Summary Report of Benefit-Risk Assessment

SPEVIGO CONCENTRATE FOR SOLUTION FOR INFUSION 450 MG/7.5 ML

NEW DRUG APPLICATION

Active Ingredient(s)	Spesolimab
Product Registrant	Boehringer Ingelheim Singapore Pte. Ltd.
Product Registration Number	SIN16883P
Application Route	Abridged evaluation
Date of Approval	12 October 2023

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Table of Contents

A INTRODUCTION

Spevigo is indicated for the treatment of generalized pustular psoriasis (GPP) flares in adults.

The active substance, spesolimab, is a humanised antagonistic monoclonal immunoglobulin G1 (IgG1) antibody that binds to IL-36R and blocks human IL-36α-, IL-36β-, and IL-36γ-induced IL-36R activation, leading to suppressed pro-inflammatory and pro-fibrotic pathways in inflammation.

Spevigo is available as a concentrate for solution for infusion containing 450 mg/vial of spesolimab. Other ingredients in the concentrate for solution for infusion are sodium acetate trihydrate (E262) glacial acetic acid (E260), sucrose, arginine hydrochloride, polysorbate 20 (E432) and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, spesolimab, and the drug product, Spevigo, are manufactured at Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany.

Drug substance:

Adequate controls have been presented for the reagents and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities have been appropriately performed. Potential and actual impurities are adequately controlled.

The drug substance specifications were established in accordance with ICH Q6B and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been appropriately validated in accordance with ICH Q2 Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented was adequate to support the approved storage condition and shelf life. The packaging is stainless steel cryovessel. The drug substance is approved for storage at -40 ± 10ºC with a shelf life of 36 months.

Drug product:

The manufacturing site involved is compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications were established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods have been appropriately validated in accordance with ICH Q2

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Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored between 2ºC and 8ºC. The in-use period after reconstitution is at 2-30ºC up to 24 hours and was supported by appropriate in-use stability testing. The container closure system is a Type I borosilicate 10 ml clear glass vial closed with a coated rubber stopper and secured with an aluminium crimp cap.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of spesolimab in the treatment of GPP flares in adults was based primarily on one pivotal Phase II study 1368-0013. This was a multi-centre, double-blind, randomised, placebo-controlled study to evaluate the efficacy, safety and tolerability of a single intravenous (IV) dose of spesolimab in patients with GPP presenting with an acute flare of moderate to severe intensity. Although this was a Phase II study, it was designed to be a comparative study of spesolimab versus placebo and was adequately powered to demonstrate superiority of spesolimab over placebo. A placebo-controlled trial was considered acceptable given that there are currently no drugs approved specifically for the treatment of GPP.

Patients in the study were randomised in a 2:1 ratio to receive a single IV dose of 900 mg of spesolimab or placebo on Day 1. An additional open-label dose of spesolimab could be administered on Day 8 if the patient's Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score was ≥2 and their GPPGA pustulation subscore was ≥2.

The primary efficacy endpoint was the proportion of patients who achieved a GPPGA pustulation subscore of 0, indicating no visible pustules, at Week 1. The key secondary efficacy endpoint was the proportion of patients who achieved a GPPGA total score of 0 or 1 (clear or almost clear) at Week 1. Other secondary endpoints included the proportion of patients who achieved ≥75% reduction in the Generalized Pustular Psoriasis Area and Severity Index (GPPASI 75) at Week 4 as well as the change from baseline in the Pain Visual Analog Scale (VAS), Psoriasis Symptom Scale (PSS), and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores at Week 4. The statistical methods appropriately employed a hierarchical testing strategy for the primary and secondary endpoints to control the type I error rate at a level of 0.025 one-sided.

A total of 53 patients were randomised in the study: 35 patients in the spesolimab arm and 18 patients in the placebo arm. The median age was 41 years (range 21 to 69 years). The majority of subjects were female (68%) and Asian (55%), and 45% of patients were White. The baseline disease characteristics were generally comparable between the two groups. Most patients had a GPPGA total score of 3 (spesolimab: 80.0%, placebo: 83.3%) and a GPPGA pustulation subscore of 3 (spesolimab: 45.7%, placebo: 38.9%) or 4 (spesolimab: 37.1%, placebo: 33.3%). The mean (SD) GPPASI total scores at baseline were 27.8 (13.4) in the spesolimab group and 24.1 (15.2) in the placebo group.

The primary analysis showed that spesolimab was statistically superior to placebo in terms of the proportion of subjects achieving GPPGA pustulation subscore of 0 at Week 1 (54.3% versus 5.6%, one-sided p=0.0004).

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Subjects who had a GPPGA total score ≥2 at Day 8 and a GPPGA pustulation sub score of ≥2 at Day 8 were eligible to receive treatment with a single open-label dose of 900 mg of spesolimab. A total of 12 out of 35 subjects who were randomised to spesolimab received a second dose of spesolimab at Day 8. In these subjects, 5 (41.7%) subjects had a GPPGA pustulation subscore of 0 (clear) at Day 15 (i.e., one week after their second dose of spesolimab). There were 15 out of 18 subjects in the placebo arm who received the open-label dose of spesolimab at Day 8. In these subjects, 11 (73.3%) subjects achieved pustular clearance at Day 15.

