Xelenka

Ministry of Food and Drug Safety

APPROVED

PART A - ADMINISTRATIVE INFORMATION		
Entered by:	**Biosimilar Product Information**	
MAH	**Name of the biosimilar medicinal product**	Xelenka
MAH	**MAH**	LG Chem, Ltd. LG Twin Tower, 128, Yeoui-daero, Yeongdeungpo-gu, Seoul, Republic of Korea 07336
NRA	**Authorisation / Licence number**	LG Chem, Ltd./ No. 5161 (40mg/0.4mL prefilled syringe). No. 5162 (40mg/0.4mL autoinjector). No. 5163 (20mg/0.2mL prefilled syringe). No. 5164 (80mg/0.8mL prefilled syringe)
MAH / NRA	**API manufacturing facilities and batch release site for the finished product** (if applicable)	N/A <Confidential>
MAH	**Name of the active substance**	Adalimumab (INN)
MAH	**Pharmaco-therapeutic group**	ATC code: L04AB04
MAH	**Substance category**	Monoclonal antibodies
MAH	**Pharmaceutical form**	Colorless and almost clear solution or a slightly opalescent solution.
MAH	**Quantitative composition**	20mg/0.2mL / syringe 40mg/0.4mL / syringe 80mg/0.8mL / syringe 40mg/0.4mL / autoinjector
MAH	**Route of administration**	Subcutaneous injection

MAH	**Packaging/material**	Glass syringe
MAH	**Package size(s)**	1 pre-filled syringe/box 1 autoinjector/box
MAH	**Local legal basis**	Pharmaceutical Affairs Act article 31 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**	14 December 2023
	Reference Biotherapeutic Product (RBP) Information	
MAH	**Name of the RBP**	Humira®
MAH	**Authorised indications for RBP**	<20mg and 40mg prefilled syringe and 40mg autoinjector> Rheumatoid arthritis Psoriatic arthritis Axial spondyloarthritis *Ankylosing spondylitis* *Axial spondyloarthritis without radiographic evidence of AS* Crohn's disease Psoriasis Ulcerative colitis Behcet's colitis Hidradenitis suppurativa (HS) Uveitis Paediatric Crohn's disease Juvenile idiopathic arthritis *Polyarticular juvenile idiopathic arthritis* *Enthesitis-related arthritis* <80mg prefilled syringe> Rheumatoid arthritis Crohn's disease Psoriasis Ulcerative colitis Behcet's colitis Hidradenitis suppurativa (HS) Uveitis Paediatric Crohn's disease
MAH	**Pharmaceutical form**	Clear to slighthly opalescent, colorless to pale brown solution

MAH	**Quantitative composition**	20mg/0.2mL / syringe 40mg/0.4mL / syringe 80mg/0.8mL / syringe 40mg/0.4mL / autoinjector
MAH	**Route of administration**	Subcutaneous injection
MAH	**Packaging/material**	Glass syringe Autoinjector
MAH	**Package size(s)**	1 pre-filled syringe/box 1 pre-filled pen/box
MAH	**Authorisation (Licence) number (of RBP)**	Abbie Korea / No. 30 (40mg/0.4mL prefilled pen). No. 31(40mg/0.4mL prefilled syringe). No. 34 (80mg/0.8mL prefilled syringe). No. 35 (20mg/0.2mL prefilled syringe).
MAH	**Date of authorisation (of RBP)**	21 June 2017
MAH	**Authorisation (Licence) Holder (of RBP)**	Abbie Korea Co., Ltd.
MAH	**Source of RBP (or other comparator) for comparability exercise**	Republic of Korea
MAH / NRA	**Availability of the RBP assessment report** (Korean)/**link**	Yes / 20mg/0.2mL prefilled syringe (Link), 40mg/0.4mL prefilled syringe (Link), 80mg/0.8mL prefilled syringe (Link), 40mg/0.4mL autoinjector (Link)
	Summary of outcomes	
MAH	**Comparability exercise to demonstrate similarity to RBP**	Extensive comparability exercise including; Physicochemical and biological characterization Non-clnical stuidies (*in vitro* and *in vivo*) Clinical studies to assess pharmacokinetics, efficacy, safety and immunogenicity studies
NRA	**Availability of full assessment report** (Korean)/**link**	Yes / 20mg/0.2mL prefilled syringe (Link), 40mg/0.4mL prefilled syringe (Link), 80mg/0.8mL prefilled syringe (Link), 40mg/0.4mL autoinjector (Link)
MAH	**Indications applied for** (if different to RBP)	All authorized indications of reference product were submitted (see 'Authorised indications for RBP')

