swissmedic

Date: 7 August 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Spevigo

International non-proprietary name: spesolimab

Pharmaceutical form:	solution for injection in pre-filled syringe
Dosage strength(s):	150 mg/1ml
Route(s) of administration:	subcutaneous use
Marketing authorisation holder:	Boehringer Ingelheim (Schweiz) GmbH
Marketing authorisation no.:	69579
Decision and decision date:	approved on 28 May 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SOC	System Organ Class
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension of the therapeutic indication
The applicant requested the addition of a new therapeutic indication with a new administration route in accordance with Article 23 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA. Orphan drug status was granted on 10 January 2022

2.2 Indication and dosage

2.2.1 Requested indication

Spevigo is indicated for the prevention of flares in adults and adolescents aged 12 years or older with generalised pustular psoriasis.

2.2.2 Approved indication

Spevigo solution for subcutaneous injection in pre-filled syringe is indicated for the prevention of flares in adults and adolescents aged 12 years or older and weighing at least 40 kg with generalised pustular psoriasis.

2.2.3 Requested dosage

Spevigo solution for injection in pre-filled syringe is administered as a subcutaneous injection. The recommended dose of Spevigo is a single dose of 600 mg (4 pre-filled syringes of 150 mg each), followed by a dose of 300 mg (2 pre-filled syringes of 150 mg each) every 4 weeks. Flares during subcutaneous treatment should be treated with Spevigo, concentrate for solution for infusion.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	2 October.2023
Formal objection	25 October 2023
Response to formal objection	28 November 2023
Formal control completed	18 December 2023
List of Questions (LoQ)	4 April 2024
Response to LoQ	2 July 2024
Preliminary decision	15 October 2024

Response to preliminary decision	13 December 2024
Labelling corrections and/or other aspects	11 March 2025
Response to labelling corrections and/or other aspects	15 April 2025
Final decision	28 May 2025
Decision	approval

3 Medical context

Generalised pustular psoriasis (GPP) is a rare, severe, and potentially life-threatening neutrophilic skin disease characterised by widespread sterile pustules and systemic inflammation. Patients with GPP often experience systemic symptoms such as high fever, fatigue, and elevated acute-phase markers such as C-reactive protein (CRP). GPP flares can lead to serious complications, including multi-organ failure (e.g., acute respiratory distress syndrome, liver/kidney failure, cardiovascular shock) and sepsis. The disease can manifest at any age, with a median diagnosis age of 50 years, and is more prevalent in females. Early-onset GPP is often associated with mutations in the IL36RN gene.

The global prevalence of GPP is low, ranging from 1–7 cases per million in most regions, but higher rates are observed in specific countries, such as Italy (180 cases per million) and Korea (88–124 cases per million). Currently, there are no specific licensed treatments for GPP in Switzerland, and off-label use of psoriasis medications (e.g., acitretin, methotrexate, ciclosporin, and topical corticosteroids) is common. This points to a significant unmet medical need for effective treatments that can resolve the symptoms of GPP and prevent flare recurrences while maintaining an acceptable safety profile.

Spevigo (spesolimab) is a humanised, antagonistic monoclonal IgG1 antibody that inhibits the human IL-36 receptor pathway (IL-36R), which plays a relevant role in the pathogenesis of GPP. Spesolimab was granted orphan drug status for GPP on 10 January 2022. On 9 August 2023, temporary marketing authorisation was granted for Spevigo (spesolimab) i.v. for the treatment of GPP flares in adults.

4 Quality aspects

4.1 Drug substance

No change to the initial description (see Spevigo concentrate for solution for infusion SwissPAR; date: 7 December 2023)

4.2 Drug product

Spesolimab solution for injection in pre-filled syringe (PFS) 150 mg/syringe (150 mg/mL) is a colourless to slightly brownish-yellow, clear to slightly opalescent solution. The spesolimab solution for injection is presented in a pre-filled syringe (incl. needle and rigid needle shield) and plunger stopper. The PFS is assembled with a needle safety device (NSD).

The excipients – sodium acetate trihydrate, glacial acetic acid, sucrose, arginine hydrochloride, polysorbate 20, and water for injection – are of compendial grade and commonly used for the formulation of biopharmaceuticals.

The materials of the type I glass syringe barrel and rubber stopper meet compendial requirements.

The PFS is stored at 2°C to 8°C protected from light. The stability data support a shelf life of 24 months including 14 days at up to 25°C (77°F) prior to administration.

4.3 Quality conclusions

No change to the initial description of the drug substance (see Spevigo concentrate for solution for infusion SwissPAR; date: 7 December 2023)

Satisfactory and consistent quality of the drug product have been demonstrated.
Safety of the product with regard to viral and non-viral contaminants is adequately addressed.

5 Nonclinical aspects

The applicant did not submit any new nonclinical studies to support the extension of the indication and new pharmaceutical form, which is considered acceptable. From the nonclinical point of view, there are no objections to the approval of the extension of the indication (for the concentrate for solution for infusion) and the new pharmaceutical form for the requested indication.

6 Clinical aspects

6.1 Clinical pharmacology

The new indication of GPP prevention with s.c. administration in adults and adolescents was supported by an updated PopPK and exposure response analysis with new PK data from the pivotal and supportive trials for prevention of GPP as well as new PK data from studies in other indications.

The PK of spesolimab following s.c. administration has been sufficiently characterised in healthy subjects and the intended adult patient population. A PopPK model that is considered adequate for simulations of expected exposures in adolescents has been developed. Due to the dependence of spesolimab exposure on body weight, adolescent subjects, especially at the lower end of the body weight range, are expected to have higher exposures compared to adults, as has been confirmed in a small number of adolescents. These elevated exposures are also expected in adults in the low body weight range (40-60 kg).

