Hadlima

Ministry of Food and Drug Safety

APPROVED

PART A - ADMINISTRATIVE INFORMATION		
Entered by:	**Biosimilar Product Information**	
MAH	**Name of the biosimilar medicinal product**	Hadlima (Company project code: SB5)
MAH	**MAH**	Samsung Bioepis (Songdo-dong) 107, Chemdan-daero, Yeonsu-gu, Incheon, Republic of Korea
NRA	**Authorisation / Licence number**	Samsung Bioepis Co. Ltd., /3
MAH / NRA	**API manufacturing facilities and batch release site for the finished product** (if applicable)	< N/A > < Confidential – Not Released >
MAH	**Name of the active substance**	Adalimumab (INN)
MAH	**Pharmaco-therapeutic group**	ATC code: L04AB04
MAH	**Substance category**	Monoclonal antibody
MAH	**Pharmaceutical form**	Solution for injection in a pre-filled syringe
MAH	**Quantitative composition**	40 mg of adalimumab in a total volume of 0.8 ml
MAH	**Route of administration**	SC (Subcutaneous)
MAH	**Packaging/material**	Syringe/glass
MAH	**Package size(s)**	1 pre-filled syringe/pack
MAH	**Local legal basis**	Pharmaceutical Affairs Act article 42 and Enforcement for the drug safety article 4
MAH	**Local biosimilar guidelines**	Guidelines on the Evaluation of Biosimilar Product(MFDS, 2014)
MAH	**Date of authorisation/licensing of biosimilar**	20 September 2017
	Reference Biotherapeutic Product (RBP) Information	
MAH	**Name of the RBP**	Humira
MAH	**Authorised indications for RBP**	Adults ▪ Rheumatoid arthritis ▪ Psoriatic arthritis

		▪ Ankylosing spondylitis ▪ Non-radiographic axial spondyloarthritis ▪ Adult Crohn's Disease ▪ Plaque psoriasis ▪ Ulcerative Colitis ▪ Intestinal Behçet's disease ▪ Hidradenitis suppurativa ▪ Uveitis Pediatric ▪ Pediatric Crohn's Disease ▪ Polyarticular juvenile idiopathic arthritis ▪ Enthesitis-related arthritis ▪ Pediatric plaque psoriasis ▪ Pediatric uveitis
MAH	**Pharmaceutical form**	Solution for injection in a pre-filled syringe Solution for injection in a pre-filled pen
MAH	**Quantitative composition**	40 mg of adalimumab in a total volume of 0.8 ml
MAH	**Route of administration**	SC (Subcutaneous)
MAH	**Packaging/material**	Syringe/glass
MAH	**Package size(s)**	1 pre-filled syringe/pack 1 pre-filled pen/pack
MAH	**Authorisation (Licence) number (of RBP)**	AbbVie Korea / 13
MAH	**Date of authorisation (of RBP)**	19 July 2006
MAH	**Authorisation (Licence) Holder (of RBP)**	Abbvie Korea
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** (language)/**link**	Initial Authorization https://www.nifds.go.kr/brd/m_88/list.do?itm_seq_1=&srchTp=0&srchWord=%ED%9C%B4%EB%AF%B8%EB%9D%BC
	Summary of outcomes	
MAH	**Comparability exercise to demonstrate similarity to RBP**	Physicochemical and biological characterization study Comparative *in vitro* and *in vivo* non-clinical studies (PK/PD study) Comparative clinical studies(PK, efficacy, safety and immunogenicity).
NRA	**Availability of full assessment report** (language)/**link**	Initial Authorization https://www.nifds.go.kr/brd/m_88/list.do?itm_seq_1=&srchTp=0&srchWord=%ED%95%98%EB%93%9C%EB%A6%AC%EB%A7%88

MAH	**Indications applied for** (if different to RBP)	Adults ▪ Rheumatoid arthritis ▪ Psoriatic arthritis ▪ Ankylosing spondylitis ▪ Non-radiographic axial spondyloarthritis ▪ Adult Crohn's Disease ▪ Plaque psoriasis ▪ Ulcerative Colitis Pediatric ▪ Polyarticular juvenile idiopathic arthritis ▪ Enthesitis-related arthritis
NRA	**Authorised indications for biosimilar**	Adults ▪ Rheumatoid arthritis ▪ Psoriatic arthritis ▪ Ankylosing spondylitis ▪ Non-radiographic axial spondyloarthritis ▪ Adult Crohn's Disease ▪ Plaque psoriasis ▪ Ulcerative Colitis Pediatric ▪ Polyarticular juvenile idiopathic arthritis ▪ Enthesitis-related arthritis

