Amelivu

Ministry of Food and Drug Safety

APPROVED

PART A - ADMINISTRATIVE INFORMATION		
Entered by:	**Biosimilar Product Information**	
MAH	**Name of the biosimilar medicinal product**	Amelivu
MAH	**MAH**	Samsung Bioepis Co. Ltd., 76, Songdogyoyuk-ro, Yeonsu-gu Incheon, Republic of Korea
NRA	**Authorisation / Licence number**	Samsung Bioepis Co. Ltd., / 9
MAH / NRA	**API manufacturing facilities and batch release site for the finished product** (if applicable)	Not Released
MAH	**Name of the active substance**	Ranibizumab (INN)
MAH	**Pharmaco-therapeutic group**	ATC code: S01LA04
MAH	**Substance category**	Monoclonal antibodies
MAH	**Pharmaceutical form**	Clear to slightly opalescent, colorless to pale yellow solution
MAH	**Quantitative composition**	0.5 mg/vial (10 mg/mL)
MAH	**Route of administration**	Intravitreal (ITV)
MAH	**Packaging/material**	Glass vial
MAH	**Package size(s)**	1 vial/pack
MAH	**Local legal basis**	Pharmaceutical Affairs Act article 42 and Enforcement for drug safety article 4
MAH	**Local biosimilar guidelines**	Guidelines on the Evaluation of Biosimilar Products (MFDS 2021)
MAH	**Date of authorisation/licensing of biosimilar**	13 May 2022

	Reference Biotherapeutic Product (RBP) Information	
MAH	**Name of the RBP**	Lucentis
MAH	**Authorised indications for RBP**	Neovascular (wet) age-related macular degeneration (AMD) Visual impairment due to diabetic macular oedema (DME) Proliferative diabetic retinopathy (PDR) Visual impairment due to macular oedema secondary to Retinal vein occlusion (branch RVO or central RVO) Visual impairment due to choroidal neovascularization (CNV) Retinopathy of prematurity (ROP) in preterm infants
MAH	**Pharmaceutical form**	Clear to slightly opalescent, colorless to pale yellow solution
MAH	**Quantitative composition**	0.5 mg/vial (10 mg/mL)
MAH	**Route of administration**	Intravitreal (ITV)
MAH	**Packaging/material**	Glass vial
MAH	**Package size(s)**	1 vial/pack
MAH	**Authorisation (Licence) number (of RBP)**	Novartis Pharma Korea ltd./
MAH	**Date of authorisation (of RBP)**	27 July 2007
MAH	**Authorisation (Licence) Holder (of RBP)**	Ranibizumab (INN)
MAH	**Source of RBP (or other comparator) for comparability exercise**	Republic of Korea European Union United States
MAH / NRA	**Availability of the RBP assessment report (Korean)/link**	https://nedrug.mfds.go.kr/pbp/CCBBB01/getItemDetailCache?cacheSeq=200708787aupdateTs2023-07-03%2017:55:00.0b
	Summary of outcomes	
MAH	**Comparability exercise to demonstrate similarity to RBP**	Extensive comparability exercise including data form: physicochemical, biological characterization, *in vitro*, *in vivo non-clinical studies*, Efficacy, safety and immunogenicity studies
NRA	**Availability of full assessment report (Korean)/link**	https://nedrug.mfds.go.kr/pbp/CCBBB01/getItemDetailCache?cacheSeq=202202008aupdateTs2023-11-09%2011:24:15.063367b

MAH	**Indications applied for** (if different to RBP)	The indications applied for were all authorized for RBP except for the treatment of retinopathy of prematurity (ROP) in preterm infants (see section Authorized indications for RBP).
NRA	**Authorised indications for biosimilar**	Neovascular (wet) age-related macular degeneration (AMD) Visual impairment due to diabetic macular oedema (DME) Proliferative diabetic retinopathy (PDR) Visual impairment due to macular oedema secondary to Retinal vein occlusion (branch RVO or central RVO) Visual impairment due to choroidal neovascularization (CNV)

MAH (Marketing Authorisation Holder) or Sponsor
NRA (National Regulatory Authority) i.e. CA (Competent Authority)

