3.1: 2).

Trial 1368-0027 (open-label overall period)

There were no patients with malignancies (data on file, analyses for EU-RMP v1.0, 'malignant tumours' 'Table A.2.4.1: 1).

SVII.3.1.3.4 Risk factors and risk groups

Malignancies are a heterogeneous group with varied risk factors, which can include according to the tumour location, genetic susceptibility, alcohol consumption, smoking, obesity, increased age, race, family history, exposure to chemicals or UV (e.g. PUVA treatment for psoriasis) or other substances, chronic inflammation, immunosuppression, infectious agents, radiation.

SVII.3.1.3.5 Preventability

Regular screening per cancer prevention guidelines should be instituted to enable early intervention in case of cancer. The preventability is unknown.

SVII.3.1.3.6 Impact on the risk-benefit balance of the product

None of the reported malignancies were considered related to trial medication and there was no discernible pattern to suggest a causal relationship between spesolimab exposure and the development of the reported malignancies. All malignancies reported in patients taking spesolimab had underlying risk factors [n00265831-02].

Overall, malignancies are not expected to have a relevant impact on the overall risk-benefit assessment.

SVII.3.1.3.7 Public health impact

A potential impact on public health is not expected.

SVII.3.1.4 Important potential risk: Peripheral neuropathy

SVII.3.1.4.1 Potential mechanisms

There is no indication from the literature, that the inhibition of the IL-36 pathway is linked to an increased risk of treatment-emergent peripheral neuropathy. Zhao et al describe that significantly higher serum IL-36α and IL-36γ levels were measured in the acute phase (of GBS) than in the remission phase and in healthy control subjects ($p<0.05$), while lower serum IL-36Ra levels were measured in the acute phase than in the remission phase and in healthy control subjects ($p<0.05$). In addition, serum IL-36α and IL-36γ levels in GBS patients were positively correlated with serum IL-17 and TNF-α levels, while serum IL-36Ra levels were negatively correlated with the levels of these 2 inflammatory factors [R21-3672]. Spesolimab acts as an antagonist to the IL-36 receptor. BI is not aware of any other data that would suggest an association between peripheral neuropathy and spesolimab's mechanism of action.

SVII.3.1.4.2 Evidence source(s) and strength of evidence

In preclinical toxicity studies with the surrogate antibody BI 674304, no histopathological changes were noted in the nervous system [c03320877-09]

Cases of peripheral neuropathy were reported in clinical trials with spesolimab (investigator reporting). After full integrated assessment by an independent external expert panel of the 3 cases in ongoing clinical trials reported by the investigator as GBS, BI has concluded that there is no change to the benefit-risk-assessment for spesolimab. These cases showed a heterogenous clinical neurologic picture. Based on Brighton criteria [R21-3668, R21-3692], only 1 case met level 4 diagnostic certainty for the diagnosis of GBS (lowest level on Brighton scale of 1 to 4); the other 2 cases were also not assessed as GBS. In the case where lowest level of Brighton scale was met, the patient had an ongoing COVID-19 infection. Based on the available data, a causal association with spesolimab is not supported. The assessment was supported by an external expert panel.

No additional risk minimisation measures for the important potential risk 'peripheral neuropathy' are planned. A PASS (1368-0128) for which the protocol is endorsed by the PRAC is in preparation, to further investigate this important potential risk.

SVII.3.1.4.3 Characterisation of the risk

Search strategy
Cases of peripheral neuropathy were analysed using the following searches (indication GPP flare prevention: MedDRA version 25.1 [DLP 13 Jan 2023, Spevigo EU-RMP v2.0]; indication GPP flare treatment: MedDRA version 23.1 [DLP 08 Jan 2021, Spevigo EU-RMP v1.0]):

- Narrow SMQ 'Guillain-Barre syndrome'
- Narrow SMQ 'Demyelination'
- Narrow SMQ 'Peripheral neuropathy'

Indication GPP flare prevention (DLP 13 Jan 2023, Spevigo EU-RMP v2.0)
Summary
There were no patients with peripheral neuropathy in the pooled GPP trials (SAF-ISS3p). In trial 1368-0027, 1 patient in the placebo group had demyelination (PT 'Multiple sclerosis').

Refer to Appendix 7, Section 2.4 for summary of results other clinical trial data from other diseases.

SAF-ISS3p
There were no patients in either treatment group with peripheral neuropathy (rmp-output-tlf-gpp-flare-prevention [c41549498], Table A.2.1.1: 1 'Peripheral neuropathy ALL').

Trial 1368-0027
Randomised treatment period
1 patient in the placebo SC group had demyelination (PT 'Multiple sclerosis'). The event was serious (requiring/prolonging hospitalisation), of severe intensity, and the patient recovered from the event (rmp-output-tlf-gpp-flare-prevention [c41549498], Tables A.2.5.3: 1, A.2.5.3: 2 'Peripheral neuropathy ALL').

Overall spesolimab treatment
There were no patients in the overall spesolimab group with peripheral neuropathy (rmp-output-tlf-gpp-flare-prevention [c41549498], Table A.2.5.4: 1 'Peripheral neuropathy ALL').

