Taiwan Food and Drug Administration

Assessment Report

Trade Name：倍優視注射劑 120 毫克/毫升 /
Beovu 120 mg/mL solution for injection

Active Ingredient：Brolucizumab

License Number： MOHW-BI 001174

Applicant：台灣諾華股份有限公司

Approval Date： 110/9/7

Indication：
治療血管新生型(濕性)年齡相關性黃斑部退化病變
Neovascular (Wet) Age-Related Macular Degeneration, wAMD

1. Background Information

Trade Name	倍優視注射劑 120 毫克/毫升 / Beovu 120 mg/mL solution for injection
Active Ingredient(s)	Brolucizumab
Applicant	台灣諾華股份有限公司
Dosage Form & Strengths	注射液劑
Indication	**治療血管新生型(濕性)年齡相關性黃斑部退化病變** **Neovascular (Wet) Age-Related Macular Degeneration, wAMD**
Posology	詳如仿單
Pharmacological Category **ATC Code**	S01LA06

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation (CMC)

Beovu® (brolucizumab) finished product is supplied as a sterile solution in vial or PFS. Each vial or PFS of brolucizumab contains the active ingredient brolucizumab in a dosage strength of 6 mg/0.05 mL, sodium citrate buffer, polysorbate 80, sucrose, and water for injection, and has a pH of approximately 7.2. Each vial contains approximately 0.230 mL solution to allow intravitreal administration of 0.05 mL. Each PFS contains approximately 0.165 mL solution to allow intravitreal administration of 0.05 mL.

2.1.1 Drug substance

Brolucizumab (INN) is a humanized single-chain Fv (scFv) antibody fragment with a molecular weight of ~26 kDa which inhibits vascular endothelial growth factor A (VEGF-A) binding to its receptors VEGFR1 and VEGFR2.

The description of the active substance manufacturing process and process controls/tests is appropriately detailed and starts with the expansion (into flasks and bioreactors) of one vial of working cell bank (WCB) of the Escherichia coli BL21(DE3), which is used to inoculate the main fermenter.

The harvest is collected by centrifugation. The following steps include homogenization, inclusion bodies (IB) isolation by centrifugation, IB refolding, and filtration.

The purification process includes three chromatography steps and two concentration/diafiltration steps. The active substance is filtered, dispensed, and stored at -60°C.

A listing of raw materials used in the manufacturing process is presented. Raw materials are tested according to pharmacopeia (where available), or according to in-house monographs. No material of animal origin is used in the brolucizumab manufacturing process.

A two-tiered cell banking system, with a WCB derived from the Master Cell Bank (MCB), has been established. The expression of the expected cDNA sequence was confirmed. The genetic stability of the production cell line has been investigated and a limit of in vitro cell age was set.

In-process controls were provided and included process/product impurities, safety/microbial control, or process consistency.

Process validation consisted of the analysis of data derived from three consecutive full-scale lots of brolucizumab. Evaluation of process performance parameters demonstrates that the proposed manufacturing process is consistent.

The structure of brolucizumab was elucidated from a variety of biochemical, biophysical, and biological tests to provide an understanding of its structure and functional properties. The product-related impurities and process-related impurities are evaluated and their residual amounts are considered acceptable.

The proposed active substance specification is in line with ICH Q6B. The selection of tests includes appearance, identity, quantity, purity and impurity, and potency assay. The drug substance should be stored at the recommended condition of less than -60°C.

2.1.2 Drug product

Beovu® (brolucizumab) has been presented either as a solution for injection in a vial, or a solution for injection in a pre-filled syringe (PFS).

The manufacturing process of Beovu starts with the dilution of bulk active substance followed by pre-filtration and sterile filtration before being aseptically filled into glass

vials or syringes.

For each presentation, the validation of the finished product manufacturing process is based on the analysis of three batches covering the claimed batch size. The results demonstrated that the manufacturing process is robust and consistently yields product capable of meeting the pre-defined quality characteristics.

The finished product specification includes tests for general attributes, identity (chromatographic), purity (chromatographic), potency, bacterial endotoxin, and sterility.

The Applicant is claiming a 24-month shelf life when stored at 2-8°C. Based on real-time/real temperature stability results of Beovu in a vial and PFS, a 24-month shelf-life can be granted.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Brolucizumab is a drug for the treatment of neovascular (wet) age-related macular degeneration (nAMD). The *in vitro* binding assay indicated that the binding affinity of brolucizumab to $VEGF_{165}$ was superior to other VEGF-A inhibitors, including bevacizumab, ranibizumab, and aflibercept. Brolucizumab could bind to VEGF-A from humans and many experimental animal species except rabbit. The ELISA assays were used to investigate the effect of brolucizumab on blocking the interaction between VEGF-A and VEGFR. The separate results indicated that brolucizumab presented similar potency to ranibizumab or aflibercept. In addition, brolucizumab blocked VEGF-induced proliferation of cultured retinal endothelial cells.