PART B - SUBMITTED DATA AND REVIEWER SUMMARY	
Procedure: <Initial Application>	
MAH	**Quality data. Composition of the biosimilar product(s)**
	Ranibizumab Histidine Histidine hydrochloride monohydrate α,α-trehalose dihydrate Polysorbate 20 Water for injection
MAH	**Quality data. State-of-the-art methods**
	Structural Chracteristics - Primary structure : Molecular weight, Amino acid sequence, N-terminal sequence, C-terminal sequence, Peptide mapping, Post translational forms, Disulfide bond analysis, Free sulfhydryl group analysis, Non-canonical amino acid analysis and Extinction coefficient analysis - High order structure analysis : CD, FTIR, ITF, DSC, SV-AUC, SEC-MALS, DLS, MFI, H/DX-MS **Physicochemical Test** - Purity and Impurities, Charge variants, Hydrophobicity, Protein concentration **Biological properties** - HUVEC anti-proliferation assay, VEGF-Λ(165, 121) neutralization assay

	Immunochemial properties - VEGF-A(165, 121, 110, 189) binding assay (ELISA), VEGF-A(165) binding assay (SPR), VEGF-A family binding assay (SPR)
NRA	**Quality data assessment outcome**
	Comprehensive head-to-head comparability studies performed using state-of-the art analytical procedures demonstrated that all major quality attributes of Amelivu were comparable to those of Lucentis with respect to primary and higher order structures, physiochemical, biological and immunochemical properties. The similarity range was determined using the sufficient characterization data from EU Lucentis and US Lucentis and the bridging data demonstrated the equivalence of EU Lucentis, US Lucentis and KR Lucentis. Comparative forced degradation studies including heat stress, exposure to basic/acidic condition, oxidation and photo stress demonstrated similar degradation profiles for Amelivu and Lucentis. Overall, based on the totality of evidence with respect to all quality characteristics and global clinical studies, the biosimilarity of Amelivu and Lucentis was concluded.
MAH	**Mechanism of action**
	Amelivu(ranibizumab) is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment directed against human vascular endothelial growth factor A (VEGF-A), which is a glycoprotein implicated in the pathophysiology of age-related macular degeneration.
MAH	**Nonclinical data. *In vitro* studies**
MAH	**Nonclinical data. *In vivo* studies**
	***In vivo* pharmacological study** **Pharmacokinetics** **Toxicity Study (including TK)** A 4-week repeat-dose toxicity study using cynomolgus monkeys
NRA	**Nonclinical data assessment outcome**
	1. *In vitro* studies All *in vitro* PD studies demonstrated the similarity between Lucentis and Amelivu. **2. *In vivo* studies** No *in vivo* PD and PK animal studies have been performed in order to provide complementary information on biosimilarity in addition to the totality of data obtained (including quality, *in vitro*, and clinical data). In a 4-week repeat-dose toxicity study using cynomolgus monkeys, all animals treated

	Amelivu or Lucentis were well tolerated at a dose level of 500 μg/eye and there were no differences in toxicity profile between two groups.
	CLINICAL STUDIES **- include relevant study data from the following (not all may be required) which have been included to demonstrate biosimilarity.** • **Pharmacokinetic (PK)** • **Pharmacodynamic (PD)** • **Efficacy** • **Safety** • **Immunogenicity**
MAH	**Clinical data. PK studies**
	No specific PK study was conducted.
NRA	**Clinical data. PK data assessment outcome**
	Not applicable
MAH	**Clinical data. PD studies**
	No specific PD study was conducted.
NRA	**Clinical data. PD data assessment outcome**
	Not applicable
MAH	**Clinical data. Efficacy studies**
	Study Number: SB11-G31- AMD • Summary of design: A randomized, double-blind, parallel group, multicenter Phase III study to compare the efficacy, safety, PK and immunogenicity between Amelivu and US Lucentis in patients with neovascular age-related macular degeneration (AMD). Eligible patients were randomized in a 1:1 ratio to receive either 0.5 mg Amelivu or 0.5 mg Lucentis), Eligible randomized patients received either Amelivu or Lucentis on Day 1 every 4 weeks into the study eye. Treatment was repeated up to Week 48 for a total of 13 doses of IP. Of the 705 subjects who were randomized, 634 (89.9%) subjects completed 52 weeks of the study. Prior to Week 52, 71 (10.1%) subjects discontinued treatment with the IP. The most common reasons for withdrawal from IP were consent withdrawal by subject (25 [3.5%] subjects) and adverse event (13 [1.8%] subjects). • Objective and primary endpoint: Demonstration of similarity in clinical efficacy between Amelivu or Lucentis in terms of change from baseline in BCVA at Week 8. • Secondary objective: Evaluation of the safety of Amelivu and Lucentis Evaluation of the immunogenicity of Amelivu and Lucentis Evaluation of the systemic exposure of Amelivu and Lucentis in subjects participating in PK evaluation

	• Dose used: 0.5 mg Amelivu or Lucentis via ITV route every 4 weeks up to Week 48 (13 doses in total)
NRA	**Clinical data. Efficacy data assessment outcome**
	The primary efficacy analysis of BCVA was performed for the Full Analysis Set (FAS) with the change from baseline in BCVA at Week 8 using ANCOVA model with the baseline BCVA as a covariate and region (country) and treatment group as factors. The equivalence in BCVA was declared if the two-sided 90% CI of the difference in terms of BCVA LS mean change from baseline at Week 8 between Amelivu and Lucentis lies within the pre-defined equivalence margin of [−3 letters, 3 letters].