Indication GPP flare treatment (DLP 08 Jan 2021, Spevigo EU-RMP v1.0)
Clinical trial data
3 cases reported by the investigator as GBS were received in ongoing clinical trials with spesolimab in different indications (UC, PPP, HS). The clinical course and symptoms of the reported cases were heterogenous and did not represent a common medical entity/diagnosis, and in all 3 cases confounding factors were present. Based on Brighton criteria (see below), 1 case met level 4 (i.e. reported event of GBS, with insufficient evidence to meet the case definition [R21-3668, R21-3674]); the other 2 cases did not meet the criteria. In 2 of the 3 cases, the investigator assessed that there was no causal relationship with spesolimab, and in one case, the investigator assessed it to be causally related. A summary of all 3 cases is provided below; additional details are provided in SVII.Table 11.

- Case 1 (reported in trial 1368-0017 in a patient with UC) was described as a tetraparesis in parallel to a SARS-CoV-2 pneumonia and evidence of cerebellar haemorrhage and resulted in a fatal outcome. The SARS-CoV-2 pneumonia and GBS occurred >9 months after start of the IMP and 20 days after the last administration of IMP. The patient was hospitalised and died 12 days later. The causes of death per death certificate were cerebellar haemorrhage, oedema and dislocation of the brain, and circulatory failure. This case was assessed by the investigator as not related to the IMP.
- Case 2 (reported in trial 1368-0024 in a patient with PPP) was described as an aggravation of pre-existing gait disturbances in a patient with a medical history including unsteady gait, chronic alcohol use, and steroid-induced diabetes. Approximately 7 months after start of the IMP, the patient was diagnosed by a neurologist to have "sensorimotor neuropathy" after self-reporting unsteady gait. A worsening of the unsteady gait led to hospitalisation and to the diagnosis of GBS >16 months after start of IMP. No pharmacologic treatment besides thiamine and folic acid was provided. Recovery was reported 3 weeks later despite continuation of IMP and without GBS-specific treatment. This case was assessed by the investigator as not related to IMP. Further, this case was determined by an independent external expert panel to be consistent with 'toxic neuropathy' from alcohol use.
- Case 3 (reported in trial 1368-0067 in a patient with HS) was described as paraesthesia and pain (for location and course see below) in an obese (BMI >40 kg/m^2) patient. The clinical course was subacute (>4 weeks from start of symptoms to the worst clinical presentation and therewith not consistent with GBS) with symptoms resolving without GBS-specific treatment and after discontinuation of the IMP and no need for hospitalisation.
  The patient initially reported joint pain (wrists) in September 2021, approximately 1 week after start of the IMP in the open-label extension trial and >3 months after start of treatment with spesolimab in the parent trial 1368-0052, which were interpreted by a rheumatologist as a possible carpal tunnel syndrome. In November 2021, the patient reported worsening of symptoms with persistence of joint

pain, paraesthesia, numbness in the fingers of both hands and feet, and observed muscle weakness, e.g. when climbing stairs or getting up from a squatting position. Trial medication was discontinued on 15 Nov 2021. The patient was referred to a neurologist whose neurological examination at the end of November 2021 was normal aside from absent reflexes in the lower limbs. The patient was prescribed gabapentin. In January 2022, an electroneuromyogram was performed which was described as non-length-dependent polyradiculoneuropathy, probably demyelinating and predominantly distal. At that point, physical examination was normal, and symptoms had mostly disappeared. This case was assessed by the investigator as related to study drug.
The patient received COVID-19 vaccination (Comirnaty) in May, June, and December 2021. The patient had an episode of cough from end of September to beginning of October 2021.

Assessment by an independent expert panel
A panel of independent neurologists and experts in the study of neuropathies assessed the 3 cases by applying the Brighton criteria [R21-3668, R21-3674, R21-3692], which have a scale of 1 to 4 for the levels of diagnostic certainty (category/level 1: highest level of diagnostic certainty, category/level 4: reported as GBS, possibly due to insufficient evidence for further classification/with insufficient evidence to meet case definition).

- 1 of the cases (case 1) met Brighton category 4 (i.e. a low diagnostic certainty, with insufficient evidence to meet the case definition). In that case, there was a coincident infection with SARS-CoV-2, and cerebellar haemorrhage.
- The other 2 cases (case 2 and case 3) were assessed as not GBS.

All 3 observed cases showed a heterogenous pattern. A causal association with spesolimab for any of the reported cases was assessed to be unlikely.

A certain diagnosis of GBS could not be verified in any of these cases. The clinical course of GBS, which has an acute onset with patients typically reaching maximum disability within 2 weeks but not longer than 4 weeks, was not in line with the described clinical course in 2 of the cases (case 2 and case 3). The non-specific symptoms and findings in case 3 may best be referred to as peripheral neuropathy.