6.2 Dose finding and dose recommendation

Dose finding and efficacy of Spevigo was evaluated in one pivotal study (Effisayil 2, study 1368-0027). This was a phase 2b, randomised, double-blind, placebo-controlled trial to evaluate three dosing regimens of spesolimab in preventing GPP flares. Given the rarity of disease and robust design, it is considered acceptable to evaluate dose finding and efficacy in single trial

6.3 Efficacy

The Effisayil 2 study was designed to include patients aged 12–75 years, with minimum weight of 40 kg and a history of GPP based on European Rare and Severe Psoriasis Expert Network (ERASPEN) diagnostic criteria and a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of 0 or 1 (clear/almost clear). A total of 123 patients were randomized 1:1:1:1 to the following spesolimab dosing regimens:

- High dose (30 patients): 600 mg loading dose followed by 300 mg every 4 weeks (q4w)
- Medium dose (31 patients): 600 mg loading dose followed by 300 mg every 12 weeks (q12w)
- Low dose (31 patients): 300 mg loading dose followed by 150 mg q12w
- Placebo (31 patients)

Patients who were on concomitant treatment with retinoids and/or methotrexate and/or cyclosporine had to stop this treatment from the day of randomisation (V2). In the event of a GPP flare (increase in GPPGA score by ≥2 from baseline and a pustular component of GPPGA >2), patients received an open-label (OL), intravenous spesolimab rescue treatment of up to two doses of spesolimab i.v. 900 mg one week apart. The baseline parameters of study participants are given in the Information for healthcare professionals.

The primary objective of the trial was to demonstrate a non-flat dose response curve and the dose-response relationship for 3 subcutaneous dosing regimens of spesolimab versus placebo, on the primary endpoint (time to first GPP flare onset up to week 48). The secondary objective was to test the superiority of each spesolimab dose versus placebo on the primary endpoint.

The primary objective was achieved, with the linear model showing the best fit within prespecified monotone response patterns (linear, Emax1, Emax2 and exponential). Only the high-dose regimen demonstrated statistically significant efficacy at the primary endpoint (time to first GPP disease flare), with a hazard ratio (HR) of 0.157 compared to placebo, and key secondary endpoint (the occurrence of at least one GPP disease flare by week 48). Further secondary endpoints did not reach statistical significance. Subgroup analyses indicated consistent efficacy across most groups, though no effect

was found in patients aged ≥65 years and those without prior systemic GPP treatment, likely due to small sample sizes.

The flare rates of the study participants under spesolimab s.c. were also numerically lower than the annual pre-study flare rates under the off-label therapies (acitretin, methotrexate, ciclosporin). The extension study (OLE 1368-0025) supported the long-term efficacy of the high-dose regimen, with a yearly flare rate of 0.11.

ADA and NAb do not seem to have a negative effect on the efficacy of the high dose subcutaneous (loading dose 600 mg s.c., 300 mg s.c. q4w) schedule.

A total of 32 adult patients received OL spesolimab i.v. 900 mg as a rescue treatment for GPP flare (day 1). Of them, 2 patients had previously received the high dose s.c. regimen. Of the 32 patients, 10 received an additional OL spesolimab i.v. 900 mg (day 8). The baseline for the analyses of flare treatment response was the last assessment before the first rescue treatment. By week 1 (day 8), 55.4% of patients achieved a partial response (defined as a reduction in GPPGA score or pustule sub-score). By week 12, 12 of 32 patients (37.5%) achieved a full response (GPPGA total score of 0 or 1), thus meeting the criteria used for initial approval. This efficacy of spesolimab in combined s.c. prophylactic and i.v. flare treatment is numerically lower than i.v. flare treatment alone in the initial approval, but still acceptable.

Although 8 adolescents were included in the study, none of them developed flares during s.c. prophylactic treatment with spesolimab. Thus, no data are available for adolescents, treated with OL spesolimab i.v. 900 mg in addition to prophylactic treatment with spesolimab s.c. Simulations suggest higher drug exposure in adolescents with a lower body weight, which raises safety concerns. Thus, an indication extension of flare treatment in adolescents is not supported.

6.4 Safety

The safety database in the proposed indication extension is based on the results of the pivotal phase 2b study (Effisayil 2). Additional available data from the non-randomised open label extension study (OLE 1368-0025) are also included. Overall, the safety database contains data from studies in other indications as well, which are relevant for rare adverse events of special interest.

The safety analyses of the pivotal study focus on a comparison of treatment groups during randomised s.c. prophylactic treatment, for which AE data were censored at first administration of OL spesolimab i.v. for flare treatment. To capture events in patients who received OL spesolimab i.v., AEs are displayed post any spesolimab treatment as well.

The mean (SD) duration of exposure to randomised prophylactic treatment was 25.4 (20.8) weeks for placebo, 33.9 (18.2) weeks for spesolimab low-dose, 31.9 (18.5) weeks for spesolimab medium-dose, and 33.1 (18.2) weeks for spesolimab high-dose.

At the SOC level, the highest proportion of patients with AEs in all treatment groups was in the SOC “skin and subcutaneous tissue disorders”, followed by “infections and infestations” and “general disorders and administration site conditions”. Pustular psoriasis was the most frequently reported AE (24.7% in all spesolimab groups vs. 53.3% in the placebo group), reflecting disease flares. The lowest incidence in the high-dose group further supports the efficacy of the high-dose regimen (10.0%, 32.3%, and 31.3% in the high, medium, and low dose groups, respectively).
Psoriasis vulgaris occurred at similar rates across all groups, indicating no effect on plaque psoriasis. Infections were common but not clearly dose-dependent, except for urinary tract infections (UTIs), which were more frequent in the high-dose group (13.3%). The most frequent AEs in the SOC “general disorders and administration site conditions” were injection site erythema (more common with high-dose) and pyrexia.

