Taiwan Food and Drug Administration

Assessment Report

Trade Name：希蓓麗活靜脈輸注液 / Spevigo Solution for infusion

Active Ingredient：Spesolimab

License Number：MOHW-BI

Applicant：台灣百靈佳殷格翰股份有限公司

Approval Date：

Indication：治療全身型膿疱性乾癬發作之成人病人。
Treatment of generalized pustular psoriasis(GPP) flares in adults.

Background Information

Trade Name	希蓓麗活靜脈輸注液 / Spevigo Solution for infusion
Active Ingredient(s)	Spesolimab
Applicant	台灣百靈佳殷格翰股份有限公司
Dosage Form & Strengths	注射液劑 60 mg/mL (450 mg/7.5 mL)
Indication	治療全身型膿疱性乾癬發作之成人病人。 Treatment of generalized pustular psoriasis (GPP) flares in adults.
Posology	單次給予 SPEVIGO 900 毫克的劑量，以靜脈輸注超過 90 分鐘給藥。 如果全身型膿疱性乾癬發作症狀持續，在給予初始劑量的 1 週後，可考慮再給予一劑 900 毫克(以超過 90 分鐘的時間給藥)。 Administer as a single 900 mg dose by intravenous infusion over 90 minutes. If flare symptoms persist, may administer an additional intravenous 900 mg dose one week after the initial dose.
Pharmacological Category **ATC Code**	L04AC22

Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Spesolimab (BI 655130 or MAB92) is a humanized, recombinant IgG1 antibody which could bind human interleukin-36 receptor (IL-36R) thus preventing its subsequent activation by cognate ligands (e.g., interleukin-36 (IL-36) α, β and γ), which is intended to block the downstream activation of pro-inflammatory and pro-fibrotic pathways.

Spesolimab consists of two identical heavy chains and two identical light chains; the theoretical MW of spesolimab including the predominant glycosylation variants is approximately 149 kDa.

Manufacturing

The spesolimab DS is manufactured in accordance with cGMPs. The DS manufacturing process involves cell culture expansion, harvest of the cell culture fluid, and the purification and formulation steps, including those introduced for inactivation and removal of the potential viral contaminants. Final DS bulk solution is then adjusted to its final formulation

and filtered into the storage bags resulting in the DS batch indicated.

Controls

Overall, the safety of spesolimab in relation to adventitious agents demonstrate by strategies used including raw material control and the down-scale viral clearance studies, is considered adequate.

Process validation and development

The validation of the spesolimab DS manufacturing process was carried out on 4 consecutive lots of commercial manufacturing scale, with focus on process consistency, impurities removal, and viral clearance.

An evaluation of the consistency and comparability among the DS used through clinical development (CMC1 process) and commercial (CMC2 process) batches, is performed. The analytical comparison data supports that batches manufactured by CMC2 processes are consistent to the historical records.

Characterization

Extensive characterization studies are conducted per the items list in below:

- ✧ Physicochemical characterization: primary sequences, PTM, size variants, charge variants and characterized higher-order structure of immunoglobulin.
- ✧ Biological and immunochemical characterization: antigen- and FcRn- binding affinity studies, as well as the cell-based bioassays, were used to demonstrate the ability of spesolimab to bind IL-36R.
- ✧ The potential impurities have been analyzed and are considered sufficiently controlled.

DS specification

The release testing of spesolimab DS includes appearance (color, clarity and visible particles), pH, osmolality, identity, purity, heterogeneity, impurities, potency, quantity, and microbiological test. The proposed specifications of DS are considered adequate and acceptable.

Reference materials

A two-tiered reference standards (RSs) consisting of a primary RS and a working standard have been established for lot release and stability testing for DS and DP.

Stability

Stability is demonstrated by real-time data from primary batches made by CMC2 process and 3 PPQ batches. It revealed that spesolimab DS is stable under long-term condition for up

to 36 months, which supports the proposed shelf-life of 36 months when stored at the recommended temperature −40 ± 10°C.

2.1.2 Drug product

Drug product (DP), **Spevigo Solution for infusion** 450 mg/vial, is supplied as a colorless to slightly brownish-yellow, clear to slightly opalescent solution in stoppered 10 mL glass vial for i.v. administration, containing spesolimab at a concentration of 60 mg/mL in formulation buffer system (at pH 5.5) with polysorbate 20.