SVII.Table 11 Case details and classification of cases reported as GBS

Trial (indication)/ Age range/sex	**Time to onset since first spesolimab[1]**	**Brighton criteria [R21-3668, R21-3674] details**	**Outcome/ Seriousness/ Relatedness as per investigator**	**Relevant confounders**	**Action taken with IMP/ treatment of AEs (if applicable)**
1368-0017 (UC)/ <60 years/M	287 days (>9 months)	Category: 4 (insufficient evidence to meet the case definition) Time from onset to worst clinical presentation: ~2 weeks	Fatal/ Serious/ Unrelated	Acute COVID-19 infection, cerebellar haemorrhage	IMP: not applicable
1368-0024 (PPP)/ <60 years/F	498 days (>16 months)	Not a case of GBS Time from onset to worst clinical presentation: Several months to >1 year	Recovered/ Serious/ Unrelated	Pre-existing neurologic symptoms, steroid-induced diabetes, chronic alcohol use	IMP: continued/ Treatment: ergotherapy, physiotherapy, thiamine (for daily alcohol consumption and elevated liver markers) and folic acid (for low folic acid levels)
1368-0067 (HS)/ <60 years/F	99 days (>3 months)	Not a case of GBS Time from onset to worst clinical presentation: ~2 months	Ongoing (improved)/ Serious/ Related	Obesity with a BMI of >40 kg/m^2	IMP: discontinued/ Treatment: gabapentin

[1] In the respective parent trial (i.e. 1368-0005 in UC, 1368-0016 in PPP, 1368-0052 in HS)

Data source: COS [c38587917-01], Table 1

No additional cases of GBS, demyelination, or peripheral neuropathy were identified in patients treated with spesolimab in any of the other clinical trials in the development programme with spesolimab.

More specifically, results from search strategies using the MedDRA SMQs ‘GBS (narrow)’ and ‘Demyelination (narrow)’ did not identify any additional cases. When using the MedDRA SMQ ‘Peripheral neuropathy (narrow)’, no additional patient treated with spesolimab and 1 patient from the placebo group of trial 1368-0016 was identified. This patient was reported with peripheral sensory neuropathy starting on day 83 after first placebo administration; the AE reached RCTC grade 2, and the patient did not recover until DLP. The patient complained about numbness, which triggered an MRI of head, neck and waist; however, no clinical findings were noted by the neurologist and the investigator, and the reason for the numbness could not be identified (COS [c38587917-01], Section 5.2.1).

Preclinical data
In preclinical toxicity studies with the surrogate antibody BI 674304, no histopathological changes were noted in the nervous system [c03320877-09].

Literature
There is no indication from the literature, that the inhibition of the IL-36 pathway is linked to an increased risk of treatment-emergent peripheral neuropathy.

The literature does not indicate an increased risk of GBS during the inhibition of the IL-36 pathway. Zhao et al. [R21-3672] describe that IL-36α and IL-36γ may aggravate inflammatory injuries in GBS patients by promoting the secretion of IL-17 and TNF-α. Simultaneously, IL-17 and TNF-α may also interact to induce the expression of IL-36α and IL-36γ in GBS. Conversely, serum IL-36Ra levels were decreased in patients with GBS during the acute phase, and the serum levels of IL-36Ra were negatively correlated with the serum levels of IL-17 and TNF-α.

Discussion
In-depth review and assessment of the 3 cases reported as GBS by a panel of external neurologists and experts in the study of neuropathies assessed 1 of the 3 cases to have the lowest diagnostic certainty of GBS on the Brighton scale (category/level 4) and the other 2 cases were assessed as "not GBS". All 3 cases showed a heterogenous clinical neurologic picture, and in all 3 cases confounding factors were present. A certain diagnosis of GBS could not be verified in any of these cases. The non-specific symptoms and findings in all 3 cases may best be described as peripheral neuropathy. Data from preclinical trials and from the published literature do not suggest a potential risk of peripheral neuropathy for spesolimab.

SVII.3.1.4.4 Risk factors and risk groups

Risk groups or risk factors are unknown.

SVII.3.1.4.5 Preventability

The preventability is unknown.

SVII.3.1.4.6 Impact on the risk-benefit balance of the product

A causal association with spesolimab to any of the reported cases of GBS was assessed to be unlikely. Overall, peripheral neuropathy is not expected to have a relevant impact on the risk-benefit balance of the product.

SVII.3.1.4.7 Public health impact

A potential impact on public health is not expected.

SVII.3.2 Presentation of the missing information

SVII.3.2.1 Missing information: Pregnant or breast-feeding women

SVII.3.2.1.1 Evidence source

The potential toxicity of IL-36R antagonism has been assessed in mice using a mouse-specific anti-IL-36R monoclonal antibody (BI 674304) which has been demonstrated to elicit pharmacological responses similar to spesolimab *in vitro* and to reduce DSS induced colitis in mice. BI 674304 has been tested in embryo-foetal and fertility and early embryonic development studies. There was no evidence of effects on fertility or embryonic development (teratogenicity) in mice after administration of 10 or 50 mg/kg/dose of BI 674304.

Spesolimab has not been investigated in pregnant or lactating women. Limited experience is available from clinical trial data.

SVII.3.2.1.2 Anticipated risk/consequence of the missing information

There are limited data from the use of spesolimab in pregnant women. Pre-clinical studies using a surrogate, mouse specific anti-IL-36R monoclonal antibody do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is recommended to avoid the use of spesolimab in pregnancy.