The results of the primary endpoint were supported by the secondary endpoints which showed that spesolimab was statistically superior to placebo in terms of the proportion of subjects achieving GPPGA total score of 0 or 1 at Week 1 (42.9% versus 11.1%, one-sided p=0.0118) and GPPASI 75 at Week 4 (45.7% versus 11.1%, one-sided p=0.0081).

For the patient reported outcomes, improvements in the pain VAS score, PSS score (measuring symptoms of pain, redness, itching, and burning), and FACIT-Fatigue score were observed at Week 4 in the spesolimab group (median change from baseline: -22.45, -2.00 and 3.00, for the pain VAS score, PSS score, and FACIT-Fatigue score, respectively).

Summary of key efficacy results (study 1368-0013)

	Placebo (N=18)	**Spevigo (N=35)**
Primary endpoint		
Patients achieving a GPPGA[a] pustulation subscore of 0 at Week 1, n (%)	1 (5.6)	19 (54.3)
Risk difference versus placebo, % (95% CI)	48.7 (21.5, 67.2)	
p-value*	0.0004	
Key secondary endpoint		
Patients achieving a GPPGA[a] total score of 0 or 1 at Week 1, n (%)	2 (11.1)	15 (42.9)
Risk difference versus placebo, % (95% CI)	31.7 (2.2, 52.7)	
p-value*	0.0118	
Other secondary endpoints		
Patients achieving a GPPASI[b] 75 at Week 4, n (%)	2 (11.1)	16 (45.7)
Risk difference versus placebo, % (95% CI)	34.6 (5.8, 55.4)	
p-value*	0.0081	
Change from baseline in pain VAS score[c] at Week 4		
Median (Q1, Q3)	NR	-22.45 (-70.41, NR)
p-value*	0.0012	
Change from baseline in PSS score[d] at Week 4		
Median (Q1, Q3)	NR	-2.00 (-9.00, NR)
p-value*	0.0044	
Change from baseline in FACIT-Fatigue score[e] at Week 4		
Median (Q1, Q3)	NR	3.00 (NR, 30.00)
p-value*	0.0012	

NR = non-response

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

[b] The GPPASI score is based on a combination of the percent body surface area (BSA) of skin affected by erythema, pustules, and scaling and the severity of erythema, pustules, and scaling over 4 body regions (head, trunk, upper limb, lower limb) and ranges from 0 to 72.

[c] The pain VAS indicates the severity of pain on a 100-mm line, with a range of scores from 0 (no pain) to 100 (very severe pain).

[d] The PSS score is a 4-item instrument that includes the symptoms pain, redness, itching, and burning, with scores of current symptom severity ranging from 0 (none) to 4 (very severe), and total score ranging from 0 to 16.

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[e] The FACIT-Fatigue score is a 13-item questionnaire that assess self-reported fatigue and its impact upon daily activities and function, with responses recorded on a 5-point Likert scale (0 to 4), leading to a total score ranging from 0 to 52, with lower scores representing greater fatigue.
*One-sided p-value

There was also limited data from other ongoing studies 1368-0027 (Phase II placebo-controlled study) and 1368-0025 (open-label extension of the pivotal study 1368-0013 and study 1368-0027 for up to 252 weeks) and which were intended to demonstrate the efficacy of subcutaneous spesolimab in the prevention of reoccurrence of GPP flares. As the studies also investigated the use of intravenous spesolimab for acute treatment of GPP flares, the results on flare treatment were available for a small number of patients (N=9 in study -0025 and N=6 in study -0027). The proportion of patients achieving pustular clearance (55.6% in study -0025 and 83.3% in study -0027) and GPPGA total score of 0 or 1 (33.3% in study -0025 and 50.0% in study -0027) in these studies were generally consistent with that observed in study 1368-0013 and supported the results of the pivotal study.

Overall, the efficacy of spesolimab for the treatment of GPP flares in adults was adequately demonstrated in terms of significantly higher proportion of patients with clearance of pustules as well as improvements in patient outcomes such as pain, PSS and FACIT-Fatigue scores compared to placebo.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety data of spesolimab was derived from the pivotal Phase II study 1368-0013 and limited data from two ongoing Phase II studies 1368-0025 and 1368-0027, comprising a total of 57 patients with GPP who received at least 1 dose of spesolimab via the IV route. Of these, 22 patients received more than 1 dose of spesolimab. The median exposure-adjusted time at risk was 3.1 months (range 0.1 to 8.3 months) across the three studies.

Overview of safety profile

AE	Study 1368-0013 (Up to Week 1) (double-blind period)		Study 1368-0013 (Up to 16 weeks post-dose)*	Study 1368-0025 Spesolimab (N=9)	Study 1368-0027 Spesolimab (N=6)
	Spesolimab (N=35)	Placebo (N=18)	Spesolimab (N=51)		
Any AE	27 (77.1%)	12 (66.7%)	47 (92.2%)	8 (88.9%)	6 (100.0%)
Treatment-related AE	12 (34.3%)	6 (33.3%)	32 (62.7%)	2 (22.2%)	3 (50.0%)
Severe (Grade 3 or 4) AE	6 (17.1%)	2 (11.1%)	11 (21.6%)	1 (11.1%)	1 (16.7%)
SAE	5 (14.3%)	3 (16.7%)	13 (25.5%)	1 (11.1%)	0
AE leading to treatment discontinuation	0	0	0	0	1 (16.7%)
Deaths due to AE	0	0	0	0	0

* Includes patients who received at least 1 dose of spesolimab, including open-label treatment.

