Taiwan Food and Drug Administration

Assessment Report

Trade Name：

特飛立注射劑 10 毫克/毫升 / Tecvayli injection 10 mg/ml
特飛立注射劑 90 毫克/毫升 / Tecvayli injection 90 mg/ml

Active Ingredient：Teclistamab

License Number：

MOHW-BI 001216
MOHW-BI 001217

Applicant：嬌生股份有限公司

Approval Date：112.01.12

Indication：

適用於治療先前曾接受至少四線療法(包括一種蛋白酶體抑制劑、一種免疫調節劑和一種抗 CD38 單株抗體)的復發性或難治性多發性骨髓瘤成人病人。

Tecvayli(teclistamab) indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

Background Information

Trade Name	特飛立注射劑 10 毫克/毫升 / Tecvayli injection 10 mg/ml 特飛立注射劑 90 毫克/毫升 / Tecvayli injection 90 mg/ml
Active Ingredient(s)	Teclistamab
Applicant	嬌生股份有限公司
Dosage Form & Strengths	注射劑 10 毫克/毫升 注射劑 90 毫克/毫升
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Posology	詳見仿單
Pharmacological Category **ATC Code**	L01X-C

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance (DS)

DS, teclistamab (JNJ-64007957) is a humanized, immunoglobulin G4-proline, alanine, alanine (IgG4-PAA) bispecific antibody against B-cell maturation antigen (BCMA) and T-cell cluster of differentiation 3 (CD3) antigen simultaneously, and therefore, could facilitate cell lysis of the BCMA-expressed malignant B cell through the engagement of an activated T cell by the CD3 binding arm.

Teclistamab consists of 2 heavy chains (HC) and 2 light chains (LC), joined by disulfide bonds with a molecular mass of 146,261 Da for the predominant G0F/G0F glycoform. It is prepared by controlled reduction and oxidation of two parental antibodies, namely JNJ-63705473 Protein A eluate (anti-BCMA mAb) and JNJ-63483043 Protein A eluate (anti-CD3 mAb), which result in an exchange of the Fab arms facilitated by specific amino

acid substitutions introduced into the CH_3 domain of the parental JNJ-63483043 (anti-CD3 mAb) HC to enable preferential refolding of the heterodimer.

Manufacturing

Teclistamab DS is manufactured in accordance with cGMPs. The DS manufacturing process involves Fab-arm exchange (stages 5-13) of two independent parental antibodies JNJ-63705473 (anti-BCMA mAb, stages 1-4) and JNJ-63483043 (anti-CD3 mAb, stages 1-4), which integrate cell culture expansion, production cultures for parental antibodies, harvest of the cell culture fluid, purifications, parental antibodies pool and reduction, ultrafiltration/diafiltration, solvent/detergent virus inactivation and virus removal filtration, and final DS bulk formulation steps. The resulting DS bulk solution is then adjusted to its final formulation and filtered into polycarbonate containers with 1-10 L volumes.

Controls

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

Process validation

The validation of the teclistamab DS manufacturing process was carried out on 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 and commercial (5 kg DS process) batches, is performed. The analytical comparison data supports that batches manufactured by commercial 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: the biological activity of techlistamab is tested using a cell-based T cell activation assay (NFAT-RE-mediated luminescence) as a read-out for target cell – effector cell co-engagement that is a surrogate measure of targeted cell killing. Expected Fc functions were confirmed by lack of observable binding or reducing binding to human Fc receptors and dose-dependent FcRn binding.
- ✧ The potential impurities have been analyzed and are considered sufficiently controlled.

DS specification

The release testing of teclistamab DS includes general appearance, pH, 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 materials (RMs) consisting of a primary standard PRM and a working standard WRM have been established for lot release and stability testing for DS and DP. The qualification and characterization criteria for them and for future PRM/WRM, were also provided.