SVII.3.2.2 Missing information: Use in patients with body weight <40 kg

SVII.3.2.2.1 Evidence source

Patients with a body weight of <40 kg were excluded from trial 1368-0027, as a higher exposure was anticipated in these patients with the proposed spesolimab doses. Since the protocol development of trial 1368-0027, more clinical trial data have been collected, suggesting a wide therapeutic window of spesolimab and absence of dose-dependency for safety:

- In trial 1368-0027 (weight range 42-160 kg), there is no dose/exposure dependent occurrence of AEs (with the exception of injection site reactions, where a slight trend of dose dependency is seen). The probability of infection did not increase with higher spesolimab concentrations (SCS [c39066527-01], Modeling and Simulation Report [c41839684-01]).
- Spesolimab was safe and well tolerated at higher doses/regimens compared with the proposed dosing regimen for GPP flare prevention (SCS [c39066527-01]). Exposures (in terms of C_{max}) achieved in trial 1368-0027 following s.c. treatment are expected to be several times lower than exposures achieved in trials in other populations (PPP, UC, AtD, HS) with a comparable and consistent safety profile.

Therefore, somewhat higher exposures in patients of lower body weight are not expected to pose any safety issue. It is expected that the safety profile in patients with body weight <40 kg is not different from the known safety profile in patients with higher body weight. Hence, no potential risk is foreseen. The same is expected for adolescents, based on similarity

in disease pathophysiology, similarity in spesolimab exposures as demonstrated by the PopPK model, and safety data from trial 1368-0027. Nevertheless, EMA requested during procedure EMEA/H/C/005874/X/0006/G a reduced dosing regimen for adolescents weighing ≥30 and <40 kg, i.e. for s.c. administration 300 mg loading dose followed by 150 mg every 4 weeks, and for i.v. infusion 450 mg.
Adolescents, like adults, have a mature immune system and have accumulated a history of antigen exposures. Thus, they are not at higher risk of infections compared to adults due to immunomodulation. Spevigo has not been studied in patients weighing less than 40 kg.

However, with a lack of clinical data in patients with body weight <40 kg, and while expecting use in this population (e.g. in adolescents), the safety profile of spesolimab in this population cannot be fully described and is considered missing information for the time being. To enable systematic collection of further data on use of Spevigo in adolescents, PASS 1368-0128 is amended to include adolescent patients treated with spesolimab i.v. for GPP flare and adult and adolescent patients treated with spesolimab s.c. for prevention of GPP flare in line with the claimed indications, provided the approval is granted. If a sufficient number of patients with body weight <40 kg is available across the data sources used in the PASS 1368-0128, analyses stratified by body weight categories will be presented in the final report.

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ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
AtD	Atopic dermatitis
BI	Boehringer Ingelheim
BIcMQ	Boehringer Ingelheim customised MedDRA query
BMI	Body mass index
CD	Crohn's disease
CD4	Cluster of differentiation 4
CFU	Colony forming unit
C_{max}	Maximum concentration

COS	Clinical overview statement
COVID-19	Coronavirus disease 2019
CSF	Cerebrospinal fluid
CT	Computed tomography
CTR	Clinical Trial Report
DRESS	Drug reaction with eosinophilia and systemic symptoms
DSS	Dextran sulphate sodium
EoS	End of study
EU	European Union
F	Female
GBS	Guillain-Barré syndrome
GPP	Generalized pustular psoriasis
HIV	Human immunodeficiency virus
HLT	High level term
HS	Hidradenitis suppurativa
i.v.	Intravenous
IgG	Immunoglobulin G
IL	Interleukin
IL-36 (R)	Interleukin 36 (receptor)
IMP	Investigational medicinal product
IRA	Immunogenicity risk assessment
ISS	Integrated Summary of Safety
KO	Knock out
M	Male
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NMSC	Non-melanoma skin cancer
PASS	Post-authorisation safety study
PopPK	Population Pharmacokinetics
PPP	Palmoplantar pustulosis
PRAC	Pharmacovigilance Risk Assessment Committee

PT	Preferred term
PUVA	Combination treatment of psoralen and UVA (long wave UV radiation)
RCTC	Rheumatology Common Toxicity Criteria
RegiSCAR	Study acronym; Multinational Registry of Severe Cutaneous Adverse Reactions (SCAR)
REP	Residual effect period
RMP	Risk Management Plan
s.c./SC	Subcutaneous
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCC	Squamous cell carcinoma
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristic
SMQ	Standardised MedDRA query
SOC	System organ class
TNF	Tumour necrosis factor
UC	Ulcerative colitis
UTI	Urinary tract infection
UV	Ultraviolet

MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

SVIII.Table 1 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

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

PART III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for:

- DRESS (included under 'Systemic hypersensitivity reaction')
- Serious or opportunistic infections
- Malignancy

Other forms of routine pharmacovigilance activities:
None.

PART III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Part III.2.1 PASS 1368-0128 summary

Study short name and title
1368-0128 - Spesolimab Post-Authorisation Safety Study (PASS) for Use in Patients with Generalised Pustular Psoriasis (GPP)

Rationale and study objectives
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; as applicable dependent on the approved age range) 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.