Manufacturing process and controls

Spevigo DP vials are manufactured, packaged into the finished DP batches, and released at BI DE (BC). The critical process parameters, key process parameters, in-process control tests that control the critical steps were provided.

Process validation and/or evaluation

3 consecutive DP batches each of different manufacturing scale are used for the Manufacturing process validation.

Overall, the validation studies have demonstrated that the manufacturing process of Spevigo Solution for infusion DP at BI DE (BC) are robust.

DP Specification

The specifications for Spevigo DP include general test (appearance, pH, osmolality, visible and sub-visible particles, volume in container), identity, quantity, purity/impurities, size and charge variants, potency, endotoxins, sterility, container closure integrity and PS20 content.

Reference materials

Reference standards used are the same as those used for DS.

Stability of the DP

The long-term stability data for three primary stability DP batches, and three PPQ batches using CMC2 process DS materials, are provided.

In addition, the photo stability and in-use stability studies have been performed on DP batches.

Overall,

1. the stability data provided could support the proposed shelf-life of 36 months when the DP is stored at the recommend condition (2-8°C) and the secondary packaging could

provide adequate protection from light.

2. Based on the in-use stability results, an additional in-use shelf life for diluted solution is 24 hours at 2 - 30°C (36 - 86°F) followed by 3 hours infusion time in clinical sets as described up to 30°C (86°F); Do not freeze. Holding of an unopened vial of Spevigo Solution for infusion 450 mg/mL (60 mg/mL) for 24 hours at 30°C does not impact the quality of the infusion solution.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

The binding affinity of spesolimab to human IL-36R was 223 pM. Spesolimab had little antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) effector functions due to mutations of two amino acid residues (L234A and L235A). Spesolimab dose-dependently inhibited NF-kB activation and IL-8 production in primary human keratinocytes and dermal fibroblasts in response to IL-36 ligands stimulation. A mouse surrogate antibody, BI 674304, was generated for in vivo pharmacology and toxicology studies due to no binding of spesolimab to IL-36R in common experimental animal species, including mouse, rat, pig, rhesus monkey, marmoset, or hamster.

BI 674304 inhibited ear swelling and IL-33 production in the IL-36-induced skin inflammation mouse model; other disease mouse models demonstrated that IL-36R antagonist reduces tissue inflammation and related symptoms. Spesolimab showed no detectable binding to human IL-1R at concentrations up to 1.0 μM. Spesolimab was specific for blocking IL-36-mediated stimulation and did not inhibit IL-1-mediated activation. No adverse changes in safety pharmacological endpoints regarding the central nervous or respiratory systems were noted in the general toxicity studies in mice. Literature review for the assessment of potential effects of spesolimab on cardiovascular function is an acceptable approach due to the practical limitations of conducting ECGs in mice; no potential risks were identified.

2.2.2 Toxicological Studies

As spesolimab is not expected to be pharmacologically active in all examined toxicological species, BI 674304 was used to identify the potential hazards of IL-36R antagonism in mice. In a 26-week repeated-dose toxicity study in mice, no adverse changes were noted up to 50 mg/kg twice weekly (the highest doses examined) via intravenous administration. According to ICH S6(R1) guidance, it is acceptable that no genotoxicity studies were conducted with spesolimab. An assessment was provided to support the low carcinogenic risk of spesolimab. In reproductive toxicity studies in mice, no adverse changes regarding male/female fertility, maternal toxicity, or embryo-fetal/infant development were noted up to 50 mg/kg (the highest dose examined) by intravenous administration. A local tolerance study in rabbits showed a low

risk of injection site irritation due to spesolimab by subcutaneous administration. In a human tissue cross-reactivity study, the staining pattern of spesolimab was observed as an epithelial expression of IL-36R. No hemolysis was observed for spesolimab under an ex vivo experimental condition. An ex vivo assay showed that spesolimab has a low cytokine release potential.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Spesolimab is a humanized monoclonal immunoglobulin G1 antibody that inhibits interleukin-36 (IL-36) signaling by specifically binding to the IL36R. Spevigo® is approved to treat acute GPP flare with posology of a single 900 mg dose by intravenous infusion over 90 minutes. If necessary, another 900 mg dose may be administered after one week.