Serious adverse events (SAEs) occurred in 9.7% of spesolimab-treated patients versus 3.3% in the placebo group. Notable SAEs included pustular psoriasis (1 high-dose, 1 medium-dose), pneumonia (low-dose), bacterial skin infection (medium-dose) and one case of breast cancer (high-dose).

In patients treated with i.v. in addition to prophylactic spesolimab s.c., the incidence of infections increased, particularly UTIs (9.3% vs. 5.4% during the randomised phase). Severe infections, including septic shock and pneumonia, were also reported. This indicates, that the combination of subcutaneous prophylaxis and i.v. flare treatment may further elevate the risk of infection due to higher drug exposure. Furthermore, one additional malignancy (basal cell carcinoma) was observed following i.v. treatment.

Due to its immunosuppressive nature, there is a general concern that spesolimab may have the potential to cause malignancy. This is supported by the development of two malignancies (breast cancer, basal cell carcinoma) in the pivotal study, as well as additional cases in OLE study (1368-0025) and in non-GPP trials. Further safety concerns include severe cutaneous adverse reactions (SCARs), of which two cases of drug reaction with eosinophilia and systemic symptoms (DRESS) were reported in earlier GPP studies. In addition, three cases of Guillain-Barré syndrome (GBS) were observed in non-GPP trials, which raises concerns about neurological risks.

Eight adolescents participated in the prophylactic study. The overall AE rate was not higher than in adults, but infections were more frequent (50% vs. 33.3% in adults). One adolescent experienced a serious pneumonia event. No clinical data exist in adolescents for i.v. flare treatment in addition to the prophylactic s.c. treatment, which is expected to result in a higher drug exposure leading to safety concerns. Lack of clinical data precludes any conclusions regarding the safety profile in adolescents.

6.5 Final clinical benefit risk assessment

The high-dose subcutaneous regimen (600 mg loading dose, 300 mg q4w) demonstrated robust efficacy in preventing GPP flares. While safety concerns exist, particularly regarding infections and malignancies, the benefits of prophylactic treatment outweigh the risks for adults and adolescents aged 12–17 years who weigh at least 40 kg. However, the i.v. flare treatment indication cannot be extended to adolescents due to the lack of clinical data and safety concerns. In particular infections occurred more frequently in adolescents, that could be related to the expected higher systemic exposure.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Spevigo solution for injection in pre-filled syringe was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.
Spevigo has temporarily authorised indications – see "Indications/Uses" section.

Spevigo®

Composition

Active substances

Spesolimab (manufactured from genetically modified CHO [Chinese Hamster Ovary] cells)

Excipients

Solution for injection in pre-filled syringe
Each syringe contains: sodium acetate trihydrate (corresp. 0.91 mg sodium), glacial acetic acid, saccharose, arginine hydrochloride, polysorbate 20, water for injection ad solutionem pro 1 mL.

Concentrate for solution for infusion
Each vial contains: sodium acetate trihydrate (corresp. 6.8 mg sodium), glacial acetic acid, saccharose, arginine hydrochloride, polysorbate 20, water for injection ad solutionem pro 7.5 mL.

Pharmaceutical form and active substance quantity per unit

Solution for injection in pre-filled syringe: one syringe with 1 mL contains 150 mg spesolimab
Concentrate for solution for infusion: one vial with 7.5 mL contains 450 mg spesolimab

Indications/Uses

Concentrate for solution for infusion
Temporarily authorised indication
Spevigo concentrate for solution for infusion is indicated for the treatment of flares in adult patients with generalized pustular psoriasis. Spevigo concentrate for solution for infusion is used as a monotherapy.
This indication has been granted temporary authorisation as the clinical data were incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is

contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an authorisation without special conditions.

Solution for injection in pre-filled syringe
Indication with non-limited authorisation
Spevigo solution for injection in pre-filled syringe subcutaneous is indicated for the prevention of flares in adults and adolescents from 12 years of age and weighing at least 40 kg with generalized pustular psoriasis.

Dosage/Administration

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

Spevigo treatment can be initiated with the Spevigo pre-filled syringe as a subcutaneous injection to prevent GPP flares or with an intravenous dose of Spevigo (only in adults) to treat a GPP flare.

Spevigo solution for injection in pre-filled syringe is only intended for subcutaneous use for GPP flare prevention in adults and adolescents from 12 years of age and weighing at least 40 kg.
Spevigo concentrate for solution for infusion is only intended for intravenous use for GPP flare treatment in adults.

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.

Dosage
Recommended dose for GPP flare prevention in adults and adolescents from 12 years of age and weighing at least 40 kg
The recommended dose of Spevigo solution for injection in pre-filled syringe for GPP flare prevention in adults and adolescents from 12 years of age and weighing at least 40 kg is a subcutaneous loading dose of 600 mg (four 150 mg injections), followed by 300 mg (two 150 mg injections) administered subcutaneously every 4 weeks.

Spevigo has not been studied in patients weighing less than 40 kg. No dose recommendations can be made (see section Pharmacokinetics).

<u>GPP flare treatment during subcutaneous GPP prevention treatment in adults:</u>

If an adult patient experiences a GPP flare while receiving subcutaneous Spevigo, the GPP flare may be treated with intravenous Spevigo (see section *Recommended dose for GPP flare treatment in adults*).

Initiating or reinitiating subcutaneous GPP prevention treatment after intravenous GPP flare treatment in adults:

Four weeks after treatment with intravenous Spevigo in adults, subcutaneous Spevigo can be initiated or reinitiated at a dose of 300 mg (two 150 mg injections) administered every 4 weeks. A subcutaneous loading dose is not required.

Missed subcutaneous dose in GPP flare prevention

If a subcutaneous dose is missed, the subcutaneous dose should be administered as soon as possible. Thereafter, dosing should be resumed at the regular scheduled time.