NRA	**Authorised indications for biosimilar**	<20mg and 40mg prefilled syringe and 40mg autoinjector> Rheumatoid arthritis Psoriatic arthritis Axial spondyloarthritis *Ankylosing spondylitis* *Axial spondyloarthritis without radiographic evidence of AS* Crohn's disease Psoriasis Ulcerative colitis Behcet's colitis Hidradenitis suppurativa (HS) Uveitis Paediatric Crohn's disease Juvenile idiopathic arthritis *Polyarticular juvenile idiopathic arthritis* *Enthesitis-related arthritis* <80mg prefilled syringe> Rheumatoid arthritis Crohn's disease Psoriasis Ulcerative colitis Behcet's colitis Hidradenitis suppurativa (HS) Uveitis Paediatric Crohn's disease

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)**
	Adalimumab Sucrose L-Methionine L-Arginine hydrochloride Polysrobate 80 Water for injection
MAH	**Quality data. State-of-the-art methods**
	Structural Chracteristics - Primary structure analysis : Amino acid composition, Peptide mapping, Full amino acid sequencing, N-terminal amino acid sequencing, C-termianl amino acid sequencing, Molecular weight, Extinction coefficient - High order structure analysis : Disulfide bond analysis, Free sulfhydryl content, CD, FT-IR, Fluorescene, DSC **Physicochemical Test** - Purity and impurity profiles, Charge variants, Monosaccharide composition, N-glycan profile, Protein concentration, Post-translational modification (Deamidation, Oxidation) **Biological properties** - Fab-related biological activity: sTNF-α Neutralization Activity, sTNF-α Binding (SPR), IL-8 Release Inhibition Activity, Apoptosis Inhibition Activity, Inhibition of TNF-α induced CAM (VCAM-1) expression, LT-α Binding(SPR), mTNF-α Binding and Induction of Apoptosis by Reverse Signaling - Fc-related biological activity: FcRn, C1q, FcγR (FcγRIIa(R), FcγRIIa(H), FcγRIIb, FcγR IIIa(V), FcγRIIIa(F), FcγRIIIb) Binding, ADCC acvitity, CDC activity **Degradation characteristics** - Temperature stress, pH stress, Photostability, Oxidation induction
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 Xelenka (LBAL) were comparable to those of Humira® with respect to physiochemical, biological and immunochemical properties. The similarity range was determined using the sufficient characterization data from KR Humira®.

