Taiwan Food and Drug Administration

Assessment Report

Trade Name：癌舒妥注射劑/
Lunsumio concentrate for solution for infusion

Active Ingredient：Mosunetuzumab

License Number：MOHW-BI 001211

Applicant：羅氏大藥廠股份有限公司

Approval Date： 111/12/12

Indication：
單獨使用，適用於治療先前已接受至少兩線全身性療法的復發型或難治型濾泡性淋巴瘤(FL)成人病人。
本適應症係依據腫瘤反應率及反應持續時間加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。

Monotherapy for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Background Information

Trade Name	癌舒妥注射劑 Lunsumio concentrate for solution for infusion
Active Ingredient(s)	Mosunetuzumab
Applicant	羅氏大藥廠股份有限公司
Dosage Form & Strengths	注射液劑 1 mg/mL
Indication	單獨使用，適用於治療先前已接受至少兩線全身性療法的復發型或難治型濾泡性淋巴瘤(FL)成人病人。 本適應症係依據腫瘤反應率及反應持續時間加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。 Monotherapy for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
Posology	詳見仿單
Pharmacological Category **ATC Code**	L01XC

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance

Mosunetuzumab is a recombinant humanized T-cell-engaging bispecific monoclonal antibody of the IgG1 subclass, directed against CD3 and CD20. Simultaneous binding by mosunetuzumab of CD20 on the surface of B cells and CD3 on the surface of T cells leads to immune synapse formation, T-cell activation, and subsequent release of cytolytic granules, which in turn kills the CD20-expressing B cells.

Mosunetuzumab is produced using CHO cell lines. The manufacturing process is sufficiently described. The in-process control tests and limits are acceptable. Control of raw materials, the manufacturing process and adventitious agents is considered adequate to ensure the safety of

mosunetuzumab. The structural, physiochemical and biological characterization of mosunetuzumab is considered sufficient. Process-related impurities and product-related impurities are well-controlled. The release tests for mosunetuzumab are acceptable. A two-tiered reference standard system has been established for commercial use. The container closure system is acceptable. The stability data provided are sufficient to support the proposed shelf life and storage conditions for mosunetuzumab.

2.1.2 Drug Product

Mosunetuzumab is the active ingredient in Lunsumio. Lunsumio, is provided as a sterile, preservative-free, colorless solution intended for intravenous infusion. The drug product is formulated as 1 mg/mL mosunetuzumab. There are two drug product configurations: 1 mg/vial (1 mL solution in a single-use, 2 mL vial) and 30 mg/vial (30 mL solution in a single-use, 50 mL vial).

Details of formulation development and manufacturing process development are provided. The drug product manufacturing process is sufficiently described and in-process controls are considered adequate. The release and stability specifications for mosunetuzumab drug product are acceptable. The extractables and leachables studies demonstrate that the primary packaging components are suitable and safe for use for the drug product. The stability data currently available for mosunetuzumab drug product are sufficient to support the proposed shelf life of 24 months when stored at 2-8°C, and protected from light.

In summary, the information on the drug substance and drug product is sufficiently provided and the quality of Lunsumio is considered to be acceptable when used in accordance with the conditions defined in the package insert.

2.2 Preclinical Pharmacology/Toxicology Evaluation

Mosunetuzumab is a humanized full-length IgG1 anti-CD20/CD3 T-cell-dependent bispecific (TDB) antibody designed to treat CD20-expressing B-cell malignancies. A comprehensive in vitro program was done to characterize the three TDBs used in the nonclinical studies. The results implicated that mosunetuzumab and 2H7v16/40G5c, a functionally equivalent antibody, had comparable potency in B-cell killing, T-cell activation, and cytokine release in human and cynomolgus monkey PBMCs. In vitro, mosunetuzumab demonstrated minimal binding to human Fc gamma receptors examined up to the highest concentration tested in the study.