Study design
5-year observational cohort study

Study population
Adult and adolescent patients diagnosed with GPP who initiate spesolimab, biologics, or systemic immunomodulatory and anti-inflammatory agents (non-biologics) for use in GPP

Milestones
Final report, 31 Dec 2031

PART III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

PIII.Table 1 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
PASS 1368-0128 Spesolimab Post-Authorisation Safety Study (PASS) for Use in Patients with Generalised Pustular Psoriasis (GPP) Planned	The primary objective is to estimate incidence rates of safety events of interest (serious or opportunistic infections, systemic hypersensitivity reaction, peripheral neuropathy and malignancies) among adult and adolescent (aged ≥12 years) patients initiating spesolimab for treatment of GPP and, if feasible, compare to relevant, contemporaneous cohorts of patients initiating other treatments for GPP (biologics or systemic immunomodulatory and anti-inflammatory agents (non-biologics)) in the routine clinical care setting.	Serious or opportunistic infections, systemic hypersensitivity reaction, peripheral neuropathy, malignancies	Final report	31 Dec 2031

PART III.4 REFERENCES

Not applicable.

ABBREVIATIONS

CHMP	Committee for Medicinal Products for Human Use
DRESS	Drug reaction with eosinophilia and systemic symptoms
GPP	Generalized pustular psoriasis
MAH	Marketing authorisation holder
PASS	Post-authorisation safety study

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

PIV.Table 1 Planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are Specific Obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due date
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Trial 1368-0120 An open-label, multicenter, single-arm, post-marketing trial to evaluate efficacy and safety and the impact of immunogenicity on efficacy, safety, and pharmacokinetics of spesolimab i.v. in treatment of patients with Generalized Pustular Psoriasis presenting with a recurrent flare following their initial GPP flare treatment with spesolimab i.v. Ongoing	To evaluate efficacy and safety and the impact of immunogenicity on efficacy, safety, and pharmacokinetics of spesolimab i.v. in treatment of patients with GPP presenting with a recurrent flare following their initial GPP flare treatment with spesolimab i.v.	Long-term efficacy and safety	Final report	31 Jan 2028

PART IV.2 REFERENCES

Not applicable.

ABBREVIATIONS

GPP	Generalized pustular psoriasis
i.v.	Intravenous

PART V RISK MINIMISATION MEASURES

RISK MINIMISATION PLAN

PART V.1 ROUTINE RISK MINIMISATION MEASURES

PV.Table 1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
Systemic hypersensitivity reaction	*Routine risk communication* EU-SmPC sections 4.3, 4.4, 4.8; PL sections 2, 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Spesolimab is available as a prescription-only medicine. <u>GPP flare prevention</u> 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. <u>GPP flare treatment</u> Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases

PV.Table 1 (cont'd) Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important potential risks	
Serious or opportunistic infections	*Routine risk communication* EU-SmPC sections 4.3, 4.4; PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Spesolimab is available as a prescription-only medicine. 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.
Malignancy	*Routine risk communication* None *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Spesolimab is available as a prescription-only medicine. 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.

PV.Table 1 (cont'd) Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important potential risks (cont'd)	
Peripheral neuropathy	*Routine risk communication* EU-SmPC section 4.4, PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Spesolimab is available as a prescription-only medicine. 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.
Missing information	
Pregnant or breast-feeding women	*Routine risk communication* EU-SmPC section 4.6; PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Spesolimab is available as a prescription-only medicine. 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.

PV.Table 1 (cont'd) Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Missing information (cont'd)	
Use in patients with body weight <40 kg	*Routine risk communication* EU-SmPC section 4.2, PL section 3 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Spesolimab is available as a prescription-only medicine. Spevigo has not been studied in patients weighing less than 40 kg. A reduced dosing regimen is recommended 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.

PART V.2 ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

PART V.3 SUMMARY OF RISK MINIMISATION MEASURES

PV.Table 2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

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 <u>GPP flare prevention</u> 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. <u>GPP flare treatment</u> 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)

PV.Table 2 (cont'd) Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risks		
Serious or opportunistic infections	*Routine risk minimisation measures* EU-SmPC section 4.3, 4.4 PL section 2 Prescription only medicine GPP flare prevention In case a loading dose is needed, this should be administered by a healthcare professional. For subsequent doses, if the healthcare professional determines that it is appropriate, patients may self-inject or caregivers may administer the Spevigo pre-filled syringe after proper training in subcutaneous injection technique. GPP flare treatment Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form None *Additional pharmacovigilance activities* PASS 1368-0128 (final report 31 Dec 2031)

PV.Table 2 (cont'd) Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risks (cont'd)		
Malignancy	*Routine risk minimisation measures* None Prescription only medicine GPP flare prevention In case a loading dose is needed, this should be administered by a healthcare professional. For subsequent doses, if the healthcare professional determines that it is appropriate, patients may self-inject or caregivers may administer the Spevigo pre-filled syringe after proper training in subcutaneous injection technique. GPP flare treatment Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form *Additional pharmacovigilance activities* PASS 1368-0128 (final report 31 Dec 2031)

PV.Table 2 (cont'd) Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risks (cont'd)		
Peripheral neuropathy	*Routine risk minimisation measures* EU-SmPC section 4.4 PL section 2 Prescription only medicine <u>GPP flare prevention</u> 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. <u>GPP flare treatment</u> 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)

PV.Table 2 (cont'd) Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information		
Pregnant or breast-feeding women	*Routine risk minimisation measures* EU-SmPC section 4.6 PL section 2 Prescription only medicine GPP flare prevention In case a loading dose is needed, this should be administered by a healthcare professional. For subsequent doses, if the healthcare professional determines that it is appropriate, patients may self-inject or caregivers may administer the Spevigo pre-filled syringe after proper training in subcutaneous injection technique. GPP flare treatment Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* None *Additional pharmacovigilance activities* None

PV.Table 2 (cont'd) Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information (cont'd)		
Use in patients with body weight <40 kg	*Routine risk minimisation measures* EU-SmPC section 4.2 PL section 3 Prescription only medicine Reduced dosing regimen for adolescents weighing ≥30 and <40 kg <u>GPP flare prevention</u> 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. <u>GPP flare treatment</u> 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)

PART V.4 REFERENCES

Not applicable.