Recommended dose for GPP flare treatment in adults

The recommended dose of Spevigo solution for infusion to treat a GPP flare is a single dose of 900 mg (two 450 mg/7.5 ml vials) administered as an intravenous infusion.

If flare symptoms persist, an additional 900 mg dose (two 450 mg/7.5 ml vials) may be administered 1 week after the initial dose.

Clinical data for treatment of subsequent flares is very limited (see section “Warnings and precautions”).

Special dosage instructions

Patients with impaired hepatic or renal function

Spevigo has not been formally studied in these patient populations. However, these conditions are not expected to have any clinically relevant impact on the pharmacokinetics of Spevigo and no dose adjustments are considered necessary.

Elderly patients

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

Children and adolescents

The safety and efficacy of Spevigo solution for injection in pre-filled syringe subcutaneous have been studied for the preventive treatment of GPP in adolescents with GPP aged 12 years and older and

weighing at least 40 kg (see section Clinical Trials). There are no data on the use of Spevigo solution for infusion for the treatment of GPP flares in adolescents aged 12 to 17 years.There are no clinical data in children below the age of 12 years and GPP patients weighing less than 40 kg. There is no relevant use of spesolimab in children below the age of 12 years.

Mode of administration

Spevigo solution for injection in pre-filled syringe

The injection should be administered subcutaneously in the upper thighs or abdomen (see section Handling Instructions). Spevigo pre-filled syringe should not be injected into areas where the skin is tender, bruised, erythematous, indurated, or scarred.

If a 600 mg subcutaneous loading dose of Spevigo is needed (see section Dosage), the loading dose should be administered by a healthcare professional. A different injection site should be chosen for each injection, at least 2 cm away from the other injection sites.

For the subsequent subcutaneous 300 mg doses of Spevigo, if the healthcare professional determines that it is appropriate, patients may self-inject or caregivers may administer the Spevigo pre-filled syringe after proper training in subcutaneous injection technique.

For a complete 300 mg dose, two 150 mg/mL pre-filled syringes are required to be injected, one right after the other. A different injection site should be chosen for each of the two injections, at least 2 cm away from the other injection site. [2, 3]

Spevigo solution for infusion

Spevigo concentrate for solution for infusion must be diluted before use (see section “Instructions for 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 µm) 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 “Warnings and Precautions”).

Contraindications

Severe or life-threatening hypersensitivity to the active substance or to any of the excipients.
Reported hypersensitivity reactions included drug reactions with eosinophilia and systemic symptoms (DRESS) (see section “Composition” and “Warnings and Precautions”).
Clinically important active infections (e.g. active tuberculosis).

Warnings and precautions

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 “Undesirable effects”).
During the placebo-controlled period of up to 48 weeks in Effisayil 2, infections were reported in 33.3% of adults and adolescents from 12 years of age with at least 40 kg body weight treated with Spevigo subcutaneous and 33.3% of patients treated with placebo. A further numerical increase in all infections was observed after additional open-label administration of spesolimab 900 mg intravenously for flare treatment in 46 patients, 43.0% over the entire study period.
In particular, urinary tract infections were observed in 13.3% (n=4) after subcutaneous administration of spesolimab at the approved dose. After the additional open-label administration of spesolimab 900 mg intravenously, urinary tract infections occurred in 9.3% (10 patients) across all subcutaneous dosing regimens (including 1 life-threatening urinary tract infection). In Effisayil 2, serious infections occurred in 3 patients (3.2%) in the Spevigo group and in no patient in the placebo group. In adolescent GPP patients (n=8) aged at least 12 years and weighing at least 40 kg, 4 out of 6 patients (66%) treated with Spesolimab experienced increased infections (pneumonia, boils/folliculitis, upper respiratory tract infections). A Covid-19 infection occurred in 1 of 2 patients (50%) treated with placebo during preventive subcutaneous treatment of GPP. 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 during or after treatment with Spevigo.

If a patient is on treatment with Spevigo subcutaneous injection for GPP flare prevention, and develops a clinically important active infection, treatment with Spevigo should be stopped. Re-initiation can be considered once the infection resolves or is adequately treated.

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. During or 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). In clinical studies with Spevigo, drug reactions with eosinophilia and systemic symptoms (DRESS) have been reported in patients with GPP.

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

If an adult patient develops mild or moderate hypersensitivity during an intravenous infusion or other 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 “Dosage/Administration”).

Use in patients with an immediate, life-threatening GPP flare
There is no experience from the use of spesolimab in patients with an immediate, life-threatening flare of GPP or a flare requiring intensive care treatment.

Concomitant use with other GPP treatments
The safety and efficacy of spesolimab in combination with immunosuppressants, including biologics, have not been evaluated systematically. In the GPP flare treatment clinical study, there was a washout period for most other treatments (biologics, other systemic immunomodulating treatments),

while some treatments were discontinued before initiation of spesolimab treatment with no washout period required (methotrexate, cyclosporine, retinoids, topical treatments) (see “Clinical efficacy”). Concomitant use of other immunosuppressants and spesolimab is not recommended. At initiation of spesolimab treatment, other GPP treatments should be stopped and other treatments (e.g. with systemic immunosuppressants) should not be used concomitantly to treat the flare.

Re-treatment with Spesolimab intravenous in adults
Very limited efficacy and safety data are available for re-treatment with spesolimab intravenous in adults with a subsequent new flare. Data are available for five patients with GPP who received re-treatment at a subsequent new flare and were followed up for a minimum of 8 weeks.

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 during and for at least 16 weeks after treatment with Spevigo.

Prior to initiating Spevigo for GPP flare prevention, completion of all appropriate immunisations should be considered according to current immunisation guidelines.

Tumor diseases
A theoretical risk of malignancy exists for Spesolimab as for any immune-modulating biologic medication. The impact of inhibition of the interleukin-36 pathway on the risk of malignancy is not established to date.