	In physico-chemical characterization, there were slight differences in N-glycan profiles, charge variants. However, the differences were appropriately justified to have no impact on efficacy and safety of Adalimumab. Biological characterization proved that there was highly similar in MoA (Mode of Action)-related activities such as TNF-α neutralizing activity and TNF-α binding affinities. Also, the effector functions related to N-glycan were similar between Humira® and Xelenka except ADCC under low IgG condition. However, in the case of ADCC under the mimic of physiological condition, it was confirmed that Humira® and Xelenka are similar. In addition to characterization study, biosimilarity was further assessed by change in impurity profile under stress. Comparative evaluations were performed under various conditions such as light exposure, heat, pH, oxidation, etc. As a result, the main stress factors affecting product quality were light exposure, heat and pH, which were the same in both Humira® and Xelenka. In particular, under light exposure condition of packaging I (nude syringe), the change in the charge profile and the oxidation content was different between Humira® and Xelenka, but it is considered to be due to the different formulation rather than the difference in characteristics. Overall, based on the totality of evidence with respect to all quality characteristics and clinical studies, the biosimilarity of Xelenka to Humira® was concluded.
MAH	**Mechanism of action**
	Adalimumab is a recombinant human monoclonal antibody that selectively binds to tumor necrosis factor α (TNF α), that is a cytokine involved in modulating the immunological responses by blocking TNF receptors to reduce inflammation in inflammatory or auto-immune diseases.
MAH	**Nonclinical data. *In vitro* studies**
	sTNF-α Neutralization Activity, Human Soluble TNF-α Binding (SPR), IL-8 Release Inhibition Activity, Apoptosis Inhibition Activity, Inhibition of TNF-α induced CAM (VCAM-1) expression, LT-α Binding, mTNF-α Binding, Induction of Apoptosis by Reverse Signaling, FcRn, C1q, FcγR, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb Binding and ADCC/CDC Activities
MAH	**Nonclinical data. *In vivo* studies**
	***In vivo* pharmacological study** *In vivo* PD study to demonstrate similarity in efficacy between Xelenka (LBAL) and Humira® (Korea and EU) in Tg197 transgenic mouse model of arthrits at dose levels of 1, 3, and 10 mg/kg twice weekly for 7 weeks. **Pharmacokinetics** PK Study to demonstrate similarity in PK profiles between Xelenka (LBAL) and Humira® (Korea and EU) following single subcutaneous administraton at a dose level of 1 mg/kg in cynomolgus monkeys.

	Toxicity Study (including TK) A 13-week repeated-dose toxicity study to demonstrate similarity in toxicity, toxicokinetics and immunogenicity profiles between Xelenka (LBAL) and Humira® (Korea) following repeated subcutaneous administraton at a dose level of 83 mg/kg in cynomolgus monkeys
NRA	**Nonclinical data assessment outcome**
	1. *In vitro* studies Xelenka (LBAL) showed its comparability to Humira® via *in vitro* PD studies. **2. *In vivo* studies** In vivo PK studies with Tg197 transgenic mouse model showed similar profile between Xelenka (LBAL) and Humira® (Korea and EU). In a 13-week repeat-dose toxicity study using cynomolgus monkeys, all of animals treated Xelenka (LBAL) or Humira® (Korea) were well tolerated at a dose level of 83 mg/kg and Xelenka (LBAL) demonstrated its similarity to the reference product in toxicity, toxicokinetics and immunogenicity through this toxicity study.

	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**
	Study LG-ALCL001 and LBAL23N811 were performed to verify pharmacokinetic (PK) similarity of Xelenaka and Humira®, then between two formulations of Xelenka. **Study LG-ALCL001** ● Summary of design : a single center, randomized, double-blind, active control, parallel-group study to compare the pharmacokinetics, safety, and tolerability of Xelenka(LBAL) and Humira® ● Randomized subjects: 116 healthy subjects (58 subjects per each group) ● Objective and primary endpoint: to demonstrate Pharmacokinetic (PK) similarity in terms of AUC_{inf}, C_{max} of Xelenka(LBAL) and Humira® in healthy subjects after the single dose injection ● Dose used : Xelenka(LBAL) 40mg/0.8mL PFS, Humira® 40mg/0.8mL PFS ● Length of the study : 65 days **Study LBAL23N81** ● Summary of design : a single center, randomized, open-label, parallel-group study to verify the bioequivalence between high-concentration (40 mg/0.4 mL) and low-concentration (40 mg/0.8 mL) of Xelenka(LBAL) ● Randomized subjects: 288 healthy subjects (144 subjects per each group)

