Boehringer Ingelheim

EU Risk Management Plan for Spevigo (spesolimab)

Doc. No.: s00088360-05

RMP version to be assessed as part of this application:	
RMP version number:	1.0
Data lock point for this RMP:	08 Jan 2021
Date of final sign off:	06 Oct 2022
Rationale for submitting an updated RMP:	Initial application for the treatment of flares in adult patients with generalized pustular psoriasis; EMA request (EMEA/H/C/005874/0000)
Summary of significant changes in this RMP:	*Post-authorisation efficacy plan* Addition of SOB 1368-0120 *Other* Addition of PASS number (Module SVII; Parts III, IV, V, VI; Appendices 2, 3c, 5, 8)
Other RMP versions under evaluation:	Not applicable
RMP version number:	--
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Date of approval (opinion date):	--
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

Indication in the EEA	*Current* Monotherapy for treatment of flares in adult patients with generalized pustular psoriasis (GPP)
	Proposed Not applicable
Dosage in the EEA	*Current* 900 mg, single dose for i.v. infusion
	Proposed Not applicable
Pharmaceutical forms and strength	*Current* Concentrate for solution for infusion, 450 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
i.v.	Intravenous
IgG1	Immunoglobulin G1
IL-36R	Interleukin 36 receptor
INN	International non-proprietary name
RMP	Risk Management Plan

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 no 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.

SI.1.2 Prevalence

Estimates of the prevalence of GPP are sparse in the literature because of the rarity of the disease. 6 publications [R16-2698, R18-1635, R20-1502, R21-3418, R21-3492, R22-0363] 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 4.6 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 to diagnose condition 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, and Sweden [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 and the prevalence was determined to be in the range of 1 per 100 000 to 10 per 100 000 persons [R21-3492].

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 as well as the estimates calculated from work done internally show GPP as a rare condition with a prevalence range of approximately 2 per 1 000 000 to 46 per 100 000 persons and is summarised in the table below.

SI.Table 1 Prevalence of GPP

Author	Country	Study years	Population source	GPP case definition	GPP prevalence
Augey 2006 [R16-2698]	France	2004	Survey of 121 dermatology clinics	Clinical diagnosis by dermatologist based on non-standardised criteria	1.76 per 1 000 000 persons
Schafer [R18-1635]	Germany	2005	National health insurance claims database	At least 1 ICD-10 code L40.1	46 per 100 000 persons
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 (crude general population prevalence) 2.7% of all psoriasis
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
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
Löfvendahl 2022 [R22-0363]	Sweden	2015	NPR	Physician visit with the primary or secondary diagnosis code L40.1	9 per 100 000 persons
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
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

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

Author	Country	Study years	Population source	GPP case definition	GPP prevalence
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
Feng 2021 [R21-3492]	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	1.4 per 100 000 persons
Proportion of GPP among individuals with psoriasis					
Dubertret [R17-3266]	Belgium, Czech Republic, Finland, France, Germany, Italy, the Netherlands	2002	Survey of EUROPSO members	Self-reported diagnosis	4% of the psoriasis population
Perez-Plaza [R21-0067]	Spain	2015	BIOBADADERM	Information collected from the patient case report form at enrolment into the registry	1% of the BIOBADADERM population
Iskandar [R21-0068]	UK/Ireland	2014	BADBIR	Information collected from the patient case report form at enrolment into the registry	1% of the BADBIR population
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%
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%
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%

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 58% to 67%) [R16-0933, R21-2844]. 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. To date, there are no approved therapies indicated for treatment of GPP flares, despite the morbidity and mortality associated with GPP flares. 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" (data on file).

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%.

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]

SI.2 REFERENCES

SI.2.1 Published references

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R21-2243 Sobell JM, Gao R, Golembesky AK, Kotowsky N, Garry EM, Comerford EO, et al. Healthcare resource utilization and baseline characteristics of patients with generalized pustular psoriasis: real-world results from a large US database of multiple commercial medical insurers. Journal of Psoriasis and Psoriatic Arthritis, published online: 9 June 2021, doi: 10.1177/24755303211021779; 2021

R21-2244 Crowley J, Golembesky AK, Kotowsky N, Gao R, Bohn RL, Garry EM, et al. Clinical characteristics and healthcare resource utilization in patients with generalized pustular psoriasis: real-world evidence from a large claims-based dataset. Journal of Psoriasis and Psoriatic Arthritis, published online: 10 June 2021, doi: 10.1177/24755303211021786; 2021