Mechanism-wise, TDB-induced B-cell killing activity depended on the presence of CD3-expressing cells and CD20+ cells but did not require the Fc function of the antibody. The granzyme-perforin pathway was involved in the B-cell killing. TDB showed B-cell killing activity against a panel of B-lymphoma cell lines with various levels of CD20 expression,

including those with low CD20 expression, rituximab-insensitive B-lymphoma cells, but no activity against CD20-negative cells. Also, the B-cell killing activity of TDB had been demonstrated in PBMCs from both healthy donors and CLL patients and was not significantly affected by a rituximab variant and dexamethasone.

In vivo, IV administration of single- or repeated-dose of mosunetuzumab or 2H7v16/40G5c up to a 26-week duration in cynomolgus monkeys led to rapid, potent, and sustained but slowly recoverable B-cell depletion in the blood and lymphoid tissues in a dose-dependent manner. Correspondingly, transient and dose-dependent T-cell activation and cytokine release occurred. Primarily associated with the first dose, a transient activation-induced T-cell reduction (margination) followed by redistribution and/or expansion was also observed. Similar PD effects were observed in studies using human CD20/CD3 double-transgenic mice or humanized NSG mice.

In a GLP single-dose toxicity study of mosunetuzumab, IV doses up to 0.1 mg/kg or SC dose at 1 mg/kg in cynomolgus monkeys were well tolerated. Toxicities observed following IV administration of 1 mg/kg were mainly attributed to cytokine release and acute phase reactions. Safety pharmacology evaluation of mosunetuzumab was incorporated into this single-dose GLP study and found no adverse effects on vital organs except reversible hypotension at 1 mg/kg IV and increased heart rate and body temperature at $\geq$ 0.1 mg/kg IV or SC, which were considered to be secondary to mosunetuzumab-induced cytokine release and acute phase reactions.

In a GLP 26-week IV repeated-dose toxicity study of mosunetuzumab in cynomolgus monkeys with a step-up dosing regimen (0.2/0.8 mg/kg on Day 1/Day 2 followed by 0.1 or 0.5 mg/kg QW), the key target organs/tissues included the systemic vasculature (brain, heart, liver, kidney, gastrointestinal tract, gall bladder), lymphoid tissues, bone marrow, kidney, adrenal gland, and pancreas. Mosunetuzumab-induced immunosuppression due to B cell depletion was found to be associated with increased susceptibility to infection. In addition, a transient and mild elevation of liver enzymes was noted and possibly due to cytokine-mediated hepatocyte damage. The HNSTD and NOAEL could not be determined in this study. The highest dose tested in this study provided exposures (AUC) similar to exposure (AUC) in patients receiving the recommended dose of 1/2/60/30 mg.

In line with ICH S9 and ICH S6(R1), genotoxicity and carcinogenicity studies have not been conducted. Regarding development and reproductive toxicity, no potential risks of mosunetuzumab on male or female fertility were identified in the monkey GLP repeated-dose toxicity studies up to a 26-week duration. A weight of evidence-based risk assessment suggested that mosunetuzumab is expected to have a low risk for teratogenicity but may be

harmful to the fetus. Warnings of the potential risk to human pregnancy are recommended. Local tolerance for the administration of mosunetuzumab via IV or SC routes was evaluated in the toxicity studies in cynomolgus monkeys, and no mosunetuzumab-related local changes were observed at the injection sites. Lastly, no TCR data was available since a reliable IHC assay for mosunetuzumab could not be developed. However, the results from the in vitro PD studies suggested that the potential off-target binding of mosunetuzumab is considered low.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Mosunetuzumab is administered intravenously. After the first two Cycles (i.e., 42 days) of the dosing with mosunetuzumab, the serum concentration reaches the C_{max} at the end of dose of Cycle 2 Day 1 of the mosunetuzumab intravenous infusion with an average maximal concentration of 17.9 μg/mL and %CV of 49.6%. The population PK analysis results suggesting that Cycle 4 AUC can serve as a surrogate for the steady state AUC for this dose regimen. The average total two cycles (42 days) mosunetuzumab model-predicted exposure $AUC_{0\text{-}42}$ was 125.7 day•μg/mL with %CV of 44.4%, while model-predicted exposure AUC_{ss} was 52.9 day•μg/mL with %CV of 40.7%, which are approximated at Cycle 4 (63 – 84 days). The population estimate of central volume of distribution for mosunetuzumab was 5.49 L after intravenous infusion.