	● Objective and primary endpoint: to verify the bioequivalence in terms of AUC_{last}, C_{max} of high-concentration (40 mg/0.4 mL) versus low-concentration (40 mg/0.8 mL) of Xelenka(LBAL) in healthy subjects after the single dose injection ● Dose used : Xelenka(LBAL) 40mg/0.4mL PFS, Xelenka(LBAL) 40mg/0.8mL PFS ● Length of the study : 65 days
NRA	**Clinical data. PK data assessment outcome**
	Study LG-ALCL001 The primary PK results: this study showed comparability between the two products as 90% CIs of the geometric mean ratios of Xelenka(LBAL) to Humira® for C_{max} and AUC_{inf} were 1.01(0.92-1.11) and 0.96(0.83-1.10) respectively and these all calculated CIs for the log-transformed ratios were within the bio-equivalence criteria range of 0.8-1.25 (the acceptance range of 80-125%). **Study LBAL23N81** The primary PK results: the statistical analysis demonstrated that the mean peak and total systemic exposure (C_{max} and AUC_{last}) were equivalent between High-concentration and Low-concentration of Xelenka(LBAL). 90% CIs of the geometric mean ratio (High-concentration LBAL versus Low-concentration LBAL) of C_{max} and AUC_{last} were 0.9402 (0.8919-0.9911) and 1.0893(1.0056-1.1800) in log-transformed, respectively and therefore within the predefined 80% to 125% equivalence margin in all instances.
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 LG-ALCL002 was conducted to assess comparability of efficacy between Xelenka and Humira®. **Study LG-ALCL002** ● Summary of design: A multicenter (Korea and Japan), randomized, double-blind, active-control, parallel-group, phase III study to investigate the comparable clinical efficacy and safety (including Immunogenicity) of Xelenka(LBAL) with Humira® when co-administered with Methotrexate in Patients with Active Rheumatoid Arthritis. Eligible patients were randomized in a 1:1 ratio to receive either Xelenka(LBAL) or Humira® for 24 weeks. Then all patients underwent the second randomization

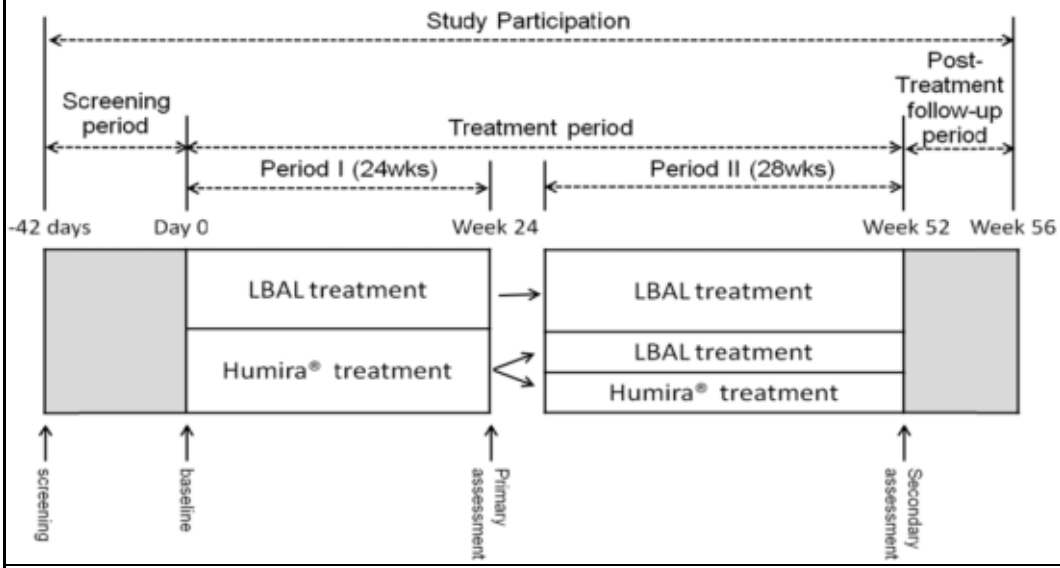
process for 28 weeks. Patients who were initially randomly assigned to Humira® were randomized again in a ratio of 1:1 to either continue Humira® or undergo transition to Xelenka(LBAL). All patients who were initially randomly assigned to Xelenka(LBAL) at Day 0 (week 0) continued their treatment with Xelenka(LBAL).

Number of subjects: total 383 rheumatoid arthritis patients. 192 cases in Xelenka(LBAL) continued treatment group, 96 cases in the transitioned treatment group and 95 cases in Humira® continued treatment group.

- Objective and primary endpoint: to investigate the comparable clinical efficacy between LBAL and Humira® at determined by clinical response according to the mean change from baseline in DAS28-ESR score at Week 24.