In study 1368-0013 during the first week after the first dose, the overall incidence of adverse events (AEs) was higher in the spesolimab group compared to the placebo group (77.1% vs 66.7%). While the most frequently reported AEs were observed at higher incidences in the placebo group which included pustular psoriasis (37.1% vs 38.9%), pyrexia (5.7% vs 22.2%), and dizziness (0% vs 11.1%), there was a higher incidence AEs of infections and infestations in the spesolimab group compared to the placebo group (17.1% vs 5.6%). All the infection AEs

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were mild or moderate in intensity except for an event of urinary tract infection in the spesolimab group which was considered serious due to hospitalisation of the patient. However, this patient had other AEs that required hospitalisation.

There were 8 serious AEs (SAEs) reported in 5 patients (14.3%) in the spesolimab group compared to 3 SAEs reported in 3 patients (16.7%) in the placebo group. Consistent with the overall AEs profile, the most frequently reported SAE was pustular psoriasis which was reported at a higher incidence in the placebo group compared to the spesolimab group (16.7% vs 11.4%). Only one SAE of septic arthritis in the spesolimab group was considered by the investigator to be probably related to the study treatment. There was one event each of drug reaction with eosinophilia and systemic symptoms (DRESS), urinary tract infection and drug-induced liver injury (DILI) which occurred in one patient in the spesolimab group. DRESS was not considered to be due to the study drug by the investigator as the onset 2 days after drug administration was too soon. In addition, the patient had history of allergy to cefuroxime hence the possibility of cephalosporin inducing both the drug eruption and liver injury could not be ruled out.

The AEs of special interest reported with spesolimab included 2 cases of DRESS as well as 1 case each of squamous cell skin carcinoma, latent tuberculosis, DILI, and torsades de pointes. Aside from the case of DRESS which was an SAE, the other case of DRESS occurred in a patient who had received spiramycin and paracetamol for tooth pain and infection, which was continued for 5 days hence causality to spesolimab cannot be established. Overall, the AEs of special interest have been adequately described as warnings and precautions in the package insert.

The safety profile of spesolimab was generally well tolerated and no major safety concerns were identified.

E ASSESSMENT OF BENEFIT-RISK PROFILE

GPP is a rare and potentially life-threatening dermatological disease characterised by widespread eruptions of sterile, macroscopically visible pustules that can occur with systemic inflammation. There is currently an unmet medical need given the lack of any approved therapies for the treatment of GPP. The systemic therapies used such as methotrexate, cyclosporin, retinoids and systemic corticosteroids have limited evidence of efficacy and are associated with toxicities.

The pivotal study 1368-0013 demonstrated a statistically significant and clinically relevant effect with a single-dose treatment of spesolimab compared to placebo for the treatment of an acute GPP flare in terms of the proportion of subjects achieving GPPGA pustulation subscore of 0 at Week 1 (54.3% versus 5.6%, one-sided p=0.0004).

The positive results in the primary endpoint were supported by the secondary endpoints in terms of a statistically significantly higher proportion of subjects achieving GPPGA total score of 0 or 1 at Week 1 (42.9% versus 11.1%, one-sided p=0.0118) and GPPASI 75 at Week 4 (45.7% versus 11.1%, one-sided p=0.0081) for spesolimab compared to placebo. In addition, improvements on patient reported outcomes such as change from baseline in the pain VAS, PSS and FACIT-Fatigue scores were observed at Week 4 in the spesolimab group (median change from baseline: -22.45, -2.00 and 3.00, for the pain VAS score, PSS score, and FACIT-Fatigue score, respectively).

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The results of the supportive studies in terms of the proportion of patients achieving pustular clearance and GPPGA total score of 0 or 1 were consistent and supported the pivotal study.

Due to the rarity of the disease, the number of patients exposed to the recommended dose was small and the duration of safety follow-up was limited. The safety profile comprised mostly mild to moderate AEs such as infections and infestations, which were generally manageable. The incidence of SAEs was comparable between the spesolimab and placebo groups, and only one case of septic arthritis was considered by the investigator to be probably related to the study treatment. The AEs of special interest have been adequately described as warnings and precautions in the package insert. There were no treatment discontinuations due to AEs or deaths.

Overall, the benefit-risk profile for the use of spesolimab for the treatment of GPP flares in adults was considered favourable as efficacy has been demonstrated and the safety profile was acceptable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Spevigo for the treatment of GPP flares in adults was deemed favourable and approval of the product registration was granted on 12 October 2023.

APPROVED PACKAGE INSERT AT REGISTRATION

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SPEVIGO

1. NAME OF THE MEDICINAL PRODUCT

Spevigo 450 mg concentrate for solution for infusion

2. QUALTITATIVE AND QUANTITATVE COMPOSITION

Each vial contains 450 mg spesolimab in 7.5 mL.

Each mL of concentrate for solution for infusion contains 60 mg spesolimab.

After dilution, each mL of the solution contains 9 mg spesolimab (see section 6.6).

Spesolimab is produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

Clear to slightly opalescent, colourless to slightly brownish-yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SPEVIGO is indicated for the treatment of generalized pustular psoriasis (GPP) flares in adults.

4.2 Posology and method of administration

Treatment with SPEVIGO should be initiated and supervised by physicians experienced in the management of patients with inflammatory skin diseases.