Peripheral neuropathy / Guillain-Barre-Syndrom (GBS)
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. Among approximately 835 subjects exposed to spesolimab during clinical development, Guillain-Barre syndrome (GBS) was reported in 3 subjects who received various doses of spesolimab-sbzo via various methods of administration in clinical studies for unapproved indications.

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

Polysorbate 20

Concentrate for solution for infusion

This medicine contains 3 mg of polysorbate 20 in each 7.5 ml vial. Polysorbates may cause allergic reactions.

Solution for injection in pre-filled syringe

This medicine contains 0.4 mg of polysorbate 20 in each 1 ml pre-filled syringe. Polysorbates may cause allergic reactions.

Interactions

Live vaccines should not be given concurrently with Spevigo (see section “Warnings and Precaution”).

Pharmacokinetic interactions

No interaction studies have been performed. In GPP patients, spesolimab is not expected to cause cytokine-mediated CYP interactions as a perpetrator.

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

Pregnancy, 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 “Preclinical data”). As a precautionary measure, the use of Spevigo should be avoided during pregnancy.

Lactation

No data are present on excretion of spesolimab in human milk. In humans, excretion of IgG antibodies in milk occurs during the first few days after birth, which is decreasing to low concentrations soon afterwards. Consequently, transfer of IgG antibodies to the newborns through milk, may happen during the first few days. In this short period, a risk to the breastfed child cannot be excluded. Afterwards, spesolimab can be used during breastfeeding if clinically needed. When treatment has occurred up to the last few months of pregnancy, breastfeeding can be started immediately after birth.

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.

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile for the treatment of GPP flares in adults with Spevigo i.v. (Effisayil 1 study)

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

The following adverse reactions are arranged according to MedDRA system organ classes and the conventional frequencies as follows:
"very common" (≥1/10)
"common" (≥1/100, <1/10),
"uncommon" (≥1/1,000, <1/100)
"rare" (≥1/10,000, <1/ 1,000)
"very rare" (<1/10,000)
"not known" (frequency cannot be estimated from the available data)

Infections and infestations
Very Common infection (17.1%)[a]

Skin and subcutaneous tissue disorders
Common pruritus
Two cases of DRESS were reported in Study Effisayil-1 in patients with GPP who were treated with intravenous SPEVIGO. RegiSCAR DRESS validation scoring (with the following categories: “no”, “possible”, “probable”, or “definite” DRESS) was applied to the reported cases. Reported cases were assessed as “no DRESS” and “possible DRESS ”.

General disorders and administration site conditions

Common:	fatigue
Not known	injection site reactions[b]

[a] The most commonly reported infections are urinary tract infection (common) and upper respiratory tract infection (common).

[b] Not reported in Effisayil 1

Additional adverse reactions that occurred through Week 17 in adult subjects treated with a single intravenous dose of open-label Spevigo at Week 1 (second dose and first dose for subjects in the Spevigo and placebo groups, respectively) were mild to moderate infections: otitis externa (7%), vulvovaginal candidiasis (4%), vulvovaginal mycotic infection (4%), latent tuberculosis (4%), diarrhea (11%), and gastritis (4%). No new adverse reactions were identified for up to 16 weeks in subjects treated with a single intravenous dose of Spevigo from Week 1 to Week 12 (range 1-3 total doses).

Summary of the safety profile of the prophylactic treatment of GPP in adolescents aged 12 years and older and adults with Spevigo subcutaneously (Effisayil-2 study)

Subcutaneous treatment with Spevigo was studied in the Effisayil-2 study, a randomized, placebo-controlled, double-blind, parallel-group study evaluating three subcutaneous doses of Spevigo or placebo in patients with generalized pustular psoriasis (GPP). Subjects were randomized (1:1:1:1) to receive a loading dose (LD) of 600 mg Spevigo, followed by 300 mg every 4 weeks (n=30) one of two other subcutaneous dosages of Spevigo or placebo (n=30) for up to 48 weeks (see Properties/Effects).

Subjects ranged in age from 14 to 75 years (mean age was 40 years); 64% of subjects were Asian and 36% Caucasian; 62% of subjects were female. Patients with a manifest tumor disease up to 5 years before study entry (except for adequately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix) and congestive heart failure were excluded from the Effisayil-2 study.

The following adverse reactions are arranged according to MedDRA system organ classes and the conventional frequencies as follows:

"very common" (≥1/10)

"common" (≥1/100, <1/10),

"uncommon" (≥1/1,000, <1/100)

"rare" (≥1/10,000, <1/ 1,000)

"very rare" (<1/10,000)

"not known" (frequency cannot be estimated from the available data)

Infections and infestations

Common Upper respiratory tract infection, Urinary tract infection, COVID-19

General disorders and administration site conditions

Very common Injection site erythema (14,0%)

Musculoskeletal and connective tissue disorders

Common Arthralgia

Skin and s.c. tissue disorders

Very common Psoriasis (14.0%)

For subjects on randomized treatment prior to receiving rescue treatment for flare or completing trial without flare, there were 3 subjects who discontinued subcutaneous spevigo in the subcutaneous spevigo cohort (600 mg LD followed by 300 mg every 4 weeks) due to treatment emergent adverse events of psoriasis compared to no subjects in the placebo cohort who discontinued placebo for any treatment emergent adverse event.

Description of specific adverse reactions and additional information

Infections

The most frequent adverse reactions that occurred in subjects treated with Spevigo were 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. In Effisayil 1, serious infection (urinary tract infection) was reported in 1 patient (2.9%) treated with Spevigo intravenous and no patients treated with placebo.