Based on population PK analysis, the estimated C_{max} and AUC for GPP patients without ADA with body weight of 70 kg were 4750 μg·day/ml and 238 μg/ml, respectively, following a single 900 mg IV dose. Over the dose range of 0.3 ~ 20 mg/kg, spesolimab AUC increased approximately linearly with dose, and clearance (CL) and terminal half-life ($T_{1/2}$) were independent of dose. The model predicted total volume of distribution at steady state was 6.39 L. Also, the clearance and terminal half-life were 0.184 L/day and 25.5 (24.4, 26.3) days.

According the results from GPP patients in two clinical trials, it can observe that about 46% ~ 50% patients developed to ADA positive, and most of them also were neutralizing Ab positive. The ADA formed at 2.3 weeks (median value; range: 1.0 ~ 11.7 weeks), and lasting to the end of the trial (Weeks 12 to 17). The present of ADA (NAb) have impact on the PK of spesolimab, especially when the ADA titer greater than 4000. The exposure (AUC) of spesolimab were reduced by approximately 50% in those patients with maximum titer >4000. Besides, it was observed that females appeared to have higher immunogenicity response. The ADA incidence for female and male were 58% and 24%, and the % of patients with maximum titer >4000 were 30% and 12%, respectively.

2.3.2 Interaction Studies

No formal in vitro or in vivo drug-drug interactions studies have been conducted with spesolimab at present.

2.3.3 Special Populations

Since spesolimab is a monoclinal antibody with high molecular weight, it is expected that hepatic or renal impairment did not have significant effect on the PK of spesolimab. And, no dedicated organ dysfunction trials were conducted is acceptable. Based on population PK

analyses, age, gender, and race did not have an effect on the PK of spesolimab. However, body weight affected the exposure of spesolimab. Lower exposure was seen in patients with heavy body weight, and vice versa. The model-predicted % change of AUC for 95kg and 54.5 kg of GPP patients were -25% and +25%, relative to typical GPP subjects with 70 kg.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

For the indication of treatment of flares in GPP patients, pivotal efficacy was evaluated in a Phase 2 study [Effisayil-1:1368-0013]. Study [Effisayil-1] is a multicenter, randomized, double-blind, placebo-controlled study in subjects with GPP presenting with an acute flare. Eligible subjects were randomized in a 2:1 ratio to receive either a single 900 mg intravenous dose of spesolimab or placebo. The primary endpoint is Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0 at Week 1. Key secondary endpoint is GPPGA total score of 0 or 1 at Week 1.

The proportion of patients achieving a GPPGA pustulation subscore of 0 at Week 1 was statistically higher in the spesolimab group. The risk difference between spesolimab [19/35 (0.543)] and placebo [1/18 (0.056)] of 48.7% was clinically and statistically significant ($p = 0.0004$). All null hypotheses for the primary, the key secondary endpoints, and the 4 selected secondary endpoints were rejected in the pre-specified hierarchical testing.

2.4.2 Safety Results

The primary safety database (trial 1368-0013) included 51 subjects with GPP flare who received at least 1 dose of spesolimab at the proposed dose of a single intravenous dose of 900 mg (includes randomized, open-label, and rescue doses) and followed for 16 weeks. Among them, 36 subjects received 1 dose, 13 subjects received 2 doses, and 2 subjects received 3 doses (maximum allowed in the trial) of spesolimab throughout trial. The supportive safety database included data from 7 subjects with GPP flare who received at least 1 dose of spesolimab at a single dose of 10 mg/kg (trial 1368-0011) and 6 subjects with GPP flare who received at least 1 dose of spesolimab at the proposed dose of a single intravenous dose of 900 mg (trial 1368-0027; by the cut-off date, 08 Jan 2021). In addition, in the open-label extension trial 1368-0025, 9 subjects with previous spesolimab i.v. flare treatment in parent trial 1368-0013 received for the treatment of a new GPP flare at least a single i.v. dose of 900 mg spesolimab. To broaden the source of evidence for the safety assessment of spesolimab, 335 patients in non-GPP trials (by the cut-off date, 08 Jan 2021) and 226 healthy volunteers who have been treated with spesolimab in the respective trials were also included in the safety data package.