Posology

The recommended dose of SPEVIGO is a single dose of 900 mg (2 x 450 mg/7.5 ml vials) administered as an intravenous infusion.

If flare symptoms persist, an additional 900 mg dose may be administered 1 week after the initial dose.

Elderly patients
No dose adjustment is required.
There is limited information in patients aged 65 years and older.

Renal and/or hepatic impairment
SPEVIGO has not been studied in these patient populations. These conditions are generally not expected to have any clinically relevant impact on the pharmacokinetics of monoclonal antibodies and no dose adjustments are considered necessary.

Paediatric population
The safety and efficacy of SPEVIGO in children below the age of 18 years have not been established. No data are available.

Method of administration

SPEVIGO must be diluted before use (see section Instructions for use/handling).

SPEVIGO is administered as a continuous intravenous infusion through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micron) over 90 minutes.

In the event that the infusion is slowed or temporarily stopped, the total infusion time (including stop time) should not exceed 180 minutes (see section 4.4).

Instructions for use/handling

Prior to use, the unopened vial may be kept at room temperature (up to 30°C) for up to 24 hours, if stored in the original package in order to protect from light.

The vial should be visually inspected before use. SPEVIGO is a colourless to slightly brownish- yellow, clear to slightly opalescent solution. If the solution is cloudy, discoloured, or contains large or coloured particulates, the vial should be discarded.

Aseptic technique must be used to prepare the solution for infusion. Draw and discard 15 ml from a 100 ml container of sterile 0.9% sodium chloride solution and replace slowly with 15 ml SPEVIGO (complete content from two vials of 450 mg/7.5 ml). Mix gently before use. The diluted SPEVIGO infusion solution should be used immediately.

SPEVIGO must not be mixed with other medicinal products. A pre-existing intravenous line may be used for administration of SPEVIGO. The line must be flushed with sterile 0.9% sodium chloride solution prior to and at the end of infusion. No other infusion should be administered in parallel via the same intravenous access.

SPEVIGO is for single-use only and does not contain preservatives.

Chemical and physical in-use stability of the diluted solution has been demonstrated for 24 hours at 2-30°C followed by 3 hours infusion time.

From a microbiological point of view the diluted solution for infusion should be used immediately. If not used immediately, in use storage conditions are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions. For the time between preparation and start of administration the solution for infusion should be protected from light following local standard procedures.

No incompatibilities have been observed between SPEVIGO and infusion sets composed of polyvinylchloride (PVC), polyethylene (PE), polypropylene (PP). polybutadiene and polyurethane (PUR), and in-line filter membranes composed of polyethersulfone (PES, neutral and positively charged) and positively charged polyamide (PA).

4.3 Contraindications

Severe or life-threatening hypersensitivity to SPEVIGO or to any of the excipients listed in section 6.1 (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded in the patient file.

Infections

SPEVIGO may increase the risk of infections. During the 1-week placebo-controlled period in the Effisayil-1 trial, infections were reported in 17.1% of patients treated with SPEVIGO compared with 5.6% of patients treated with placebo (see section 4.8).

In patients with a chronic infection or a history of recurrent infection, the potential risks and expected clinical benefits of treatment should be considered prior to prescribing SPEVIGO. Treatment with SPEVIGO should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. Patients should be instructed to seek medical advice if signs or symptoms of clinically important infection occur after treatment with SPEVIGO.

Pre-treatment evaluation for tuberculosis

Patients should be evaluated for tuberculosis (TB) infection prior to initiating treatment with SPEVIGO. SPEVIGO should not be administered to patients with active TB infection.

Anti-TB therapy should be considered prior to initiating SPEVIGO in patients with latent TB or a history of TB in whom an adequate course of treatment cannot be confirmed. After SPEVIGO treatment, patients should be monitored for signs and symptoms of active TB.

Hypersensitivity and infusion-related reactions

Hypersensitivity and infusion-related reactions may occur with monoclonal antibodies such as SPEVIGO. Hypersensitivity may include immediate reactions such as anaphylaxis and delayed reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS).

If a patient develops signs of anaphylaxis or other serious hypersensitivity, SPEVIGO should be discontinued immediately and appropriate treatment should be initiated (see section 4.3).

If a patient develops mild or moderate infusion-related reaction, SPEVIGO should be stopped and

appropriate medical therapy should be considered (e.g., systemic antihistamines and/or corticosteroids). Upon resolution of the reaction, the infusion may be restarted at a slower infusion rate with gradual increase to complete the infusion (see section 4.2).

Immunisations

No specific studies have been conducted in patients who have recently received live viral or live bacterial vaccines. The interval between live vaccinations and initiation of SPEVIGO therapy should be at least 4 weeks. Live vaccines should not be administered for at least 16 weeks after treatment with SPEVIGO.

Peripheral neuropathy
The potential for peripheral neuropathy with SPEVIGO is unknown. Cases of peripheral neuropathy have been reported in clinical trials with spesolimab. Physicians should be vigilant for symptoms potentially indicative of new-onset peripheral neuropathy.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per 900 mg dose, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Live vaccines should not be given concurrently with SPEVIGO (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of spesolimab in pregnant women. Pre-clinical studies using a surrogate, mouse specific anti-IL36R monoclonal antibody do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Human immunoglobulin (IgG) is known to cross the placental barrier. As a precautionary measure, it is recommended to avoid the use of SPEVIGO in pregnancy, unless the expected clinical benefit clearly outweighs the potential risks.

