Taiwan Food and Drug Administration

Assessment Report

Trade Name：波替立久濃縮靜脈輸注液 / POTELIGEO 4 mg/mL concentrate for solution for infusion

Active Ingredient：Mogamulizumab

License Number： MOHW-BI 001279

Applicant：台灣協和麒麟股份有限公司

Approval Date： 2025/01/15

Indication：

適用於已接受至少一種全身性治療的蕈狀肉芽腫(mycosis fungoides)或Sézary 症候群(Sézary syndrome)成人病人的治療。

Indicated for the treatment of adult patients with mycosis fungoides or Sézary syndrome who have received at least one systemic therapy.

Background Information

Trade Name	波替立久濃縮靜脈輸注液 / POTELIGEO 4 mg/mL concentrate for solution for infusion
Active Ingredient(s)	Mogamulizumab
Applicant	台灣協和麒麟股份有限公司
Dosage Form & Strengths	Solution for Infusion；4 mg/ml
Indication	Indicated for the treatment of adult patients with mycosis fungoides or Sézary syndrome who have received at least one systemic therapy.
Posology	Please refer to package insert for detail.
Pharmacological Category ATC Code	L01FX09

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance

General Information of Drug Substance (DS)

POTELIGEO DS (mogamulizumab) is a recombinant human IgG1 antibody for CC-chemokine Receptor 4 (CCR4). The mechanism of action (MoA) of POTELIGEO is enhanced antibody-dependent cellular cytotoxicity (ADCC) activity, that is established via interactions between the CCR4 antigen on the target cells, the antibody, and the Fc gamma Receptor IIIa (FcγRIIIa) on the natural killer (NK) effector cells.

Manufacture

POTELIGEO DS is manufactured at Kyowa Kirin Co., Ltd. in Japan. All sites for manufacture, control, testing and storage are compliance with Good Manufacturing Practice (GMP). The information of manufacturing process and control strategy are included in the dossier. The critical process parameters (CPP), non-CPP, critical material attribute (CMA), in-process tests for control (IPC), in-process tests for monitoring (IPM), and hold time for each step were established to ensure consistent manufacturing. Materials of animal origin used during the manufacture of DS have been identified, and appropriate information states that all meet the requirements of EMA/410/01. The cell banks used to produce POTELIGEO DS is Chinese hamster ovary (CHO) cells, and are free of adventitious contaminations, and genetically stable. The proposed process validation is acceptable to ensure the quality of POTELIGEO DS. There are two manufacturing processes (Process 1 & Process 2) for pre-clinical, clinical and commercial batches. The process changes and manufacturing improvements history are summarized in the dossier. The results of the comparability testing demonstrate that the quality of DS manufactured from Process 1/2 are comparable.

Characterization

The analytical techniques and methodologies applied for POTELIGEO DS characterization are capable of evaluating primary structure, characterization of glycosylation, physicochemical characteristics, biological and other relevant characteristics, and characterization of product-related variants. Process-related impurities, product-related impurities, and potential contaminants have been evaluated appropriately. Overall, the results conclude that POTELIGEO DS has the expected structure, relative biological activity, and the impurities are well controlled.

Control of Drug Substance

The specification of POTELIGEO DS is provided and the acceptance criteria is well justified. Compendial and non-compendial analytical procedures used for release and stability testing have been well qualified. Batch analysis from two manufacturing processes (process 1 and process 2), and Certification of Analysis (CoA) of representative batch are given to demonstrate that all data meet the acceptance criteria. Overall, the information provided is sufficient to demonstrate the consistency of the manufacturing process capabilities.

Stability

The proposed shelf-life of POTELIGEO DS is based on storage under the designated conditions. The long-term stability results of at least three clinical DS batches support that all quality attributes are expected to remain within the acceptance criteria.

2.1.2 Drug Product

Description of Drug Product (DP)

POTELIGEO DP is presented as a sterile, single-use, ready-to-use, preservative-free, and clear to slightly opalescent, colorless solution for intravenous (IV) administration. The excipients include polysorbate 80, glycine, citric acid monohydrate, sodium hydroxide, hydrochloric acid, and Water for Injection (WFI).

Pharmaceutical Development and Manufacture

For the manufacturing development, the comparability assessment demonstrates that the two process differences did not impact the overall final product quality and consistency. The overall manufacturer process, process controls and parameters are described in details, and process validation results demonstrate the robustness and consistency of the DP manufacturing process.