In vivo studies demonstrated that brolucizumab inhibited VEGF-induced retinal vascular permeability and reduced retinal neovascularization in mice and rats. The secondary pharmacology study was not conducted since the antibody drug has high selectivity on target. Safety pharmacology studies were not conducted since brolucizumab would be intravitreally administered; the systemic exposure was very low and would not produce pharmacologic effects.

2.2.2 Toxicological Studies

The pivotal toxicity studies were repeated-dose studies in cynomolgus monkeys. Brolucizumab was intravitreally administered Q3W, or Q4W for up to 6 doses did not induce significant systemic changes. The ocular signs were considered to be caused by

the injection procedure since the signs presented in control and treatment groups. The half-life (t1/2) of brolucizumab in cynomolgus monkey is about 59 hours (in serum) and 82 hours (in the retina) following a single intravitreal injection; therefore the dosing frequency (Q3W or Q4W) in repeated-dose studies could be considered a design of many single-doses. The half-life of brolucizumab in humans is about 103 hours following a single intravitreal injection; the maximum frequency (Q4W) of clinical use could also be considered a single-dose. The 5-month dosing duration in repeated-dose toxicity studies could support the safety of brolucizumab. The results indicated that intravitreal administration of brolucizumab ophthalmic solution of 6 mg/eye was well tolerated in monkeys. Most of the findings were attributed to the injection procedure.

The anti-drug antibody (ADA) was detected, but the titers were not correlated with systemic exposure or toxicity. The other T cell proliferation assay was used to evaluate the immunogenicity. The results suggested that the immunogenic potential of brolucizumab in humans was low. Based on the ICH S6(R1) guideline, genotoxicity study and carcinogenicity study were not suggested to conduct. Since the low systemic exposure following intravitreal administration and the patient population of nAMD is usually >50 years old, the lack of reproductive and developmental toxicity studies was acceptable.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Brolucizumab is administered directly into the vitreous to exert local effects in the eye. After intravitreal administration of 6 mg brolucizumab per eye to patients with nAMD, the geometric mean C_{max} of free brolucizumab in the plasma was 49.0 ng/ml (range: 8.97 to 548 ng/ml) and was attained in 1 day. Brolucizumab concentrations were near or less than 0.5 ng/mL (LLOQ) at approximately 4 weeks after repeat dose administration and no accumulation in serum was observed in most patients.

Metabolism of brolucizumab has not been fully characterized. However, free brolucizumab is expected to undergo metabolism via proteolysis. The excretion of brolucizumab has not been fully characterized. However, free brolucizumab is expected to undergo target-mediated disposition and/or passive renal excretion. The estimated mean (± standard deviation) systemic half-life of brolucizumab is 4.4 days (± 2.0 days) after a single intravitreal dose.

2.3.2 Interaction Studies

No formal drug-drug interaction studies have been conducted. Brolucizumab is not

metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

2.3.3 Special Populations

90% of nAMD patients enrolled in pivotal study were elder than 65 years old and there were no relevant differences in systemic pharmacokinetics following intravitreal injection in a study with 22 patients aged 65 to 74 years, 18 patients aged 75 to 84 years and 3 patients aged ≥85 years.

While the mean systemic clearance values for patients with mild or moderate renal impairment were generally lower than patients with normal renal function, no significant impact of mild and moderate renal impairment on the overall systemic exposure to brolucizumab was observed. No patients with severe (<30 ml/min) renal impairment were studied. Brolucizumab has not been studied in patients with hepatic impairment. As significant increases in serum brolucizumab exposures are not expected with intravitreal route of administration, no dosage adjustment is needed based on renal or hepatic impairment status.

After dosing with brolucizumab for 88 weeks, treatment-emergent anti-brolucizumab antibodies were detected in 23 to 25% of patients. The significance of anti-brolucizumab antibodies on PK of brolucizumab is not known.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Study HAWK and HARRIER were both multinational, multicenter, randomized, double-blinded, active-controlled phase III studies. A total of 1825 subjects were enrolled and randomized in these two studies. The demographic and baseline ocular characteristics were generally similar between treatment arms in each study. Enrolled subjects were required not receiving prior anti-VEGF treatment.

Brolucizumab treatment was initiated with 3 monthly intravitreal injections at Week 0, 4, and 8 (loading phase). After the loading phase, subjects in the brolucizumab arm were scheduled for injections every 12 weeks (Q12W) unless disease was identified resulting in permanent adjustment to injections every 8 weeks (Q8W).