ABBREVIATIONS

AE	Adverse event
DRESS	Drug reaction with eosinophilia and systemic symptoms
EU	European Union
GPP	Generalized pustular psoriasis
PASS	Post-authorisation safety study
PK	Pharmacokinetic
PL	Package leaflet
SmPC	Summary of Product Characteristics

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR SPEVIGO (SPESOLIMAB)

This is a summary of the risk management plan (RMP) for Spevigo. The RMP details important risks of Spevigo, and how more information will be obtained about Spevigo's risks and uncertainties (missing information).

Spevigo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Spevigo should be used.

This summary of the RMP for Spevigo should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Spevigo's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Spevigo is authorised as monotherapy for treatment of flares in adults and adolescents from 12 years of ages with generalized pustular psoriasis (see SmPC for the full indication). It contains spesolimab as the active substance and it is given by i.v. infusion (concentrate for solution for infusion, 450 mg). In addition, it is authorised for prevention of flares in adult and adolescents from 12 years of age with generalized pustular psoriasis (see SmPC for the full indication). It contains spesolimab as the active substance and it is given by s.c. injection (concentrate for solution for injection, 150 mg and 300 mg).

Further information about the evaluation of Spevigo's benefits can be found in Spevigo's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Spevigo, together with measures to minimise such risks and the proposed studies for learning more about Spevigo's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.
If important information that may affect the safe use of Spevigo is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Spevigo are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Spevigo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information

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

II.B Summary of important risks

Important identified risks

Systemic hypersensitivity reaction	
Evidence for linking the risk to the medicine	General risk from proteins to cause hypersensitivity reactions. As the antibody is humanised, the risk for hypersensitivity reactions (including DRESS) in patients treated with spesolimab is considered low. In many cases of hypersensitivity events observed in clinical trials, alternative risk factors were present; however, contribution of spesolimab to these events cannot be fully excluded. Post-approval, clinical trial and post-marketing cases triggered a signal assessment report. The signal was confirmed, and systemic hypersensitivity (specified as hypersensitivity comprising immediate systemic hypersensitivity reactions, including anaphylactic reaction) is considered an ADR.
Risk factors and risk groups	Risk groups or risk factors are unknown. Potential intrinsic risk for spesolimab to induce a T-cell humoral immune response.
Risk minimisation measures	Routine risk minimisation measures: EU-SmPC sections 4.3, 4.4, 4.8 PL sections 2, 4 Prescription only medicine <u>GPP flare prevention</u> 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. <u>GPP flare treatment</u> Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS 1368-0128 See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risks

Serious or opportunistic infections	
Evidence for linking the risk to the medicine	No increased occurrence observed in clinical trials with spesolimab.
Risk factors and risk groups	Increased age, impaired immune function, comorbidities, and duration of exposure to and number of concomitant immunosuppressive therapies.
Risk minimisation measures	Routine risk minimisation measures: EU-SmPC sections 4.3, 4.4 PL section 2 Prescription only medicine <u>GPP flare prevention</u> 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. <u>GPP flare treatment</u> Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS 1368-0128 See section II.C of this summary for an overview of the post-authorisation development plan.

Malignancy	
Evidence for linking the risk to the medicine	Clinical data on malignancy associated with IL-36R inhibition is limited by duration and number of treated individuals. In related mechanisms, meta-analyses of cancer incidence among patients with immune suppression therapy (e.g. TNFs, methotrexate) did not yield clear correlation between tumour incidence and therapies not intended to completely ablate immune function.
Risk factors and risk groups	Tumour location, genetic susceptibility, alcohol consumption, smoking, obesity, increased age, race, family history, exposure to chemicals or UV (e.g. PUVA treatment for psoriasis) or other substances, chronic inflammation, immunosuppression, infectious agents, radiation
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine <u>GPP flare prevention</u> 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. <u>GPP flare treatment</u> Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS 1368-0128 See section II.C of this summary for an overview of the post-authorisation development plan.

Peripheral neuropathy	
Evidence for linking the risk to the medicine	In preclinical toxicity studies with a surrogate antibody, no histopathological changes were noted in the nervous system. Cases of peripheral neuropathy reported in clinical trials were not assessed as related to spesolimab.
Risk factors and risk groups	Risk factors and risk groups are unknown.
Risk minimisation measures	Routine risk minimisation measures: EU-SmPC section 4.4 PL section 2 Prescription only medicine <u>GPP flare prevention</u> 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. <u>GPP flare treatment</u> Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS 1368-0128 See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information

Pregnant or breast-feeding women	
Risk minimisation measures	Routine risk minimisation measures: EU-SmPC section 4.6 PL section 2 Prescription only medicine <u>GPP flare prevention</u> 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. <u>GPP flare treatment</u> Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases Additional risk minimisation measures: None
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 <u>GPP flare prevention</u> 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. <u>GPP flare treatment</u> Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases Additional risk minimisation measures: PASS 1368-0128 See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

SOB 1368-0120
Purpose of the study: To evaluate efficacy and safety and the impact of immunogenicity on efficacy, safety, and pharmacokinetics of spesolimab i.v. in treatment of patients with GPP presenting with a recurrent flare following their initial GPP flare treatment with spesolimab i.v.