During the placebo-controlled period of up to 48 weeks in Effisayil 2, infections were reported in 33.3% of the adults and adolescents from 12 years of age with at least 40 kg body weighttreated with Spevigo subcutaneously and 33.3% of patients treated with placebo. A further numerical increase in all infections was observed after additional open-label administration of spesolimab 900 mg intravenously for flare treatment in 46 patients, 43.0% over the entire study period. In particular, urinary tract infections were observed in 13.3% (n=4) after subcutaneous administration of spesolimab at the approved dose. After additional open-label administration of spesolimab 900 mg intravenously, urinary tract infections occurred in 9.3% (n=10) of all subcutaneous dosing regimens (including 1 life-threatening urinary tract infection). The average duration of therapy for urinary tract infections was 8 days. In Effisayil 2, serious infections were reported in 3 patients (3.2%) in the Spevigo group and no patient in the placebo group.

In adolescent GPP patients aged at least 12 years and weighing at least 40 kg, 4 out of 6 patients (66%) treated with Spesolimab experienced increased infections (pneumonia, boils/folliculitis, upper

respiratory tract infections). A Covid-19 infection occurred in 1 out of 2 patients (50%) treated with placebo during preventive subcutaneous treatment of GPP.
Infections observed in clinical trials with spesolimab were with no distinct pattern regarding pathogen or infection type and included also life-threatening infections such as septic shock, pneumonia or life-threatening urinary tract infectionsInfections observed in clinical trials with spesolimab were with no distinct pattern regarding pathogen or infection type and included also life-threatening infections such as septic shock, pneumonia or life-threatening urinary tract infections.

Tumor diseases
A theoretical risk of malignancy exists for Spesolimab as for any immune-modulating biologic medication. The impact of inhibition of the interleukin-36 pathway on the risk of malignancy is not established to date.

Injection site reactions
During clinical development, injection site reactions (including erythema, swelling, pain, induration, warmth, exfoliation, papule, pruritus, rash, and urticaria at the injection site) occurred with spesolimab. 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 intravenous spesolimab 900 mg, 46% of patients were ADA-positive and 24% of patients had a maximum ADA titer greater than 4 000. A total of 40% of patients developed Neutralising antibody (Nab)-positive by end of the trial (Weeks 12 to 17). In Effisayil 2, anti-drug antibodies (ADA, 46.2%) formed with a median onset of 8 weeks. Of these, 43.0%were Nab. Following administration of a 600 mg subcutaneous loading dose of spesolimab followed by 300 mg spesolimab subcutaneously every 4 weeks for a total duration of 48 weeks, 24.1% of patients with the approved dose had a maximum ADA titer greater than 4 000 and were Nab-positive.

In Effisayil 1, following intravenous spesolimab, females appeared to have higher immunogenicity response; the percentage of patients with positive ADAs were 58% in females compared with 24% in males. Maximum ADA titer greater than 4 000 was 30% in females, and 12% in males, respectively. In Effisayil 2, following administration of subcutaneous spesolimab, the data on immunogenicity response in males versus females were inconclusive.

In some ADA-positive patients, plasma spesolimab concentrations were reduced with larger effect seen at higher titers. In the presence of ADA, efficacy was observed upon re-treatment of subsequent flares with Spevigo in an open label extension trial. In patients receiving the recommended Spevigo dose in Effisayil 2 (see section Clinical Trials), there was no apparent impact of ADA presence on efficacy.

There was no apparent correlation between the presence of ADA to spesolimab and hypersensitivity reactions.

Paediatric population
The available data for adolescents with subcutaneous use are limited (see section Clinical Trials). There are no data on the use of intravenous spesolimab for flares treatment in GPP (see indications/uses). Based on the limited number of treated adolescent patients, infections were detected more frequently (in 4 out of 6 adolescents treated with spesolimab, 66%) compared to adults.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no clinical experience with overdoses of Spevigo.
The highest dose of Spevigo administered in clinical trials was 1200 mg intravenously or subcutaneously. 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.

Properties/Effects

Pharmacotherapeutic group:

Immunosuppressants, Interleukin inhibitors

ATC code

L04AC22

Mechanism of action

Spesolimab is a humanised antagonistic monoclonal immunoglobulin G1 (IgG1) antibody blocking human interleukin 36 receptor (IL36R) signalling. Binding of spesolimab to IL36R prevents the subsequent activation of IL36R by its ligands (IL36 α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways. The precise mechanism linking reduced IL36R activity and the treatment of flares of GPP is unclear.

Pharmacodynamics

Following treatment with intravenous 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 markers, neutrophilic mediators, and proinflammatory cytokines were observed in serum and skin at Week 1 compared to baseline and were 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

Effisayil 1 (1368.13) Spevigo intravenous in adult patients
A randomised, double-blind, placebo-controlled study (Effisayil-1) was conducted to evaluate the clinical efficacy and safety of Spevigo intravenous 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. Patients with an immediate life-threatening flare of GPP or requiring intensive care treatment were excluded from the study.

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.

A total of 53 adult 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 flare 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 1).

Table 1 GPPGA Pustulation Sub Score and GPPGA Total Score at Week 1 (Effisayil 1, adult patients with Spevigo intravenous)

	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 randomised to Spevigo intravenous, 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 .

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 acknowledging the small sample sizes.

Effisayil 2 (1368.27) Spevigo subcutaneous in adults and adolescents from 12 years of age and weighing at least 40 kg

A randomised, double-blind, placebo-controlled phase II b study (Effisayil 2) evaluated the efficacy and safety of Spevigo for subcutaneous administration in adult and adolescent patients from 12 years of age and weighing at least 40 kg with a history of GPP, as diagnosed per ERASPEN criteria, regardless of IL36RN mutation status, and with at least two GPP flares of moderate-to-severe intensity in the past. Patients were randomised if they had a GPPGA total score of 0 or 1 at screening and randomisation. Patients were required to discontinue systemic and topical therapy for GPP prior to or at randomisation. These patients must have had a history of flaring while on concomitant treatment for GPP or a history of flaring upon dose reduction or discontinuation of these concomitant medications. Patients with manifest tumor disease up to 5 years prior to study entry (except for adequately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix) and congestive heart failure were excluded from the Effisayil-2 study.