Stability

Stability has been demonstrated by real-time data from 4 process validation batches made by intended commercial DS process. It revealed that teclistamab DS is stable under long-term condition for up to 18 months, which supports the proposed shelf-life of 18 months stored at the recommended temperature −40 ± 10°C.

2.1.2 Drug product

Drug product (DP), Tecvayli® injection, contains two different presentations, namely, 10 mg/mL or 90 mg/mL, both supplied in sodium acetate trihydrate, glacial acetic acid, sucrose, polysorbate 20, EDTA disodium salt dihydrate, at pH 5.2 and stored at 2- 8ºC.

Manufacturing process and controls

Tecvayli DP vials are manufactured, packaged into the finished DP batches at Patheon, and then released by Janssen Biologics B.V. The critical process parameters, key process parameters, in-process control tests that control the critical steps were provided.

Process validation and/or evaluation

Consecutive DP batches each of presentation are used for the manufacturing process validation. Overall, the validation studies have demonstrated that the manufacturing process of Tecvayli® injection are robust.

DP Specification

The specifications for Tecvayli DP include general test (appearance, pH, osmolality, visible and sub-visible particles, extractable 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 four process validation DP batches (two of 10 mg/mL presentation, and the other two for 90 mg/mL), and for four clinical supportive batches, are provided.

In addition, the photo stability studies have also been performed on DP batches, which demonstrate that the surrogate package representative of the commercial secondary package will provide DP with adequate protection from the effects of the light conditions specified in ICH guideline.

Overall,

1. the stability data provided could support the proposed shelf-life of 6 months when the DP is stored at the recommend condition (5 ± 3°C) and protection from light.
2. the photostability study demonstrate that the surrogate package representative of the commercial secondary package will provide DP with adequate protection from the effects of the light conditions specified in ICH Q1B guideline.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

In vitro pharmacodynamic studies revealed that teclistamab bound to BCMA+ and CD3+ cells and induced T cell-dependent activation, cytotoxicity, and various cytokines release with EC_{50} values in the low nanomolar range. *In vivo* tumor-bearing mice studies showed that teclistamab induced healthy donors' PBMC or pan T cells-mediated elimination of MM tumor compared with PBS-, CD3xnull-, or BCMAxnull-treated groups. Cardiovascular, neurological, and respiratory system safety has been investigated for teclistamab and revealed no significant liabilities in monkeys.

2.2.2 Toxicological Studies

Teclistamab was evaluated in GLP-compliant toxicity studies for up to 5-week duration in monkeys. Cynomolgus monkey is the only relevant species of teclistamab, but the teclistamab has a 36-fold lower binding affinity for cynomolgus monkey BCMA than that for human BCMA. Toxicity findings of teclistamab were sporadic, transient, or were of a magnitude of change that was not considered test article-related at doses of up to 30 mg/kg/weekly.

Genotoxicity and carcinogenicity studies are not warranted. No animal reproductive or

developmental toxicity studies have been conducted with teclistamab. However, teclistamab is an antibody that redirects T-cells and can potentially cause risks such as the release of cytokines and resulting inflammation due to T-cell activation, which could potentially harm the pregnancy or the developing fetus. Although lower exposure of teclistamab resulted from ADA formation was noted, this IgG-based bsAb may cross the placenta or nursing to the fetus. The patients should be implemented contraception and avoid breastfeeding while receiving teclistamab. Teclistamab had no unexpected cross-reactivity in human or monkey tissues, and no evidence of potential risk of cytokine release syndrome or precipitation/hemolysis with human serum was identified in non-clinical studies.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Teclistamab exhibited dose-proportional pharmacokinetics following IV administration across a dose range of 0.0192 to 0.72 mg/kg and SC administration across a dose range of 0.08 to 3 mg/kg. The observed individual T_{max} occurred 3 to 8 days after the SC administration of teclistamab on Cycle 1 Day 1. Bioavailability following SC weekly administration for the treatment dose was 69.2%.