II.C.2 Other studies in post-authorisation development plan

PASS 1368-0128
Purpose of the study: Spesolimab Post-Authorisation Safety Study (PASS) for Use in Patients with Generalised Pustular Psoriasis (GPP)

ABBREVIATIONS

DRESS	Drug reaction with eosinophilia and systemic symptoms
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GPP	Generalized pustular psoriasis
i.v.	Intravenous
IL-36 (R)	Interleukin 36 (receptor)
MAH	Marketing authorisation holder
PASS	Post-authorisation safety study
PL	Package Leaflet
PUVA	Combination treatment of psoralen and UVA (long wave UV radiation)
RMP	Risk Management Plan
s.c.	Subcutaneous
SmPC	Summary of Product Characteristics
SOB	Specific Obligation
TNF	Tumour necrosis factor
UV	Ultraviolet

PART VII APPENDICES

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APPENDIX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Appendix - Table of Contents

Questionnaire: DRESS Event Form - Draft Version 7.0

Question ID	BI Questionnaire owner / TA	Questionnaire Name	Question
Q:DRESS01	Inflammation	DRESS event form	Maculopapular skin eruption developing two or more weeks after spesolimab initiation [Yes/No]
Q:DRESS02	Inflammation	DRESS event form	Please provide details of any concomitant medication started within last 4 weeks
Q:DRESS03	Inflammation	DRESS event form	Did the patient present with new onset widespread rash (>50% Body Surface Area [BSA]):

Questionnaire: DRESS Event Form - Draft Version 7.0

Q:DRESS04	Inflammation	DRESS event form	Did the patient present with any of the following skin specific signs or symptoms? [Yes/No]. Please provide details if yes. - New onset rash suggesting DRESS (Purpuric lesions other than legs, infiltration, facial oedema, desquamation):
Q:DRESS05	Inflammation	DRESS event form	Did the patient present with any of the following general signs or symptoms? [Yes/No] Please provide details if yes: -New onset enlarged lymph nodes (please specify if more than 2 sites) -Acute fever (≥38 °C)
Q:DRESS06	Inflammation	DRESS event form	Please provide a description of lesion(s) on the skin, please specify: -Type: erythematous macules, papules, plaques, eczema, vesicled, blisters, etc. - Topography: sun exposed areas only, trunk and upper extremities, face, etc. - Start and stop date(s) of skin lesion(s)
Q:DRESS07	Inflammation	DRESS event form	Is there any photo documentation available? [Yes/No] If yes, please provide/attach

Questionnaire: DRESS Event Form - Draft Version 7.0

Q:DRESS08	Inflammation	DRESS event form	Was there any documented Liver involvement during the same period as the skin erruption? [Yes/No]. If yes, please provide relevant lab results, e.g.: - Abnormal liver function tests - AST, ALT - bilirubin - gamma-glutamyl transferase - alkaline phosphatase (2-fold elevated on 2 different days)
Q:DRESS09	Inflammation	DRESS event form	Was there any other organ involvement during the same period as the skin erruption? [Yes/No]. Please provide details if yes: -Kidney -Lung -Muscle -Heart -Pancreas -Any other organ
Q:DRESS10	Inflammation	DRESS event form	Were any of the following diagnostic tests performed? [Yes/No]. Please provide details including date; results, reference ranges: -Eosinophilia (≥10% or, ≥0.7 x 10*9 L*-1) -Atypical lymphocytes -Antinuclear antibody (ANA) -Blood culture -Serology for HAV/HBV/HCV -Quantitative PCR for HHV-6, EBV, and CMV -Test for Chlamydia/Mycoplasma
Q:DRESS11	Inflammation	DRESS event form	Were any of the following diagnostic skin tests performed? [Yes/No]. Please provide details including date; results: - Direct immunofluorescence results of skin biopsy - Histology of skin lesion biopsy (example: mild spongiosis, infiltrate of atypical lymphocytes, increased eosinophils, dermal edema etc.)

Questionnaire: Serious or Opportunistic Event Form - Draft Version 10.0

Q:SOI01	Inflammation	Serious or Opportunistic infection Form	Questionnaire	What was/were the affected organ/organs?
Q:SOI02	Inflammation	Serious or Opportunistic infection Form	Questionnaire	What diagnostic tests were performed to characterize the event? Please provide the results
Q:SOI03	Inflammation	Serious or Opportunistic infection Form	Questionnaire	Was a causative organism identified? If so, what is it? How/by which test was it identified?
Q:SOI04	Inflammation	Serious or Opportunistic infection Form	Questionnaire	How was the infection treated? Please provide substance, dose, dosing schedule, date of treatment initiation, date of treatment completion.
Q:SOI05	Inflammation	Serious or Opportunistic infection Form	Questionnaire	Was surgery required? If so, what kind and what was the outcome?
Q:SOI06	Inflammation	Serious or Opportunistic infection Form	Questionnaire	Does the patient have a history of similar infections? Please provide specifics.
Q:SOI07	Inflammation	Serious or Opportunistic infection Form	Questionnaire	What risk factors for the reported infection were present, if any? - Does the patient have a history of immune suppressive medication? If so, what specifically? - Does the patient have susceptibility to opportunistic infection (HIV, organ transplant, immune deficiency, other)? - Any others?
Q:SOI08	Inflammation	Serious or Opportunistic infection Form	Questionnaire	Were any preventive measures in place (vaccination, previous infection, current antibiotic/antiviral/antifungal/antiparasitic treatment)?