Control of Drug Product

The specification of POTELIGEO DP has been established, the analytical procedures have been validated appropriately, and the acceptance criteria are thoroughly justified. Batch release results and CoAs further confirm the quality consistency.

Stability

Based on the stability studies, the POTELIGEO DP shelf-life of 36 months is well justified when stored at 2 ~ 8°C in container closure system.

Overall, the CMC quality data, including the manufacturing process, control strategy, characterization, specifications, container closure system, and stability, support that the manufacturing of POTELIGEO is well-controlled and quality consistency.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Mogamulizumab is a recombinant humanized monoclonal antibody targeting CCR4, a receptor expressed on leukemic cells in cutaneous T-cell lymphoma (CTCL) and primary cutaneous anaplastic large cell lymphoma (pcALCL).

Non-clinical pharmacodynamic studies included in vitro assays, xenograft mouse models, and studies in cynomolgus monkeys. Binding characteristics were evaluated using surface plasmon resonance (SPR) and flow cytometry, which confirmed mogamulizumab's binding to both CCR4 and FcγRIIIa. Mogamulizumab demonstrated binding affinity to the CD4-positive subset in human and monkey lymphocytes, specifically targeting peripheral lymphocytes in humans and cynomolgus monkeys but not in dogs, rats, or mice. Mogamulizumab mediated ADCC activity against CCR4-transfected cell lines, ATL patient-derived tumor cells, and monkey PBMCs.

In vivo, mogamulizumab reduced CCR4-expressing lymphocytes in the peripheral blood of monkeys at doses of 0.01, 0.1, and 1 mg/kg. Weekly administration of mogamulizumab (20 mg/kg, once weekly for 4 weeks) significantly inhibited tumor growth in SCID mouse xenograft models of CTCL and ATL. Secondary pharmacology studies indicated that mogamulizumab did not impact platelet function in humans or monkeys. Although it did not induce IFN-γ release in whole blood, it elevated TNF-α and IL-6 levels in PBMC samples.

Safety pharmacology studies were integrated into the repeated-dose toxicity studies in both male and female cynomolgus monkeys. Mogamulizumab showed no significant effects on cardiovascular, respiratory, renal, or central nervous systems.

2.2.2 Toxicological Studies

Single-dose toxicity studies of mogamulizumab at doses up to 100 mg/kg (intravenous) in monkeys revealed no signs of toxicity. In the GLP-compliant pivotal IV repeated-dose toxicity studies in cynomolgus monkeys (up to 26

weeks), mogamulizumab was generally well-tolerated, with no deaths or treatment-related toxicities observed. The NOAELs determined in 13-week and 26-week studies in monkeys provided safety margins of 85-fold and 78-fold, respectively, compared to the clinical dose of 1 mg/kg (based on AUC).

Following ICH S6 (R1) and S9 guidance, genotoxicity and carcinogenicity studies were not conducted. An EFD study in monkeys with intravenous administration showed no treatment-related embryo-fetal lethality, teratogenicity, or fetal growth retardation. No pre- and postnatal development study was performed. The NOAELs from this study provided a safety margin of 27-fold to the human dose of 1 mg/kg (based on AUC).

Local tolerance was evaluated through clinical observations and pathological examination of injection sites in the toxicity studies. Mild and transient erythema was observed in aged monkeys treated with mogamulizumab, with no dermatitis observed during either the dosing or post-dosing observation periods. Overall, the local tolerance of mogamulizumab in non-clinical studies was acceptable.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Mogamulizumab is a defucosylated humanized IgG1 monoclonal antibody targeting CC chemokine receptor 4 (CCR4). Mogamulizumab is dosed via intravenous route and therefore is immediately and completely bioavailable. The exposure to mogamulizumab increased proportionally with dose over the dose range of 0.1 to 1.0 mg/kg. Based on a population PK (PPK) analysis, the geometric mean (CV%) central volume of distribution (V_c) was 3.57 L (20.1%). Mogamulizumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. Based on a population PK analysis, the geometric mean (CV%) clearance is 12.0 mL/h (83.7%) and geometric mean elimination half-life ($t_{1/2}$) is 17 days (65.5%). Based on a population PK analysis, the steady-state concentrations of mogamulizumab were reached after 12 weeks of repeated dosing when administered using the recommended regimen, and systemic accumulation was 1.7-fold.

2.3.2 Interaction Studies

No interaction studies have been performed.