The most important potential risks associated with spesolimab include infections (including the risk of latent tuberculosis) and systemic hypersensitivity reactions (including DRESS). Additionally, a few cases of suspected Guillain-Barré syndrome were reported in trials for non-GPP indications (see below).

There is limited safety data when comparing spesolimab to placebo as the effective duration for the randomized, double-blind period for trial 1368-0013 was 1 week. During the 1-week placebo-controlled period, infections were reported in 17.1% of subjects treated with spesolimab compared with 5.6% of subjects treated with placebo. Serious infection (urinary tract infection) was reported in 1 subject (2.9%) treated with spesolimab and no subjects treated with placebo. In the open label period, one case of latent tuberculosis was reported 84 days after receiving open-label spesolimab when a planned Quantiferon test was positive without clinical symptoms. Serious hypersensitivity reactions including drug reaction with eosinophilia and systemic symptoms (DRESS) were reported in two subjects exposed to spesolimab in trial 1368-0013 (one case assessed as “score 1: no case” and another case “score 3: possible” under the Regi-SCAR criteria). Among approximately 750 subjects exposed to spesolimab during clinical development, 3 subjects who received various doses of spesolimab via various methods of administration in clinical trials for 3 non – GPP clinical trials (Ulcerative colitis, palmoplantar psoriasis and hidradenitis suppurative trials) had adverse events reported as Guillain Barre syndrome (GBS). However, the diagnosis of GBS was not confirmed in none of these cases after a clinical review from a panel of external neurologists and experts in the field of GBS and demyelinating polyneuropathies.

In GPP trials, anti-drug antibodies (ADAs) were formed in 46% of patients with a median onset of 2.3 weeks. Among ADA-positive patients, those with ADA titer values greater than 4000 (24%), were observed to have significantly decreased plasma spesolimab concentrations. ADA development did not impact the efficacy or safety of treatment of a first flare in Study 1368-013 as ADAs generally did not develop until after treatment and resolution of a flare. The impact of ADAs on safety or efficacy for subsequent flares that are treated with spesolimab is unknown due to the limited number of patients who experienced a recurrent flare in Studies 1368-0013 and 1368-0025to-date.

2.5 Bridging Study Evaluation

Under the cross studies comparison, there was no significant AUC difference between Japanese, Chinese and Caucasian healthy subjects. But in GPP patients, the exposure between East Asian and non-East Asian increased to 40% ~50%, this can be supposed to result from the difference of body weight and presence of ADA, after regard to the PK characteristics of spesolimab. No ethnic difference between East Asian and non-East Asian,

and an additional bridging study was not necessary from PK point of view.

In pivotal study 1368-0013, the East Asian subpopulation included 13 subjects from sites in Taiwan, Japan and China.

- Similar to the entire study population (53 subjects), in the East Asian subpopulation, the proportion of subjects achieving the primary efficacy endpoint "GPPGA pustulation subscore of 0 at week 1" was higher in the spesolimab group than in the placebo group.
- The safety results in the East Asian subpopulation were generally similar to those in the entire study population. No additional safety signal was identified in the East Asian population.

In summary, the submitted PK, clinical efficacy and safety data can support the proposed dosage of spesolimab for the claimed indication for Taiwanese patients. No further bridging study was needed.

2.6 Conclusion

Based on review of the submitted package, the review team considered spesolimab to demonstrate a favorable risk-benefit profile with adequate evidence to support regular approval for the following indication: treatment of generalized pustular psoriasis (GPP) flares in adults.

3. Post-Marketing Requirements

(1) Submit the clinical study report once available required by US FDA which is planned to assess the effect of immunogenicity on the pharmacokinetics, safety, and efficacy on re-treatment of GPP flares that occur after the first flare has been treated and has resolved.
(2) Submit the final reports with safety results from ongoing trials: Study 1368-0025 and study 1368-0027.
(3) Submit the final report for the planned voluntary European Post-Authorization Safety Study (PASS)
(4) RMP is required.