Breast-feeding

It is unknown whether spesolimab is excreted in human milk. There are no data on the effects on the breastfed infant, or the effects on milk production. Spesolimab is a monoclonal antibody and is expected to be present in human milk. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to abstain from SPEVIGO therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data available on the effect of spesolimab on human fertility. Pre-clinical studies in mice using a surrogate, mouse specific anti-IL36R monoclonal antibody, do not indicate direct or indirect

harmful effects with respect to fertility from antagonism of IL36R.

4.7 Effects on ability to drive and use machines

SPEVIGO has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety data provided in the following are based on Effisayil-1, a double-blind, randomised trial comparing a single intravenous 900 mg dose of SPEVIGO (n=35) with placebo (n=18) in patients with generalized pustular psoriasis for up to 12 weeks after treatment and four double-blind, placebo-controlled trials of 254 spesolimab-treated patients who received doses up to 1200 mg intravenous or subcutaneous spesolimab for other diseases.

The most frequent adverse reactions associated with SPEVIGO are infections.

Tabulated summary of adverse reactions

Table 1 Summary of Adverse Reactions

MedDRA System Organ Class terminology	**SPEVIGO adverse reactions**
Infections and infestations	Urinary tract infection Upper respiratory tract infection
Skin and subcutaneous tissue disorders	Pruritus
General disorders and administration site conditions	Injection site reactions* Fatigue

*Not reported in Effisayil-1

Description of selected adverse reactions

Infections
During the 1-week placebo-controlled period in Effisayil-1, infections were reported in 17.1% of patients treated with SPEVIGO compared with 5.6% of patients treated with placebo. Serious infection (urinary tract infection) was reported in 1 patient (2.9%) in the SPEVIGO group and no patients in the placebo group. Infections observed in clinical trials with spesolimab were generally mild to moderate with no distinct pattern regarding pathogen or type of infection.

Injection site reactions
Injection site reactions include injection site erythema, injection site swelling, injection site pain, injection site induration, and injection site warmth. Injection site reactions were typically mild- to-moderate in severity.

Immunogenicity
As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody

formation is highly dependent on the sensitivity and specificity of the assay.

In patients with GPP treated with Spesolimab in Effisayil-1, anti-drug antibodies (ADA) formed with a median onset of 2.3 weeks. Following administration of i.v. spesolimab 900 mg, 24% of patients had a maximum ADA titer greater than 4000 and were Neutralising antibody (Nab)-positive by end of the trial (Weeks 12 to 17).

Females appeared to have higher immunogenicity response; the percentage of patients with ADA titer greater than 4000 was 30% in females, and 12% in males, respectively.

In some patients with ADA titer values greater than 4000, plasma spesolimab concentrations were reduced, with no apparent impact on pharmacokinetics at ADA titers below 4000. There are limited data on the impact of ADAs on safety and efficacy upon retreatment as the majority of subjects did not experience a subsequent, new flare in an open-label extension trial. There was no apparent correlation between the presence of ADA to spesolimab and hypersensitivity reactions.

4.9 Overdose

There is no clinical experience with overdoses of SPEVIGO.

The highest dose of SPEVIGO administered in clinical trials was 1200 mg. Adverse events observed in subjects receiving single or repeated doses up to 1200 mg were consistent with the known safety profile of SPEVIGO.

In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and symptomatic treatment be instituted as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Interleukin inhibitors. ATC code: L04AC22

Mechanism of action

Spesolimab is a humanised antagonistic monoclonal immunoglobulin G1 (IgG1) antibody blocking human IL36R signalling. Binding of spesolimab to IL36R prevents the subsequent activation of IL36R by cognate ligands (IL36 α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways. IL-36R signalling is differentiated from TNF-α, integrin and IL-23 inhibitory pathways by directly and simultaneously blocking both inflammatory and pro-fibrotic pathways. Genetic human studies have established a strong link between IL36R signalling and skin inflammation.

Pharmacodynamic effects

Following treatment with SPEVIGO in patients with GPP, reduced levels of C-reactive protein (CRP), interleukin (IL)-6, T helper cell (Th1/Th17) mediated cytokines, keratinocyte-mediated inflammation, neutrophilic mediators, and proinflammatory cytokines were observed in serum and skin at week 1 compared to baseline and was associated with a decrease in clinical severity. These reductions in

biomarkers became more pronounced at the last measurement at week 8 in Effisayil 1.

Clinical efficacy and safety

A randomised, double-blind, placebo-controlled study (Effisayil-1) was conducted to evaluate the clinical efficacy and safety of SPEVIGO in adult patients with flares of Generalized Pustular Psoriasis (GPP), as diagnosed per European Rare And Severe Psoriasis Expert Network (ERASPEN) criteria, regardless of IL36RN mutation status. Patients were randomised if they had a flare of GPP of moderate-to-severe intensity, as defined by a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score (which ranges from 0 [clear] to 4 [severe]) of at least 3 (moderate), presence of fresh pustules (new appearance or worsening of pustules), GPPGA pustulation sub score of at least 2 (mild), and at least 5% of body surface area (BSA) covered with erythema and the presence of pustules. Patients were required to discontinue systemic and topical therapy for GPP prior to receiving study drug.