Given that mogamulizumab is an IgG_1-class antibody protein, it is expected to be catabolized into amino acids by general protein degradation process and is unlikely to affect the metabolic enzymes of low-molecular-weight drugs used in

chemotherapy. Metabolic enzymes, transporters, and protein binding, factors generally involved in interactions with low-molecular-weight drugs, are not considered to play a role in the PK of mogamulizumab. In addition, low-molecular-weight drugs are unlikely to affect the PK of mogamulizumab. Thus, no in vitro or in vivo drug-drug interaction studies were conducted.

2.3.3 Special Populations

Age was not identified as a statistically significant covariate on mogamulizumab clearance based on population PK analysis.

Sex was identified as a statistically significant covariate on mogamulizumab clearance based on PPK analysis. However, sex effects are not considered clinically meaningful and dose adjustment is not needed based on sex.

No dedicated clinical studies were conducted in special populations including subjects with renal or hepatic impairment. Renal function was not identified as a statistically significant covariate on mogamulizumab clearance based on PPK analysis. No clinically important differences in the clearance of mogamulizumab were found between patients with mild to severe renal impairment and patients with normal renal function. No dose adjustment is recommended in patients with mild to severe renal impairment.

The hepatic function category was determined based on the National Cancer Institute Organ Dysfunction Working Group (NCI ODWG) classification. No clinically important differences in the clearance of mogamulizumab were found between patients with mild to moderate hepatic impairment and patients with normal hepatic function. Based on a PPK analysis, no dose adjustment is recommended in patients with mild or moderate hepatic impairment. Mogamulizumab has not been studied in patients with severe hepatic impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

For the primary efficacy endpoint (PFS based on Investigator assessment), mogamulizumab was statistically superior to vorinostat (HR:0.53, 95% CI: 0.41, 0.69, 2-sided $p<0.0001$). Results of PFS based on independent review were consistent with the primary analysis results (HR:0.64, 95% CI: 0.49, 0.84, 2-sided $p=0.0007$). The results for the key secondary endpoints (ORR, Change in Skindex-29 score from baseline through the 6-month assessment and Change in FACT-G total score from baseline through the 6-month assessment) also demonstrated a statistically significant effect for mogamulizumab compared to vorinostat.

2.4.2 Safety Results

Major risks included skin eruptions (including Stevens-Johnson syndrome), infusion reactions, infections, pyrexia, fatigue, nausea, chills, hepatitis B reactivation, graft versus host disease (GVHD), neutropenia, lymphopenia, thrombocytopenia, anemia, calcium decreased/increased and phosphate decreased.

2.5 Bridging Study Evaluation

In Study 0761-010, a randomized, Phase 3 study conducted in the US, EC, Japan and Australia in subjects with relapsed or refractory cutaneous T-cell lymphoma (CTCL), mogamulizumab was administered at a dose of 1 mg/kg by intravenous infusion on Days 1, 8, 15 and 22 for the first 28-day cycle and on Days 1 and 15 for subsequent 28-day cycles. Serum mogamulizumab concentrations after repeated intravenous administration of mogamulizumab at a dose of 1.0 mg/kg in Study 0761-010 were compared by registry (Japanese or non-Japanese). The serum concentrations did not differ significantly between Japanese (n=9) and non-Japanese (n=175) populations.

In addition, the effects of race on the PK of mogamulizumab were assessed in population PK (PPK) analysis. Race was not identified as a statistically significant covariate on mogamulizumab clearance based on the PPK analysis, which included 87 Japanese (20%) and 357 Non-Japanese subjects (80%).

In conclusion, no significant differences in PK of mogamulizumab were observed between Asian and non-Asian patients. Therefore, no adjustment of dose nor a PK bridging study is warranted for Asian patients.

There were 37 Japanese subjects in Phase II Study 0761-004 and 15 Japanese subjects (overall 372 subjects) in Phase III Study 0761-004; there is no strong evidence suggesting that there is any clinically relevant ethnic difference between the East Asian patients and patients from the Western countries.

2.6 Conclusion

The benefit of mogamulizumab was demonstrated in Study 0761-010 as prolonged PFS, the difference of median PFS was 4.6 months as compared to active control vorinostat. Main risks were infusion reactions, skin rash, infections, hematological toxicities, electrolytes abnormalities, GVHD and hepatitis B reactivation. The B/R ratio is favorable for the second-line therapy of CTCL. Approval of claimed indication is recommended.

3. Post-Marketing Requirements

Routine pharmacovigilance