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R21-2844 Ohkawara A, Yasuda H, Kobayashi H, Inaba Y, Ogawa H, Hashimoto I, et al. Generalized pustular psoriasis in Japan: two distinct groups formed by differences in symptoms and genetic background. Acta Derm Venereol 1996; 76; 68-71

R21-3418 Feldman SR, Kotowsky N, Gao R, Brodovicz KG, Leonardi C, Menter A. Prevalence of generalized pustular psoriasis in the USA: results from multiple administrative claims databases. 2021

R21-3492 Feng J, Guo J, Zhang Q, et al. Epidemiology and disease burden of GPP in urban China from 2012 to 2016 and a systematic review. Abstract No. 974 at the EADV 30th congress 2021

R22-0363 Lofvendahl S, Norlin JM, Schmitt-Egenolf M. Prevalence and incidence of generalised pustular psoriasis in Sweden - a population-based register study. British Journal of Dermatology 2022. Doi: 10.1111/bjd.20966

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
EU	European Union
EUROPSO	European Federation of Psoriasis Patient Associations
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
JMDC	Japan Medical Data Center Company
MDV	Medical Data Vision
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

SII.2.1 Published references

R17-3632 Mahil SK, Catapano M, Meglio P di, Dand N, Ahlfors H, Carr IM, et al. An analysis of IL-36 signature genes and individuals with IL1RL2 knockout mutations validates IL-36 as a psoriasis therapeutic target; Sci Transl Med 9, eaan2514 (2017)

SII.2.2 Unpublished references

n00232540-01 BI 674304: A four-week intravenous study in the mouse to assess tolerability and pharmacodynamics. 29 Jan 2015

n00234384-01 A 4-week study of BI 674304 by intravenous injection in the mouse. 18 Aug 2014

n00235413-01 BI 674304: A 4-week intravenous injection study in the mouse with a 4-week recovery period. 13 Apr 2015

n00239291-01 A tissue cross-reactivity study of biotinylated BI 655130 in normal human tissues. 31 Mar 2015

n00243849-01 BI 674304: An intravenous injection embryo-fetal development study in Mice. 22 Jun 2016

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

n00254965-01 BI 674304: An intravenous injection fertility and early embryonic development study in the mouse. 21 Sep 2017

n00257882-01 BI 674304: 26-week (twice weekly) intravenous injection toxicity study in the mouse with a 4-week recovery period. 01 Sep 2017

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

For exposure calculations, the safety analysis set including all patients with GPP and who received at least 1 dose of spesolimab i.v. (SAF-ISS3) was considered. Exposure for SAF-ISS3 is presented in the following.

In addition, an overview of all safety analysis sets is given in SIII.Table 1, together with an overview on patient exposure for all safety analysis sets in SIII.Table 2. For further details on exposure for SAF-ISS0 (healthy volunteers), SAF-ISS1 (patients from all randomised placebo-controlled trials that are completed/have a completed primary analysis period), and SAF-ISS2 (patients from controlled and uncontrolled trials), and SAF-ISS2 GPP (subset of SAF-ISS2, all GPP trials), refer to Appendix 7.

SIII.Table 1 Overview of safety analysis sets

SAF	Description	Trials included
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
SAF-ISS0	Exposure in healthy volunteers from all completed trials	1368-0001, 1368-0002, 1368-0003, 1368-0009, 1368-0029
SAF-ISS1	Exposure in patients from all randomised placebo-controlled trials that are completed or have a completed primary analysis period	1368-0005 and 1368-0013 up to week 12; 1368-0016 and 1368-0032 up to week 16; 1368-0010 and 1368-0015 up to the end of REP
SAF-ISS2	Exposure in patients from controlled (SAF-ISS1) and uncontrolled (1368-0004, 1368-0011, 1368-0017, 1368-0025, 1368-0027) trials, including open-label extension trials, until end of trial or cut-off date	See under “description”
SAF-ISS2 GPP	Subset of SAF-ISS2; all patients with GPP receiving at least 1 dose of either spesolimab or placebo	1368-0011, 1368-0013, 1368-0025, 1368-0027

Data source: SCS spesolimab (GPP indication) [c32483404-01], Section 1.1.3.1; and SAP for RMP for spesolimab (GPP indication) [c35174241-01], Table 4.2.1: 1