Pharmacokinetic steady state was attained in Cycle 3 (the 7^{th} treatment dose; Day 43) following 1.5 mg/kg teclistamab SC administered weekly. Following multiple 1.5 mg/kg SC weekly doses, the mean accumulation ratio was 2.71- and 3.05-fold for C_{max} and AUC_{tau}, respectively. The model estimated typical volume of distribution for the central compartment was 4.09 L. The typical peripheral volume was estimated to be 1.29 L. Moreover, teclistamab is not metabolized via cytochrome P450 (CYP) enzymes and is not expected to directly affect the CYP enzymes. Time-independent clearance (CL_1), clearance associated with time-dependent clearance (CL_2), inter-compartmental clearance (Q) were 0.545 L/day, 0.327 L/day, 0.0473 L/day, respectively. Mean $t_{1/2}$ following the first IV treatment dose was 91.5±41.1 hours.

2.3.2 Interaction Studies

Because of the metabolic properties of teclistamab, no nonclinical or clinical drug-drug interaction studies were performed.

The initial release of cytokines associated with the start of teclistamab treatment could suppress CYP enzymes. CYP substrates with a narrow therapeutic index should be used with caution in patients receiving teclistamab.

2.3.3 Special Populations

Based on population PK analysis, no dose adjustment is required by age, gender and body

weight.

The effect of renal impairment as defined normal (n=90, 29.2%), mild (n=141, 45.8%), moderate (n=76, 24.7%), and severe (n=1, 0.3%) was evaluated in population PK analysis and was not identified as significant covariate on teclistamab pharmacokinetics. The simulated teclistamab $C_{ave,1stdose}$ and $C_{trough,ss}$ at proposed recommended Phase 2 dose (RP2D) were similar between subjects with normal versus mild renal impairment, and between moderate or severe versus mild renal impairment. Therefore, no dose adjustment is required for mild and moderate renal impairment. Limited data are available from patients with severe renal impairment (n=1).

In the population PK analysis, hepatic impairment was not identified to significantly influence the pharmacokinetics of teclistamab. The simulated teclistamab $C_{ave,1stdose}$ and $C_{trough,ss}$ at RP2D were similar between subjects with normal hepatic function (n=274, 89%) and mild hepatic impairment (n=34, 11%). Therefore, no dose adjustment is required for mild hepatic impairment. However, no data for moderate or severe hepatic impairment are available, and hence the effect of moderate or severe hepatic impairment on pharmacokinetics of teclistamab is unknown.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Study 64007957MMY1001 (MajesTEC-1) is a single-arm, open-label, multicenter study of teclistamab administered as monotherapy to adult subjects with relapsed or refractory multiple myeloma. The submitted data describes the results of the primary analysis of the study by clinical cutoff of 07 September 2021, which contained 165 subjects received at least 1 dose of teclistamab at RP2D.

The median age of these subjects was 64.0 years (range: 33 to 84), with 14.5% of the study population being at least 75 years of age. Ninety-six subjects (58.2%) were male. Most subjects (134 [81.2%]) were White and 21 subjects (12.7%) were Black or African American. Most subjects (109 [66.1%]) had an ECOG score of 1. The median time from diagnosis of multiple myeloma to enrollment in the study was 6.0 years (range: 0.8 to 22.7). 128 subjects (77.6%) were triple-class refractory (PI, IMiD, and anti-CD38 monoclonal antibody) and 50 (30.3%) were penta-refractory. Subjects treated at pivotal RP2D received a median of 5.9 months of therapy (range: 0.2 to 18.0).

Efficacy data by clinical cutoff of March 2022 demonstrated the overall response rate assessed by the IRC (primary endpoint) was 63.0% with a median follow-up of 14.1 month. The median duration of response was 18.4 months (95% CI, 14.9 to not estimable). The

median duration of progression-free survival was 11.3 months (95% CI, 8.8 to 17.1). The median OS based on IRC assessment was 18.3 months (95% CI: 15.1 months to NE) and not yet mature.