The primary endpoint of the study was the proportion of patients with a GPPGA pustulation sub score of 0 (indicating no visible pustules) at Week 1 after treatment. The key secondary endpoint of the study was the proportion of patients with a GPPGA total score of 0 or 1 (clear or almost clear skin) at Week 1. Additional secondary endpoints at Week 4 were the proportion of patients with a 75% reduction in the Psoriasis Area and Severity Index for Generalized Pustular Psoriasis (GPPASI 75), and patient-reported outcomes including change from baseline in Pain Visual Analog Scale (VAS) score, change from baseline in Psoriasis Symptom Scale (PSS) score, and change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue score.

A total of 53 patients were randomised (2:1) to receive a single intravenous dose of 900 mg SPEVIGO (n= 35) or placebo (n=18). Patients in either treatment arm who still experienced flare symptoms at Week 1 were eligible to receive a single intravenous dose of open-label 900 mg SPEVIGO, resulting in 12 patients (34%) in the SPEVIGO arm receiving a second dose of SPEVIGO and 15 patients (83%) in the placebo arm receiving one dose of SPEVIGO on Day 8. In addition, 6 patients (4 SPEVIGO arm; 2 placebo arm) received rescue treatment with a single 900 mg dose of intravenous SPEVIGO for reoccurrence of a flare after Day 8.

The study population consisted of 32% men and 68% women. The mean age was 43 (range: 21 to 69) years; 55% of patients were Asian and 45% were Caucasian. Most patients included in the study had a GPPGA pustulation sub score of 3 (43%) or 4 (36%), and patients had a GPPGA total score of 3 (81%) or 4 (19%). 24.5% of patients had been previously treated with biologic therapy for GPP.

At Week 1, there was a statistically significant difference in the proportion of patients achieving a GPPGA pustulation sub score of 0 (indicating no visible pustules) and GPPGA total score of 0 or 1 (clear or almost clear skin) in the SPEVIGO arm compared with placebo (see Table 2).

Table 2 GPPGA Pustulation Sub Score and GPPGA Total Score at Week 1

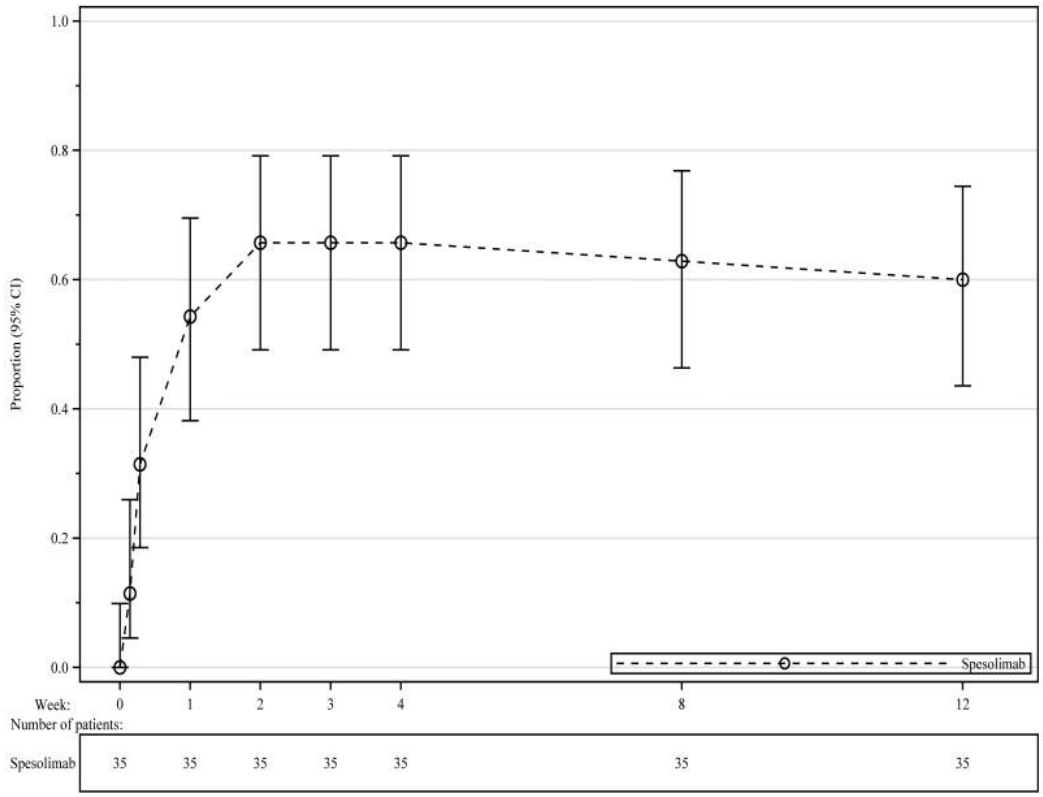
	Placebo	SPEVIGO 900mg iv
Number of Patients analysed	18	35
Patients achieving a GPPGA pustulation sub score of 0, n (%)	1 (5.6)	19 (54.3)
Risk difference versus placebo, % (95% CI)	48.7 (21.5, 67.2)	
p-value*	0.0004	

Patients achieving a GPPGA total score of 0 or 1, n (%)	2 (11.1)	15 (42.9)
Risk difference versus placebo, % (95% CI)	31.7 (2.2, 52.7)	
p-value*	0.0118	

GPPGA = Generalized Pustular Psoriasis Physician Global Assessment; iv = intravenous
*One-sided p-value