The primary endpoint of the study was the time to the first GPP flare up to Week 48 (defined by a GPPGA pustulation subscore of > 2 and an increase in GPPGA total score by ≥ 2 from baseline). The key secondary endpoint of the study was the occurrence of at least one GPP flare up to Week 48.

A total of 123 patients were randomised (1:1:1:1) to receive one of the four subcutaneous treatments (see Table 2).

Table 2 Treatment arms in Effisayil 2

	Loading dose	*Subsequent doses*
Spevigo	600 mg subcutaneously	300 mg subcutaneously every 4 weeks
Spevigo	600 mg subcutaneously	300 mg subcutaneously every 12 weeks
Spevigo	300 mg subcutaneously	150 mg subcutaneously every 12 weeks
Placebo	subcutaneous treatment	subcutaneous treatment every 4 weeks

In the Effisayil-2 study, a subcutaneous loading dose of Spevigo 600 mg followed by a subcutaneous dose of Spevigo 300 mg every 12 weeks, and a subcutaneous loading dose of Spevigo 300 mg followed by a subcutaneous dose of Spevigo 150 mg every 12 weeks, were also studied, but these other subcutaneous doses are not approved. The recommended dose of Spevigo subcutaneously for

the treatment of GPP in the absence of disease flare is a 600 mg subcutaneous loading dose followed by 300 mg subcutaneously administered every 4 weeks (see Dosage and administration section). The study population consisted of 38.2% men and 61.8% women. The mean age was 40.4 (range: 14 to 75) years with 8 (6.5%) adolescent patients (2 per treatment arm aged 14 to 17 years); 64.2% of patients were Asian and 35.8% were Caucasian. Patients included in the study had a GPPGA pustulation sub score of 1 (28.5%) or 0 (71.5%), and patients had a GPPGA total score of 1 (86.2%) or 0 (13.8%). At the time of randomisation, 74.8% of patients were treated with systemic therapy for GPP, which was discontinued at the start of the randomised study treatment.

The results summarised below are those for the approved dosing regimen with a 600 mg subcutaneous loading dose followed by 300 mg subcutaneously every 4 weeks (see section "Dosage and administration").

Patients who experienced a flare despite prophylactic therapy were eligible to receive up to two open-label, intravenous doses of 900 mg Spevigo (see section Dosage and Administration). 2 (6.7%) patients in the Spevigo arm for the approved dose with a 600 mg subcutaneous loading dose, followed by 300 mg subcutaneously and 15 (48.4%) patients in the placebo arm received intravenous flare treatment. There are no data with intravenous treatment for GPP disease flare in the 12 to 17 year age group that met the criteria defined in the study protocol (see indications/uses).

Treatment with the recommended Spevigo dose compared to placebo resulted in statistically significant improvement based on the primary and key secondary endpoint (see Table 3).

Table 3 Time to the first GPP flare and occurrence of at least one GPP flare up to Week 48 (Effisayil 2)

	Placebo	Recommended subcutaneous Spevigo dose
Number of patients analyzed, N	31	30
Patients with GPP flares, N (%)*	16 (51.6)	3 (10.0)
Hazard ratio (HR)** for the time to the first flare vs placebo (95% CI)	0.157 (0.046, 0.541)	
p-value***	0.0005	
Risk difference for GPP flare occurrence vs placebo (95% CI)	-39.0% (-62.1, -15.9)	
p-value****	0.0013	

*The use of intravenous Spevigo treatment or investigator-prescribed standard of care to treat GPP worsening were considered as onset of GPP flare

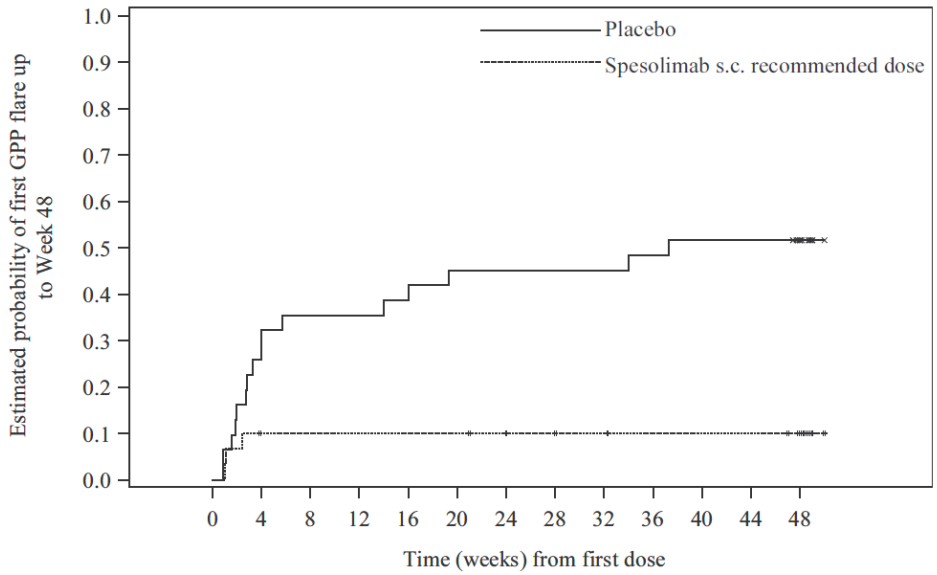
**Cox regression model stratified by the use of systemic GPP medications at randomisation

***Log-rank test stratified by the use of systemic GPP medications at randomisation, one-sided p-value

****Cochran-Mantel-Haenszel test after multiple imputation, stratified by the use of systemic GPP medications at randomisation, one-sided p-value

The efficacy of the subcutaneous recommended Spevigo dose compared with placebo was observed shortly after randomisation and was maintained up to Week 48 (see Figure 1).