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> <Variation / Supplement> **<Variation number and scope: [Quality / Safety / Efficacy / Risk Management] and description>**	
MAH	**Quality data. Composition of the biosimilar product(s)**
	Adalimumab 40 mg Sodium citrate Critric acid monohydrate Histidine Histidine hydrochloride monohydrate Sorbitol Polysorbate 20 Water for Injection
MAH	**Quality data. State-of-the-art methods**
	Structural Characteristics - Primary Structure analysis: Molecular weight, Amino acid sequence, N- terminal sequence, C-terminal sequence, Peptide map, Disulphide bridges, Free sulphydryl groups, Methionine oxidation, Asparagine deamidation - High order structure analysis **Physiochemical Test** - Purity and impurity profiles, Charge variants, N-glycan profile, protein concentration **Biological Activities** - Fab-related biological properties: TNF-α binding, TNF-α neutralisation, and apoptosis activity - Fc-related biological properties: FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa, FcRn, C1q binding and ADCC/CDC activities - Additional biological properties: inhibition of cytokine release assay (in vitro IBD model), inhibition of apoptosis assay (in vitro IBD model), regulatory macrophage function assay, inhibition of adhesion molecule expression, transmembrane TNF-α binding assay, FcγRIIIa (158F/F) binding, FcγRIIIb binding and LTα3 binding assay **Degradation characteristics** - Temperature stresses, Photostability, Oxidation induction
NRA	**Quality data assessment outcome**
	Comprehensive head-to-head comparability studies were performed using orthogonal, highly sensitive test methods to evaluate similarity between Hadlima and Humira. The similarity assessment demonstrated that major quality attributes of Hadlima were comparable to those of Humira with respect to the primary and higher order structures, post-translational modifications, physicochemical and biophysical properties, and biological activities. The similarity range was defined using the sufficient batches of EU Humira, and the bridging data demonstrated the equivalence of EU Humira, US Humira, KR Humira, and Hadlima. Due to the complex heterogeneity in the structure of Adalimumab, slight differences were found in non-glycosylated havy chain (NGHC), charge variants, binding affinity to FcγR

	and post-translational modifications including N-glycan profile, C-terminal Lys variants, and oxidation compared to Humira; higher levels of NGHC, Afucose, and acidic variants, and lower levels of G0F, C-terminal Lys, and basic variants. However, those differences were not considered clinically meaningful since those had no impact on the biological activities associated with the known primary mechanism of action including binding affinity to TNF-a, C1q, FcγR, and FcγRn, apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement dependent cytotoxicity (CDC), as determined by Structure-activity relationship (SAR) studies. Overall, based on the totality of evidence with respect to all quality characteristics and global clinical studies, the biosimilarity of Hadlima to the Humira was concluded
MAH	**Mechanism of action**
	Hadlima (Adalimumab) is a genetically engineered recombinant human immunoglobulin IgG1 monoclonal antibody that neutralises the biological function of both soluble and transmembrane forms of TNF-α by blocking its interaction with the p55 and p75 cell surface TNF receptors and modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration
MAH	**Nonclinical data. *In vitro* studies**
	Non-clinical studies conducted during development of SB5 include examination of TNF-α neutralization assay, Apoptosis activity, ADCC/CDC activity, TNF-α binding activity, FcγRIa binding assay, FcγRIIa binding assay, FcγIIb binding assay, FcγRIIIa binding assay, FcγRIIIb binding assay, FcRn binding assay, C1q binding assay, Apoptosis assay in *in vitro* IBD model, Inhibition of IL-8 cytokine release in *in vitro* IBD model, Inhibition of sVCAM-1 adhesion molecule expression, tmTNF-α binding assay, Evaluation of regulatory macrophage induction function, FcγRIIIa binding assay (158 F/F), FcγRIIIb binding assay and TNF-β (LTα3) binding assay.
MAH	**Nonclinical data. *In vivo* studies**
	***In vivo* pharmacological study** *In vivo* PD study to demonstrate similarity in efficacy between SB5 and US Humira in Tg197 transgenic mousde model of arthritis at dose levels of 0.5, 3, and 10 mg/kg twice weekly for 7 weeks. **Pharmacokinetics/Toxicokinetics** Similarity in the PK/TK profiles between SB5 and US Humira in cynomolgus monkeys following repeated subcutaneous administraton at a dose level of 32 mg/kg, as part of the 4-week repeat-dose toxicity study. **Toxicity study** A 4-week comparative repeat-dose toxicity study in cynomolguos monkey to demonstrate similarity in toxicity, toxicokinetic, and immunogenicity profiles of SB5 and US Humira® at a dose level of 32 mg/kg.
NRA	**Nonclinical data assessment outcome**
	1. *In vitro* studies See Quality assessment data outcome. *2. In vivo* studies