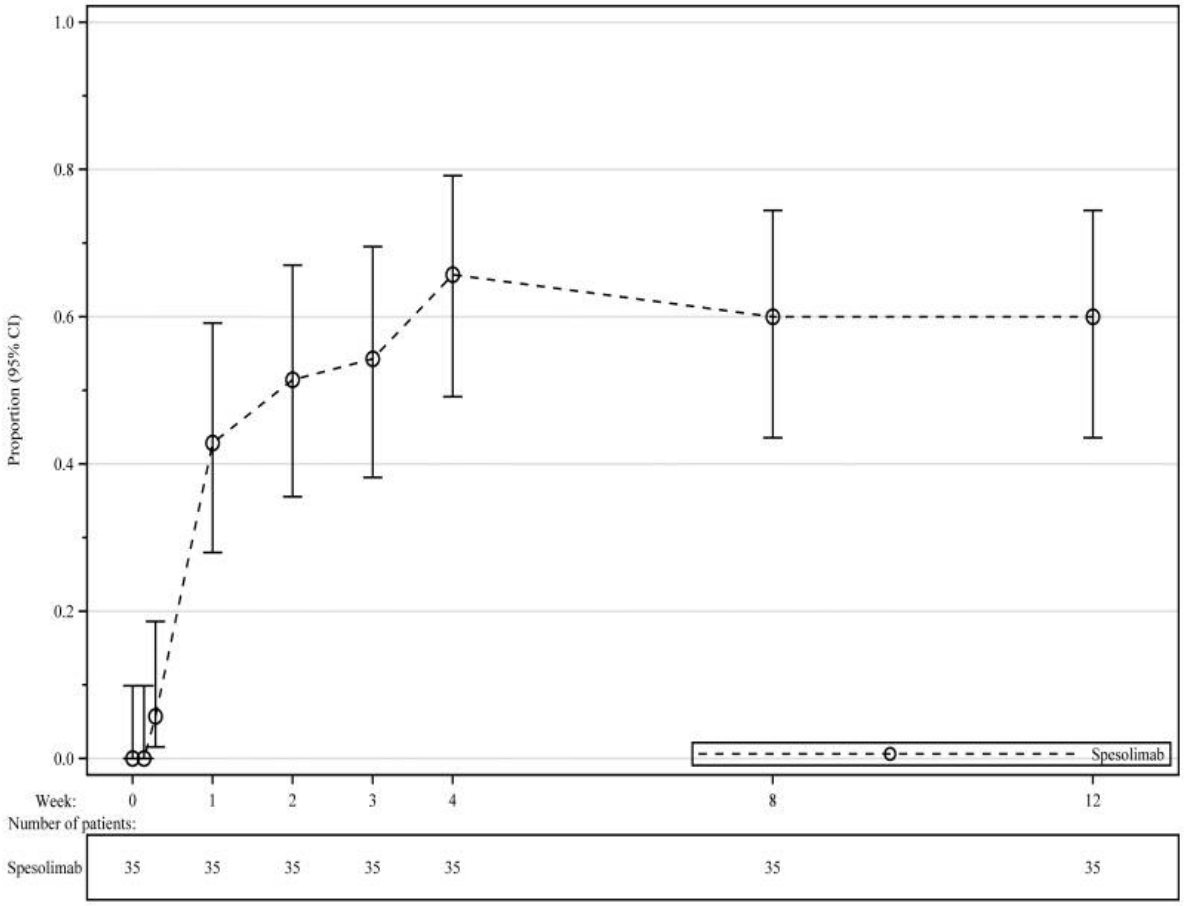
In patients randomized to SPEVIGO, pustular clearance (GPPGA pustulation sub score of 0) was achieved as early as one day after treatment in 11.4% (4/35) of patients. The effect of up to two doses of SPEVIGO on GPPGA pustulation sub score and GPPGA total score was sustained until Week 12 (see Figures 1 and 2).

Figure 1 Proportion of Patients with a GPPGA Pustulation Sub Score of 0 Over Time



GPPGA = Generalized Pustular Psoriasis Physician Global Assessment

Figure 2 Proportion of Patients with a GPPGA Total Score of 0 or 1 Over Time



GPPGA = Generalized Pustular Psoriasis Physician Global Assessment

The results of the primary and key secondary endpoints were consistent across subgroups including sex, age, race, GPPGA pustulation sub score at baseline, GPPGA total score at baseline, mutation status in IL36RN, and irrespective of any GPP treatment prior to randomization.

At Week 4, 16 patients (46%) randomized to SPEVIGO achieved a GPPASI 75.

In patients randomized to SPEVIGO, improvements in the pain VAS score, PSS score (measuring symptoms of pain, redness, itching, and burning), and FACIT Fatigue score were observed at Week 4 (median change from baseline: -22.45, -2.00 and 3.00, for the pain VAS score, PSS score, and FACIT Fatigue score, respectively).

5.2 Pharmacokinetics properties

A population pharmacokinetic model was developed based on data collected from healthy subjects, patients with GPP and patients with other diseases. After a single i.v. dose of 900 mg, the population PK model-estimated $AUC_{0-\infty}$ (95% CI) and C_{max} (95% CI) in a typical ADA-negative patient with GPP were 4750 (4510, 4970) µg·day/mL and 238 (218, 256) µg/mL, respectively.

Distribution

Based on the population pharmacokinetic analysis, the typical volume of distribution at steady state was 6.4 L.