SIII.Table 2 Overview exposure per safety grouping

	Placebo N/mean time at risk [months]	Spesolimab overall N/mean time at risk [months]	Overall N/mean time at risk [months]
SAF-ISS3	18/0.596	57/3.482	59/3.545
SAF-ISS0	38/3.008	196/3.316	234/3.266
SAF-ISS1	129/3.381	305/3.475	434/3.447
SAF-ISS2	129/3.548	401/7.646	455/7.745
SAF-ISS2 GPP	18/0.596	66/8.230	66/8.392

Data source: data on file, analyses for EU-RMP v1.0; SAF-ISS3, Table A.1.1.1: 1; SAF-ISS0, Table A.1.3.1: 1; SAF-ISS1, Table A.1.4.1: 1; SAF-ISS2, Table A.1.5.1: 1; SAF-ISS2 GPP, Table A.1.2.1: 1

Indication GPP

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 3 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 4 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 5 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.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

c32483404-01 Summary of Clinical Safety. Spesolimab. Treatment of flares in adult patients with Generalized Pustular Psoriasis SCS spesolimab (GPP indication). Aug 2021

ABBREVIATIONS

EU	European Union
GPP	Generalized pustular psoriasis
i.v.	Intravenous
ISS	Integrated Summary of Safety
NC	Not calculable
REP	Residual effect period
RMP	Risk Management Plan
SAF	Safety analysis set
SAP	Statistical analysis plan
SCS	Summary of Clinical Safety

MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

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

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"). Systemic hypersensitivity reaction is defined as an important potential 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 are 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=2 (both 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 5 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] BI 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

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

MODULE SV POST-AUTHORISATION EXPERIENCE

Not applicable, as spesolimab is not yet marketed.

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.3.1.1.3.

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.3.1.2.3.

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

This section is not applicable as the marketing authorisation for spesolimab has not yet been obtained.

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

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 1 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

There are no important identified risks for spesolimab.

SVII.3.1.1 Important potential risk: Serious or opportunistic infections

SVII.3.1.1.1 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.3.1.1.2 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.

The MAH is planning a voluntary PASS (1368-0128) to further investigate this potential risk.

SVII.3.1.1.3 Characterisation of the risk

Cases of serious or opportunistic infections were analysed using the following searches (MedDRA version 23.1):

- 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)

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.3.1.1.4 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.3.1.1.5 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.3.1.1.6 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.3.1.1.7 Public health impact

A potential impact on public health is not expected.

SVII.3.1.2 Important potential risk: Systemic hypersensitivity reaction

SVII.3.1.2.1 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.3.1.2.2 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).

Based on the results from trial 1368-0013, there was no evidence that events of hypersensitivity were associated with spesolimab treatment. No additional risk minimisation measures for the important potential risk ‘systemic hypersensitivity reactions’ are planned.

The MAH is planning a voluntary PASS (1368-0128) to further investigate this potential risk.

SVII.3.1.2.3 Characterisation of the risk

Cases of systemic hypersensitivity reaction were analysed using a combined search of the narrow SMQs ‘Anaphylactic reaction’, ‘Angioedema’, and ‘Hypersensitivity’ (MedDRA version 23.1).
Cases of DRESS were analysed using the narrow SMQ ‘Drug reaction with eosinophilia and systemic symptoms syndrome’ (MedDRA version 23.1).

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, including 2 DRESS cases 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, there is 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.

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 2 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 3 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 4 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.3.1.2.4 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.3.1.2.2).

SVII.3.1.2.5 Preventability

The preventability is unknown.

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

There is a theoretical 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.3.1.2.7 Public health impact

No impact on public health is 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.

The MAH is planning a voluntary PASS (1368-0128) to further investigate this potential risk.

SVII.3.1.3.3 Characterisation of the risk

Cases of malignancy were analysed using the following searches (MedDRA version 23.1):

- 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

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 of the patients reporting malignancies while taking spesolimab had underlying relevant 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. The MAH is planning a PASS (1368-0128) to further investigate this potential risk.

SVII.3.1.4.3 Characterisation of the risk

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 5.

- 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 5 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.4 REFERENCES

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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
CD4	Cluster of differentiation 4
CFU	Colony forming unit
COS	Clinical overview statement
COVID-19	Coronavirus disease 2019
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
ID	Identifier
IgG	Immunoglobulin G
IL	Interleukin
IL-36 (R)	Interleukin 36 (receptor)
IMP	Investigational medicinal product
IRA	Immunogenicity risk assessment
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
PPP	Palmoplantar pustulosis
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
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
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	None
Important potential risks	Serious or opportunistic infections
	Systemic hypersensitivity reaction
	Malignancy
	Peripheral neuropathy
Missing information	Pregnant or breast-feeding women

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:

Important potential risks

- Serious or opportunistic infections
- DRESS (included under 'Systemic hypersensitivity reaction')
- 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 - A 5-year active surveillance, post-authorisation safety study to characterise the safety of spesolimab for flare treatment in patients with GPP.