Mosunetuzumab is expected to undergo metabolism via catabolic pathways similar to the metabolism of other IgG1-based antibodies, for which the metabolic pathways are well-established. The serum concentration-time data was well-described by a population PK model with two-compartment and time-dependent clearance (CL), which was parameterized as an initial baseline clearance (typical value CL_{base} ~ 1.08 L/day) which transitions over time to a steady state clearance (typical value CL_{SS} ~ 0.584 L/day) with a transition half-life (HL_{trans}) of 16.3 days. The steady-state geometric mean (CV%) terminal elimination half-life of mosunetuzumab was 16.1 (17.3%) days. The CL values are higher than the normal range of clearance of a typical IgG1 antibody, suggesting potential impact of target-mediated drug disposition (TMDD).

2.3.2 Interaction Studies

No formal drug-drug interaction studies have been conducted. Mosunetuzumab is not metabolized by cytochrome P450 enzymes. However, initiation of mosunetuzumab treatment causes a transient increase in cytokine levels which may cause inhibition of CYP450 enzymes. A transient clinically relevant effect on CYP450 substrates with a narrow therapeutic index (e.g., warfarin, voriconazole, cyclosporine, etc) cannot be excluded. Thus, when patients received mosunetuzumab and be treated with CYP450 substrates with a narrow therapeutic index, the therapeutic monitoring should be considered and the dose adjustment of the

concomitant medicinal product is required as needed.

2.3.3 Special Populations

Age was tested as a potential continuous covariate in the population PK analysis and it was not found statistically significant. Among the 439 patients included in the analysis, 241 patients (54.9%) were below 65 years, 129 patients (29.4%) were between 65 and 74 years, 57 patients (12.9%) were between 75 and 84 years and 12 patients (2.7%) >85 years, and exposure (AUC_{0-42}) is comparable across age groups. No dose adjustment is required by age. Population PK analysis showed that body weight is a significant covariate for mosunetuzumab PK. However, based on exposure-response analysis and clinical exposure margins, no dose adjustment is required by body weight.

IgGs are mainly eliminated via intracellular catabolism, thus, renal and hepatic impairment are not expected to influence clearance of mosunetuzumab. Based on population PK analysis, at the clinical dose of 1/2/60/30 mg, the simulated PK exposure were similar for the renal impairment categories of normal (CrCl ≥ 90 mL/min, n=200), mild (CrCl 60 to 89 mL/min, n=178) and moderate (CrCl 30 to 59 mL/min, n=53) respectively. There were too few data in the severe group to be summarized and no patients with end-stage renal disease and/or who are on dialysis have been studied. Meanwhile, at the same dose regiment, the simulated PK exposure were similar for the hepatic impairment categories of normal (n=384), mild (total bilirubin > ULN to 1.5 x ULN or AST > ULN, n=53), respectively. The number of patients with moderate hepatic impairment is limited (total bilirubin > 1.5–3 x ULN, any AST, n=2) and no patients with severe hepatic impairment have been studied. In summary, no dose adjustment is required by renal and hepatic impairment.

As of the ADA cutoff date of 4 December 2020, 418 ADA-evaluable patients received mosunetuzumab single-therapy IV treatments in Study GO29781 were tested for ADAs against mosunetuzumab. No ADAs were detected in these 418 ADA-evaluable patients. The immunogenicity of mosunetuzumab will continue to be monitored in Study GO29781.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The Applicant provided an open label phase I/II trial (Study GO29781) to evaluate mosunetuzumab as a monotherapy in subjects with relapsed or refractory (R/R) FL. The single-arm expansion cohort enrolled 90 patients with relapsed or refractory FL (Grade 1-3A) who had received at least two prior systemic therapies, including an anti-CD20 monoclonal

antibody and an alkylating agent. The median age was 60 years (range 29 to 90 years). The median number of prior therapies was 3 (range: 2 to 10). Seventy-nine percent of patients were refractory to prior anti-CD20 monoclonal antibody therapy and 53% were refractory to both anti-CD20 monoclonal antibody and alkylator therapy. Sixty nine percent of patients were refractory to the last prior therapy and 52% had progression of disease within 24 months of first systemic therapy.