Non-inferiority of brolucizumab 6mg to aflibercept 2mg in terms of BCVA improvement from baseline to Week 48 with the non-inferior margin of 4 letters was demonstrated in

two studies (6.6 letters vs. 6.8 letters in Study HAWK and 6.9 letters vs. 7.6 letters in Study HARRIER). The treatment difference (brolucizumab 6mg -aflibercept 2mg) was -0.2 [95% CI: (-2.1, 1.8)] in Study HAWK and -0.7 [95% CI: (-2.4, 1.0)] in Study HARRIER. The lower bounds of the 95% CIs for the treatment differences were larger than the pre-specified noninferiority margin of -4 letters.

The estimated probability for a subject to maintain on the Q12W treatment interval at Week 44 was 55.6% in Study HAWK and 51.0% in Study HARRIER.

Overall, the two studies provided adequate evidence to support the efficacy of brolucizumab 6 mg for the treatment of neovascular (wet) age-related macular degeneration.

2.4.2 Safety Results

The safety data from Study HAWK and HARRIER were pooled for analysis.

The incidences of ocular adverse events (AEs) in the study eye were similar between the brolucizumab and active-controlled groups. The most frequently reported ocular AEs in the study eye were visual acuity reduced and conjunctival hemorrhage. The incidence of these 2 AEs was comparable between the two groups.

The incidence of serious ocular AEs in study eye was slightly higher in the brolucizumab group compared with the active-controlled group. The most frequently reported serious ocular AEs in study eye in the brolucizumab group was endophthalmitis.

There was a higher incidence in the overall incidence of ocular AEs of potential relevance to intravitreal anti-VEGF for the study eye in the brolucizumab group compared with the active-controlled group. The major difference was driven by intraocular inflammation or endophthalmitis. Besides, the incidences of arterial thromboembolic events, retinal arterial occlusive events and venous thromboembolic events were also slightly higher in the brolucizumab group compared with the active-controlled group.

Retinal vasculitis and retinal vascular occlusion associated with brolucizumab were reported after its initial approval in the United States.

The Applicant submitted the latest information of Study MERLIN voluntarily. This was a multinational, multicenter, randomized, double-blinded, active-controlled phase III study in subjects with nAMD who had poor response to prior anti-VEGF treatment. After the 3 monthly doses in the loading phase, subjects in the brolucizumab arm were scheduled for

injections every 4 weeks (Q4W). Subjects in the brolucizumab arm experienced a higher incidence of intraocular inflammation (including retinal vasculitis) and retinal vascular occlusion than subjects who received brolucizumab Q8W or Q12W maintenance dosing in Study HAWK and HARRIER. The interval between two brolucizumab doses during maintenance treatment should not be less than 8 weeks.

Based on the identified risks of intraocular inflammation, retinal vasculitis and retinal vascular occlusion associated with brolucizumab, a Risk Management Plan (RMP) is mandatory to assure safe use.

2.5 Bridging Study Evaluation

After single IVT 3 mg in target Japanese patients, the C_{max} and AUC_{inf} of serum brolucizumab were 0.58-fold and 0.24-fold in non-Japanese patients (within study). After single IVT 6 mg in target Japanese patients, the C_{max} and AUC_{inf} of serum brolucizumab were 1.74-fold and 1.46-fold in non-Japanese patients (within study). Due to no apparently accumulation after multiple dosing, the single dose comparison is acceptable.

Highly variable in serum brolucizumab was found. Brolucizumab is administered by intravitreal injection and its major site of action is the eye. It is not adequate to use the systemic data to determine the ethnic difference; therefore, it cannot be determined from PK aspect.

A total of 154 (14.3%) subjects in Japan were enrolled in Study HAWK and 45 (6.1%) subjects in Singapore, South Korea, Taiwan and Vietnam were enrolled in Study HARRIER. The trend of efficacy in Asian and non-Asian subjects was similar. The safety data between Asian and non-Asian subjects were generally comparable. The incidence of intraocular inflammation was higher in Asian subjects compared to non-Asian subjects. However, the severity and outcomes of these AEs were comparable between the two populations.

Considering the product characteristics, the indication and the provided Asian clinical information, the bridging study of brolucizumab was recommended waived.

2.6 Conclusion

The Applicant submitted supplements after queries. Based on the above multidiscipline review, the benefit-risk assessment for brolucizumab for the proposed indication was positive and review team recommends approval of brolucizumab.

A RMP is necessary.

3. Post-Marketing Requirements

- Implement the RMP, including the early intensive monitoring program.
- Submit the final clinical study report or complete safety assessment of Study MERLIN.