Questionnaire: Serious or Opportunistic Event Form - Draft Version 10.0

Q:SOI_Add01	Inflammation	Serious or Opportunistic infection Form - Sepsis	Questionnaire	Please answer the following questions based on Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-Related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive CareMed. 1996;22(7):707-710)
Q:SOI_Add02	Inflammation	Serious or Opportunistic infection Form - Sepsis	Questionnaire	What was the patient's initial SOFA score?
Q:SOI_Add03	Inflammation	Serious or Opportunistic infection Form - Sepsis	Questionnaire	What was the patient's peak SOFA score? By what criteria? -What was the patient's nadir PaO2/FIO2 ratio? -What was the patient's nadir platelet count? -What was the patient's nadir MAP? -What was the patient's nadir GCS score?
Q:SOI_Add04	Inflammation	Serious or Opportunistic infection Form - Sepsis	Questionnaire	Please provide the following lab results based on peak SOFA score: -What was the patient's peak total bilirubin? -What was the patient's peak serum creatinine? -What was the patient's peak serum lactate?
Q:SOI_Add05	Inflammation	Serious or Opportunistic infection Form - Sepsis	Questionnaire	Did the patient have septic shock?
Q:SOI_Add06	Inflammation	Serious or Opportunistic infection Form - Sepsis	Questionnaire	Did the patient require intensive care treatment?
Q:SOI_Add07	Inflammation	Serious or Opportunistic infection Form - Sepsis	Questionnaire	Did the patient require vasopressors? If so, which ones and what dose(s)?
Q:SOI_Add08	Inflammation	Serious or Opportunistic infection Form - Sepsis	Questionnaire	Did the patient require invasive monitoring modalities? If so, which one(s)?
Q:SOI_Add09	Inflammation	Serious or Opportunistic infection Form - Sepsis	Questionnaire	Did the patient require respiratory support? If so, which modality(ies)?
Q:SOI_Add10	Inflammation	Serious or Opportunistic infection Form - Sepsis	Questionnaire	Did the patient require emergent dialysis/hemofiltration?

Malignancy questionnaire- Version 5.1

Question ID	Questionnaire Name	Question
Q:M01	Malignancy Questionnaire	Diagnosis of the Malignancy /Neoplasm Event
Q:M02	Malignancy Questionnaire	Date (dd/mm/yyyy) of diagnosis of the Malignancy /Neoplasm Event
Q:M03	Malignancy Questionnaire	Cytology or Biopsy (site(s) and results including histological typing of tumor and immunophenotyping if appropriate. Please provide copy of pathology report, lymph node biopsy or an English summary as well as gene rearrangement studies if performed)

Malignancy questionnaire- Version 5.1

Q:M04	Malignancy Questionnaire	Date (dd/mm/yyyy) of Cytology or Biopsy
Q:M05	Malignancy Questionnaire	Staging of the Neoplasm [T; N; M]

Malignancy questionnaire- Version 5.1

Q:M06	Malignancy Questionnaire	Were any of the following tests performed? [Yes; No; Date; Result] - Genetic analysis for known mutations associated with malignancy - Bone marrow aspiration - Complete Blood Count - Biomarkers (e.g. PSA, AFP, CA19.9, HER-2, etc.) - Imaging tests (e.g. X-ray, CT scan, MRI, PET Scan, Mammogram) - Postoperative pathology results
Q:M07	Malignancy Questionnaire	Does the patient has a history of any of the following prior to the start of the suspect drug? [Yes; No; Provide details as applicable] - Exposure to Ionizing Radiation - UV exposure, PUVA/UVB - Family History of Malignancy - Personal History of Malignancy - History of Radioiodine Exposure - Immunosuppressive Condition (incl. therapeutic) - Smoking or Tobacco Chewing - Alcohol Abuse

Malignancy questionnaire- Version 5.1

Q:M08	Malignancy Questionnaire	Does the patient has a history of any of the following prior to the start of the suspect drug? [Yes; No; Provide details as applicable] - Previous Chest X-Ray - Previous Colonoscopy - Previous Mammogram - Previous PSA
Q:M09	Malignancy Questionnaire	Did the patient has a history of any of the following prior to the start of the suspect drug? [Yes; No; Provide details as applicable] - Infection (e.g., HIV, HCV, HPV) - Type 3c Diabetes Mellitus - History of Treatment with Pancreatic Enzymes

Malignancy questionnaire- Version 5.1

Q:M010	Malignancy Questionnaire	Any further information?

APPENDIX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

There are no proposed additional risk minimisation activities for spesolimab.