- Secondary objective: to evaluate additional efficacy (DAS28-ESR change of the LBAL-LBAL versus Humira®-Humira® arm at week 12 and 52, DAS28-ESR remission rate - DAS28-ESR < 2.6 , proportion of responders with EULAR response, ACR20, ACR50, ACR70 response rate at week 12, 24, 52), pharmacokinetics (PK) and overall safety, including immunogenicity.

- Dose used: LBAL 40 mg or Humira® 40 mg by SC injection every other week



NRA

Clinical data. Efficacy data assessment outcome

Primary endpoint : The change from baseline in DAS28-ESR at 24 weeks. The estimated difference [two-sided 95% confidence interval] for LBAL arm versus Humira® arm in the change of DAS28-ESR (least-squares mean) at 24 weeks by FAS1 was 0.083 [-0.1385 to 0.3044] (analysis by ANCOVA modelling).
Both this estimate and the two-sided 95% confidence interval fell within the pre-defined equivalence margin of clinical efficacy between Xelenka (LBAL) and Humira® arms (-0.6 to 0.6).

		Least Square Means with 95% CI
	The change from baseline in DAS28-ESR	
	Xelenka (LBAL) (N=191)	-2.448 [-2.6308, -2.2659]
	Humira® (N=190)	-2.531 [-2.7077, -2.3549]
	Estimated treatment difference	0.083 [-0.1385, 0.3044]

Analysis by ANCOVA modelling. DAS28-ESR at baseline were used as factors, with RDs and without drug group, national and Biological DMARDs use history, and as covariates.

As the secondary endpoint observed at week 12, the estimate of two-sided 95% confidence interval for the difference in DAS28-ESR change (least squares) of the LBAL-LBAL versus Humira®-Humira® arm was 0.210 [-0.0512 to 0.4713], which was not significantly different between two arms. At the same time point, other secondary endpoints (DAS28-ESR remission rate - DAS28-ESR < 2.6 , proportion of responders with EULAR response, ACR20 response rate, and ACR70 response rate) were not meaningfully different between two arms as well. At weeks 24 and 52, any of the secondary endpoints showed no significant differences between the LBAL-LBAL and Humira®-Humira® arms including those endpoints observed differently at week 12 (proportion that achieved good EULAR response, ACR50 response rate).

MAH	**Clinical data. Safety/ Immunogenicity studies**
	Safety and immunogenicity data were collected from three clinical studies: LG-ALCL001, LBAL23N81 and LG-ALCL002
NRA	**Clinical data. Safety/ Immunogenicity data assessment outcome**
	Safety The overall safety profiles were similar between Xelenka(LBAL) and Humira® treatment groups. Immunogenicity The overall immunogenicity profiles were similar between Xelenka(LBAL) and Humira® treatment groups.
MAH	**Interchangeability data**
	Interchangeability with reference product is not claimed by MAH (Data to support interchangeability with reference product was not submitted.)
MAH	**Additional information about the comparability exercise** — Not applicable
MAH	**Post-authorization measures**
	Re-examination study in Korea. - Period: 14 December 2023 ~ 14 December 2027

NRA	**Post-authorization risk measures: assessment outcome.**	
	Post-marketing surveillance study (re-examination study) plan was considered to be acceptable.	
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 the product of appropriate quality, with satisfactory control of impurities. Manufacturing operations are carried out according to GMP requirements.

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

Nonclinical

No major differences in nonclinical data were observed for Xelenka compared to the reference biotherapeutic product Humira®.

Clinical Studies

The Phase I and Phase III studies conducted in healthy volunteers and RA patients to demonstrate the bio-similarity provided robust evidence that there are no clinically meaningful differences between Xelenka and the reference bio-therapeutic product Humira®. Besides, an additional clinical study showed the PK equivalency between two formulations (Low and High-concentration) of Xelenka.

The safety profile (ADRs) observed in Xelenka were similar to that observed in the reference bio-therapeutic product, Humira®. In general The proportion of patients who got ADA developed with Xelenka was similar to that of the reference bio-therapeutic product Humira®.

Extrapolation of indications: Based on the totality of evidence, all indications requested for Humira® (see Section A, summary of outcomes) were considered to be extrapolated to Xelenka.

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 Humira® was considered approvable.