Rationale and study objectives
To evaluate the risks of serious or opportunistic infections, systemic hypersensitivity reaction, malignancy, and peripheral neuropathy in adult patients (aged ≥18 years) experiencing a GPP flare who are treated with spesolimab or other treatments in the routine clinical care setting. Considering the low frequency of the outcome together with a long follow-up required to adequately evaluate malignancy, this specific outcome may be pulled into a specific separate study.

Study design
5-year observational cohort study

Study population
Adult patients experiencing a GPP flare

Milestones
Protocol submission, 30 Jun 2023
Final report, 30 Sep 2029

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 A 5-year active surveillance, post-authorisation safety study to characterise the safety of spesolimab for flare treatment in patients with GPP. Planned	To evaluate the risks serious or opportunistic infections, systemic hypersensitivity reaction, malignancy, and peripheral neuropathy in adult patients (aged ≥18 years) experiencing a GPP flare who are treated with spesolimab or other treatments in the routine clinical care setting.	Serious or opportunistic infections, systemic hypersensitivity reaction, malignancy, peripheral neuropathy	Protocol submission Final report	30 Jun 2023 30 Sep 2029

PART III.4 REFERENCES

Not applicable.

ABBREVIATIONS

DRESS	Drug reaction with eosinophilia and systemic symptoms
GPP	Generalized pustular psoriasis
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. Planned	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	Draft protocol submission Final report	31 Mar 2023 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	
None	
Important potential risks	
Serious or opportunistic infections	*Routine risk communication* EU-SmPC sections 4.3, 4.4; PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Spesolimab is available as a prescription-only medicine. Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases.
Systemic hypersensitivity reaction	*Routine risk communication* EU-SmPC sections 4.3, 4.4; PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Spesolimab is available as a prescription-only medicine. Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases.

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

Safety concern	Routine risk minimisation activities
Important potential risks (cont'd)	
Malignancy	*Routine risk communication* None *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Spesolimab is available as a prescription-only medicine. Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases.
Peripheral neuropathy	*Routine risk communication* EU-SmPC section 4.4, PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Spesolimab is available as a prescription-only medicine. Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases.
Missing information	
Pregnant or breast-feeding women	*Routine risk communication* EU-SmPC section 4.6; PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Spesolimab is available as a prescription-only medicine. Administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases.

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		
None		
Important potential risks		
Serious or opportunistic infections	*Routine risk minimisation measures* EU-SmPC section 4.3, 4.4 PL section 2 Prescription only medicine, 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 (protocol submission 30 Jun 2023, final report 30 Sep 2029)
Systemic hypersensitivity reaction	*Routine risk minimisation measures* EU-SmPC sections 4.3, 4.4 PL section 2 Prescription only medicine, 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 (protocol submission 30 Jun 2023, final report 30 Sep 2029)

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, 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 (protocol submission 30 Jun 2023, final report 30 Sep 2029)
Peripheral neuropathy	*Routine risk minimisation measures* EU-SmPC section 4.4 PL section 2 Prescription only medicine, 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 (protocol submission 30 Jun 2023, final report 30 Sep 2029)

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, 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

PART V.4 REFERENCES

Not applicable.

ABBREVIATIONS

AE	Adverse event
DRESS	Drug reaction with eosinophilia and systemic symptoms
EU	European Union
PASS	Post-authorisation safety study
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 adult patients 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).

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	None
Important potential risks	Serious or opportunistic infections
	Systemic hypersensitivity reaction
	Malignancy
	Peripheral neuropathy
Missing information	Pregnant or breast-feeding women

II.B Summary of important risks

Important identified risks
None

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, 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.
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. Hypersensitivity events observed in trial 1368-0013 were not related to spesolimab treatment.
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 PL section 2 Prescription only medicine, 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, 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, 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, administration in a healthcare setting by physicians experienced in the management of patients with inflammatory skin diseases Additional risk minimisation measures: None

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: A 5-year active surveillance, post-authorisation safety study to characterise the safety of spesolimab for flare treatment in patients with 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)
PASS	Post-authorisation safety study
PL	Package Leaflet
PUVA	Combination treatment of psoralen and UVA (long wave UV radiation)
RMP	Risk Management Plan
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

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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?

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.)

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

There are no proposed additional risk minimisation activities for spesolimab.