Figure 1 Time to the first GPP flare up to Week 48 (Effisayil 2) in adults and adolescent subjects (12 years and older and weighing at least 40 kg)



Patients at risk													
Placebo	31	23	20	20	19	17	17	17	17	16	15	15	11
Spesolimab s.c. recommended dose	30	26	26	26	26	26	25	24	23	22	22	22	18

The results of the primary and key secondary endpoints were generally consistent across subgroups including sex, age, race, BMI, body weight, mutation status in IL36RN, concurrent plaque psoriasis, GPPGA total score at baseline, and irrespective of any systemic GPP treatment at randomisation.

Pharmacokinetics

Absorption

A population pharmacokinetic model was developed based on data collected from healthy subjects, patients with GPP and patients with other diseases. After a single intravenous dose of 900 mg, the population PK model-estimated AUC0-∞ (95% CI) and Cmax (95% CI) in a typical ADA-negative patient with GPP were 4 750 (4 510, 4 970) µg*day/mL and 238 (218, 256) µg/mL, respectively. After a 600 mg subcutaneous loading dose of spesolimab followed by 300 mg spesolimab subcutaneously every 4 weeks, the mean steady-state trough concentration ranged from 33.4 µg/mL to 42.3 µg/mL.

Following subcutaneous single dose administration of spesolimab in healthy volunteers, peak plasma

concentrations were achieved between 5.5 to 7.0 days after dosing. After subcutaneous administration in the abdomen, absolute bioavailability was slightly higher at higher doses with estimated values of 58%, 65%, and 72% at 150 mg, 300 mg, and 600 mg, respectively. Based on limited data, absolute bioavailability in the thigh was approximately 85% following a subcutaneous dose of 300 mg spesolimab.

Distribution

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

Metabolism

The metabolic pathway of spesolimab has not been investigated. 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. In patients with ADA titers greater than 4000 the geometric mean clearance of spesolimab was nearly doubled (see *Immunogenicity).*

Linearity/non-linearity

When administered intravenously, spesolimab exhibited linear pharmacokinetics with dose-proportional increase in exposure across single dose ranges of 0.3 to 20 mg/kg. Both clearance (CL) and terminal half-life were independent of dose in this dose range. Following subcutaneous single dose administration, spesolimab exposure increased slightly more than dose-proportionally across the dose range of 150 mg to 600 mg due to slightly increased bioavailability at higher doses.

Kinetics in specific patient groups

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 renal impairment as having an influence on the systemic exposure of spesolimab.

Body weight
Spesolimab clearance increased with body weight in a less-than-proportional manner, such that a -/+50% change in body weight resulted in a -45% to 41% change in clearance. The clinical relevance of the effect of body weight on spesolimab plasma concentrations is unknown.

Geriatric patients/Sex/Ethnicity

Based on population pharmacokinetic analyses, age (range: 18 to 76 years), gender (47% male, 53% female) and race (71% White, 24% Asian) do not have an effect on the pharmacokinetics of spesolimab.

Children and adolescents

The pharmacokinetics of spesolimab in paediatric patients below the age of 12 years have not been studied.
The plasma pharmacokinetics of spesolimab after subcutaneous administration observed in adolescents (age: 14-17 years; body weight: 44.0-90.8 kg) were consistent with that observed in adults.

Preclinical data

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.

Genotoxicity
Genotoxicity studies have not been conducted with spesolimab.

Carcinogenicity
Carcinogenicity studies have not been conducted with spesolimab.

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.

Other information

Incompatibilities

Spevigo must not be mixed with other medicinal products.

Shelf life

This medicinal product may only be used until the date marked with “EXP” on the container.

Shelf life after opening of Spevigo concentrate for solution for injection
From a microbiological point of view, once opened, the medicinal product should be diluted and infused immediately.

Shelf life after preparation of infusion of Spevigo concentrate for solution for injection
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

Special precautions for storage

Store in the original package in order to protect from light.
Keep medicines out of the reach of children.

Spevigo solution for injection in pre-filled syringe
Store in a refrigerator (2°C-8°C).

Spevigo pre-filled syringe must not be used if frozen, even if it has been thawed.
Prior to use, Spevigo pre-filled syringe may be kept at temperatures up to 25 °C one-time up to 14 days, if stored in the original package in order to protect from light. Spevigo pre-filled syringe must be discarded if it has been kept at temperatures up to 25 °C for more than 14 days.

Spevigo concentrate for solution for infusion
Store in a refrigerator (2°C-8°C).
Do not freeze.
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.

Instructions for handling

Spevigo solution for injection in pre-filled syringe
The pre-filled syringes should be taken out of the refrigerator and removed from the carton 15 to 30 minutes before injecting to allow to reach room temperature (up to 25 °C). Do not place the prefilled syringes in direct sunlight.
The injection of two pre-filled syringes is required for the full 300 mg dose.
Prior to use, a visual inspection of each pre-filled syringe is recommended. The solution should be clear to slightly opalescent, colourless to slightly brownish-yellow. The solution may contain a few translucent to white product-related particles. Spevigo should not be used if the solution is cloudy or discoloured, or contains large particles.
Do not use if the pre-filled syringes have been dropped or look damaged.
Do not remove the cap until you are ready to inject.
Comprehensive instructions for use are provided in the package leaflet.
Each pre-filled syringe is for single use only.

Spevigo concentrate for solution for infusion
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.

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

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).

Authorisation number

68625, 69579 (Swissmedic)

Packs

Packs of 2 pre-filled syringes (each with 150 mg spesolimab in 1 mL) [B].
Packs of 2 vials (each with 450 mg spesolimab in 7.5 mL) [A].

Marketing authorisation holder

Boehringer Ingelheim (Schweiz) GmbH, Basel, Switzerland.

Date of revision of the text

February 2025