2.4.2 Safety Results

All 165 subjects treated at pivotal RP2D had experience TEAE. 152 (92.1%) subjects experienced TEAEs more than Grade 3. Serious TEAE(s) were reported for 88 subjects (53.3%). There were 18 deaths (10.9%). Nine of these subjects had cause of death reported as AE (7 were COVID-19) and the remaining 9 had cause of death reported as progressive disease. Cytokine release syndrome (CRS) was the most common TEAE (71.5 %), followed by neutropenia(65.5%). Grade 3 or 4 events were most frequently reported in the SOCs of Blood and Lymphatic System Disorders (83.0% with different bone marrow insufficiencies) and Infection and Infestations (35.2%). The following serious TEAEs were reported in ≥5% of subjects by preferred term: CRS (7.9%), COVID-19 (7.3%), Pneumonia (6.7%), General physical health deterioration (5.5%).

The main safety concerns for teclistamab are CRS and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS). CRS and neurologic toxicity occurred in 72 % and 52% of subjects, respectively. Most patients experienced CRS following doses in the initial step-up dosing schedule, which includes step-up dose 1(42.4% of subjects), step-up dose 2(34.5% of subjects) and the first full treatment dose (24.2% of subjects). Recurrent CRS occurred in 33 % of patients. Fortunately, all CRS events were Grade 1 or 2. Neurologic AEs were reported in ≥5% of subjects: Headache (21.8%), Encephalopathy (grouped term) (9.1%), Insomnia (6.1%). There were three additional neurologic AEs, including cerebrovascular accident (Grade 3), Guillain-Barre Syndrome (Grade 5), and seizure (Grade 4) reported in updated safety data.

2.5 Bridging Study Evaluation

Teclistamab is an antibody drug and exhibited dose-proportional pharmacokinetics following SC administration. No steep effect-concentration curve for both efficacy and safety was observed in the therapeutic dose range. Based on ADME properties of teclistamab, race is not likely to be a sensitive factor on teclistamab PK.

In the population PK analysis, race or ethnicity was not identified to significantly influence the pharmacokinetics of teclistamab. The results indicated that $C_{ave,1stdose}$ and $C_{trough,ss}$ at RP2D were similar across White (n=260, 84.4%), Black (n=25, 8.1%), or Other (n=23, 7.5%). However, the majority of subjects (84.4%) in the pharmacokinetic analysis dataset were White. Additional PK data from subjects of Asian descent in ongoing Studies 64007957MMY1001 (including global cohort and on-going China cohort) and

64007957MMY1002 (on-going Japan study) were submitted but the number of subjects was still limited.

Efficacy and safety data of 6 patients in China Cohort with median follow-up of 0.64 months was submitted for ethnic difference evaluation. The information was too limited to draw any conclusion on ethnic difference from the clinical perspective.

Therefore, it is required to submit more East Asian data after approval.

2.6 Conclusion

This multidisciplinary review recommends accelerated approval for Tecvayli (teclistamab) indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

3. Post-Marketing Requirements

1) Submit more PK, efficacy and safety data of East Asian patients treated with teclistamabthe in MajesTEC-1 China Cohort, Study 64007957MMY1002 and MajesTEC-3 to evaluate ethnic difference.
2) Submit the CSR of Study 64007957MMY1001 (MajesTEC-1) after trial completion.
3) Submit the CSR of the confirmatory study, MajesTEC-3(A Phase 3 Randomized Study Comparing Teclistamab in Combination with Daratumumab SC (Tec-Dara) versus Daratumumab SC, Pomalidomide, and Dexamethasone (DPd) or Daratumumab SC, Bortezomib, and Dexamethasone (DVd) in Participants with Relapsed or Refractory Multiple Myeloma) after trial completion.
4) Submit the results of neurologic toxicities in patients receiving teclistamab (PMR 4334-2 by USFDA) while available.
5) Risk management plan is required to lower the risk of Cytokine Release Syndrome (CRS) and neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).