When comparing efficacy of the primary endpoint, CR (complete response) rate as assessed by an independent review facility, with a historical control CR rate assumed to be 14%, a CR rate of 60% (95% CI: 49.1, 70.2) was observed. The lower bound of the CI was greater than the pre-defined reference level. Subgroup analyses were consistent with the main analysis result. Thus, this study met the primary objective.

The median DOR was 22.8 months (95% CI: 9.7, NE). Among responders, the event-free rates at 12 and 18 months after the first response were 61.8% and 56.9%, respectively. The median DOCR was not estimable (95% CI: 14.6, NE). The K-M estimated event-free rates among complete responders at 12 months and 18 months after the first complete response were 71.4% and 63.7%, respectively.

2.4.2 Safety Results

Common treatment emergent adverse events (TEAEs) include cytokine release syndrome (CRS), neutropenia, fatigue, hypophosphatemia, pyrexia, rash, and headache. Grade 3/4 AEs were reported in 66.5% of patients and were manageable with dose modification or interruption.

CRS occurred in 39.4% of patients, and the most common signs and symptoms of CRS were pyrexia (98%), hypotension (35%), chills (36%), tachycardia (24%), hypoxia (22%), and headache (16%).

The incidence of hepatic adverse events was 13.3%, and the most frequent hepatic events (>5% of patients) were ALT and AST increases. An analysis of laboratory results identified 10 potential Hy's Law cases, and all 10 were confounded by concurrent cytokine release syndrome (CRS) or underlying disease progression. None of the cases were confirmed to be drug induced liver injury (DILI) cases.

2.5 Bridging Study Evaluation

Based on the population PK analysis including Korean (n=57) and non-Asian (n=362) patients, the model-predicted exposure (AUC_{0-42}) of the Korean patients was similar with that of non-Asian, while the model-predicted exposure (AUC_{0-168}) of the Korean patients was similar with that of the non-Asian at steady state. The credibility of population PK model was further evaluated in a new drug application assessment report and proved that the model-predicted exposure as presented is the appropriate PK parameter to evaluate the ethnic difference between East Asian and non-Asian.

Although moderate to high pharmacokinetic variability for mosunetuzumab was observed and characterized by inter-individual variability (IIV) ranging from 18% to 86% CV for mosunetuzumab PK parameters, no steep pharmacodynamic (effect-concentration) relationship is noted for both efficacy and safety in the range of the recommended dosage and dose regimen. In conclusion, mosunetuzumab is considered to be none to minimally ethnically sensitive after the evaluation of credibility of the population PK model.
There were too few East Asian subjects (4 FL and 14 NHL) for evaluation of efficacy and safety among East Asians.

2.6 Conclusion

The efficacy of mosunetuzumab monotherapy for R/R FL was demonstrated by Study GO29781 as CR of 60 %, the survival benefit had not been established. Therefore, this NDA can only be assessed through the accelerated approval pathway. Study GO42909 (CELESTIMO) is a confirmatory phase III study evaluating the efficacy and safety of mosunetuzumab in combination with lenalidomide vs rituximab in combination with lenalidomide in patients with FL after receiving at least one prior systemic therapy; the primary endpoint is PFS while OS will also be explored.
Mosunetuzumab may cause extensive adverse events which warrant dose modifications. There is limited number of subjects for thorough safety evaluation, especially for liver toxicity.

Ethnic difference is another uncertainty, there were only 4 East Asian subjects of FL for clinical evaluation.

The uncertainty of survival benefit, risks of liver toxicity and ethnic difference can be evaluated in the confirmatory trial GO42909 in which 141 East Asian subjects were planned to be enrolled.

3. Post-Marketing Requirements

The sponsor should provide the study report of confirmatory trial GO42909 for regular approval.