Biotransformation

The metabolic pathway of spesolimab has not been characterized. As a humanized IgG1 monoclonal antibody, spesolimab is expected to be degraded into small peptides and amino acids via catabolic pathways in a manner similar to endogenous IgG.

Elimination

In the linear dose range (0.3-20 mg/kg), based on the population PK model, spesolimab clearance (95% CI) in a typical GPP patient without ADA, weighing 70 kg was 0.184 (0.175, 0.194) L/day. The terminal-half-life was 25.5 (24.4, 26.3) days.

Linearity/non-linearity

At low doses, spesolimab exhibited target-mediated drug disposition (TMDD) kinetics after single i.v. dose administration. At doses from 0.01 to 0.3 mg/kg, both clearance (CL) and terminal half-life were dose dependent, and systemic exposure (AUC) increased more than dose proportionally with dose. The saturation of the nonlinear elimination pathway occurred at about 0.3 mg/kg as spesolimab AUC increased approximately linearly with dose from 0.3 to 20 mg/kg, and CL and terminal half-life were independent of dose.

Elderly/Gender/Race

Based on population pharmacokinetic analyses, age, gender and race do not have an effect on the pharmacokinetics of spesolimab.

Hepatic and renal impairment

As a monoclonal antibody, spesolimab is not expected to undergo hepatic or renal elimination. No formal trial of the effect of hepatic or renal impairment on the pharmacokinetics of spesolimab was conducted.

Population PK analysis did not identify mild hepatic impairment or mild or moderate renal impairment as having an influence on the systemic exposure of spesolimab.

Body weight

Spesolimab concentrations were lower in subjects with higher body weight. The impact of body weight on spesolimab plasma concentrations is not expected to be clinically meaningful.

Paediatric population

The pharmacokinetics of spesolimab in paediatric patients has not yet been studied.

Drug-Drug Interactions (studies)

No formal drug interactions studies have been conducted with spesolimab. Population PK analyses

indicated that concomitant use of immunosuppressants or oral corticosteroids did not have a direct impact on the pharmacokinetics of spesolimab.

5.3 Preclinical safety data

Toxicology

Pre-clinical data reveal no special hazard for humans.

Repeat dose toxicology studies were conducted in mice using a surrogate, mouse specific anti-IL36R monoclonal antibody by twice weekly intravenous injection for 26 weeks at a dose (50 mg/kg) that was 5 fold higher than the dose that was protective in an experimental mouse colonic inflammation model. No adverse changes in body weight, food consumption or clinical observations were noted at this dose. No adverse effects on clinical pathology parameters including haematology, immunophenotyping, clinical chemistry and histopathology, including lymphoid tissues, have been observed.

The binding specificity of spesolimab to human tissues was evaluated in a tissue cross-reactivity study. No unexpected tissue binding was observed.

Developmental and Reproductive Toxicity

Pre-clinical studies conducted in mice using a surrogate antibody directed towards murine IL-36R do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development or fertility, at intravenous doses up to 50 mg/kg twice weekly.

Genotoxicity

Genotoxicity studies have not been conducted with spesolimab.

Carcinogenicity

Carcinogenicity and mutagenicity studies have not been conducted with spesolimab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate (E262)
Glacial acetic acid (E260) (for pH adjustment)
Sucrose
Arginine hydrochloride
Polysorbate 20 (E432)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

3 years.

After opening

From a microbiological point of view, once opened, the medicinal product should be diluted and infused immediately.

After preparation of infusion

Chemical and physical in-use stability of the diluted solution has been demonstrated for 24 hours at 2 °C to 30 °C.

From a microbiological point of view, the diluted solution for infusion should be used immediately. If not used immediately, in use storage conditions are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions. For the time between preparation and start of administration the solution for infusion should be protected from light following local standard procedures.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Store in the original package in order to protect from light.

Prior to use, the unopened vial may be kept at temperatures up to 30 °C for up to 24 hours, if stored in the original package in order to protect from light.

For storage conditions after opening and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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

Pack size of 2 vials.

6.6 Special precautions for disposal and other handling

This medicinal product is compatible with infusion sets composed of polyvinylchloride (PVC), polyethylene (PE), polypropylene (PP), polybutadiene and polyurethane (PUR), and in-line filter membranes composed of polyethersulfone (PES, neutral and positively charged) and positively charged polyamide (PA).

Handling instructions

- The vial should be visually inspected before use. If the solution is cloudy, discoloured, or contains large or coloured particulates, the vial should be discarded.
- Spevigo is for single use only.
- Aseptic technique must be used to prepare the solution for infusion. Draw and discard 15 mL from a 100 mL container of sodium chloride 9 mg/mL (0.9%) solution for injection and replace slowly with 15 mL spesolimab sterile concentrate (complete content from two vials of 450 mg/7.5 mL). Mix gently before use. The diluted spesolimab infusion solution should be used immediately.
- Spevigo must not be mixed with other medicinal products. A pre-existing intravenous line may be used for administration of diluted spesolimab infusion solution, if the compatibility information above is considered. The line must be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection prior to and at the end of infusion. No other infusion should be administered in parallel via the same intravenous access.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

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Germany

for

Boehringer Ingelheim International GmbH
Ingelheim am Rhein
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8. PRODUCT REGISTRATION NUMBER

SINXXX

9. DATE OF REVISION

09 October 2023