Analysis Set	Treatment (N)	Least Squares Mean (SE)	Difference (SB11-Lucentis)	
			Mean (SE)	90% CI
FAS	SB11 (N=351)	6.18(0.52)	-0.80(0.62)	[-1.827, 0.219]
	Lucentis (N=353)	6.99(0.51)		

To explore the robustness of the change from baseline in BCVA at Week 8 for the FAS, the same analysis was also performed for the Per-protocol Set for BCVA (PPS-BCVA). In addition, the change from baseline in BCVA at Week 8 was analyzed for the FAS by using available case, last observation carried forward (LOCF), and MI-MNAR approaches. For the PPS, the treatment difference between Amelivu and Lucentis was −0.76 and the 90% CI of the adjusted treatment difference of Amelivu and Lucentis was [−1.808, 0.286]. The ad-hoc analysis of adjusted treatment difference in between Amelivu and Lucentis® was −0.76 letters and the 95% CI of the adjusted treatment difference was [−2.010, 0.487], both were equivalence margin of [−3 letters, 3 letters].

Analysis Set	Treatment (N)	Least Squares Mean (SE)	Difference (SB11-Lucentis)	
			Mean (SE)	90% CI
PPS	SB11(N=336)	6.39(0.52)	-0.76(0.64)	[-1.808, 0.286]
	Lucentis(N=333)	7.15(0.52)		

The 90% CI for the changes from baseline in BCVA at Week 8 in the PPS and FAS were entirely contained within the equivalence margin. In addition, further efficacy endpoints as vial between Amelivu and Lucentis treatment groups were similar.

MAH	**Clinical data. Safety/ Immunogenicity studies**
	Safety and immunogenicity data were collected from all clinical studies: SB11-G31-AMD.
NRA	**Clinical data. Safety/ Immunogenicity data assessment outcome**
	Safety. The overall safety profiles were similar between Amelivu and Lucentis treatment groups.

	Immunogenicity. The overall immunogenicity profiles were similar between the Amelivu and Lucentis treatment groups.	
MAH	**Interchangeability data**	
	No additional data were provided	
MAH	**Additional information about the comparability exercise**	Not applicable
MAH	**Post-authorization measures**	
	Re-examination study in Korea. - Period: 2022.5.13~2026.8.12	
NRA	**Post-authorization risk measures: assessment outcome.**	
	Post-marketing surveillance study (re-examination study) plan was considered to be acceptable. A sufficient number of subjects was planned for re-examination study of Amelivu (about 600 subjects)	
MAH	**Availability of additional relevant information in the local language/ link**	Not applicable

PART C - REVIEWER CONCLUSIONS	
NRA	**Conclusions on biosimilarity, approval**

The data provided by the Applicant were in line with the local legislation and guidelines.

Quality

The biosimilar manufacturer has developed and validated a process capable of consistently manufacturing a product of appropriate quality, with satisfactory control of impurities. Manufacturing operations are carried out according to cGMP requirements.

The quality attributes of high relevance for clinical safety and efficacy, e.g. physicochemical characteristics and biological activities of Amelivu were comparable to those of the reference biotherapeutic product Lucentis

Nonclinical

No major differences in nonclinical data were observed for Amelivu compared to the reference biotherapeutic product Lucentis.

Clinical Studies

The Phase III studies to demonstrate biosimilarity conducted in neovascular AMD patients provided robust evidence that there are no clinically meaningful differences between Amelivu and the reference biotherapeutic product Lucentis.

Safety: The adverse events (AEs) observed with Amelivu were in the similar range as the AEs observed with the reference biotherapeutic product Lucentis.

Immunogenicity: The proportion of patients who developed anti-drug antibody (ADA) with Amelivu was generally similar to the reference biotherapeutic product Lucentis.

Extrapolation of indications: Based on the totality of evidence, all indications except for 'Retinopathy of prematurity (ROP) in preterm infants' requested for Lucentis (see Section A, summary of outcomes) were considered to be extrapolated to Amelivu.

Risk Management

The risk management plan was considered to be acceptable.

Overall Conclusion

Satisfactory assurance of biosimilarity was demonstrated using an appropriate comparability exercise. The biosimilar product Amelivu was considered approvable.