	In vivo pharmacological study (Tg197 transgenic mouse model of arthritis) showed similar result between the SB5 and US Humira® treated groups. TK studies in 4-week repeat-dose toxicity in cynomolgus monkey, showed similar PK profile between the SB5 and US Humira® treated groups ($C_{max,}$ and AUC_{0-t}). A 4-week comparative repeat-dose toxicity study in cynomolgus monkeys was conducted to demonstrate similarity in toxicity, toxicokinetic, and immunogenicity profiles of SB5 and US Humira®
	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 Number: SB5-G11-NHV - Summary of design : Comparative PK study for randomized, single-blind, three-arm, parallel group, single-dose, phase I trial in healthy male subjects (Randomized 189: 63 subjects in each of the 3 treatment groups) - Objective and primary endpoint: Demonstration of equivalence PK in terms of area under the concentration-time curve (AUC) from time zero to infinity (AUC_{inf}), Area under the concentration-time curve (AUC) from time zero to the last quantifiable concentration (AUC_{last}), Maximum serum concentration (C_{max}) between SB5 and Humira® in healthy male volunteers after the single dose injection. - Dose used : Single dose subcutaneous injection of 40 mg of either SB5, EU Humira or US Humira - Length of the study: 10 weeks
NRA	**Clinical data. PK data assessment outcome**
	The primary PK endpoint, the geometric LSMean ratio for the comparison of SB5/EU Humira® for AUC_{inf}, AUC_{last} and C_{max} were comparable in the Hadrima and Humira ® (both EU sourced and US sourced). SB5 and EU Humira® showed comparability between the two products as the ratios (90% CI) of geometric means for primary PK endpoints AUC_{inf}, AUC_{last} and C_{max} were 0.990, 1.027 and 0.957, respectively and hence were all within equivalence margin for 0.8 to 1.25. SB5 and US Humira® showed comparability between the two products as the ratios (90% CI) of geometric means for primary PK endpoints AUC_{inf}, AUC_{last} and C_{max} were 1.001, 1.025 and 0.972, respectively and hence were all within equivalence margin for 0.8 to 1.25. Therefore, DB5, EU Humira and US Humira were concluded to be similar.
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: SB5-G31-RA - Summary of design :A randomized phase III, double-blind, parallel group, multicenter study to compare the efficacy, safety, tolerability, immunogenicity and pharmacokinetics between SB5 and EU Humira in subjects with moderate to severe RA despite MTX therapy. Subjects were randomized in a 1:1 ratio to receive either SB5 or EU Humira. At Week 24, subjects receiving EU Humira were randomized to either continue EU Humira of be transitioned to SB5 up to Week 50. Subjects receiving SB5 continued to receive SB5 up to Week 50, but they also followed the randomization procedure to maintain blinding (Randomized 544: 271 subjects in SB5 treatment group and 273 subjects in EU sourced Humira treatment group). - Objective and primary endpoint: Demonstration of the equivalence of SB5 to EU Humira at Week 24, in terms of the ACR20 response rate. - Secondary efficacy endpoints: 9 efficacy endpoints including ACR20 at Week 52, ACR50, 70 at Week 24 - Dose used: 40 mg subcutaneous injection of SB5 of EU Humira every other week - Length of the study: 60 weeks (52 weeks of active treatment and 8 weeks of safety follow-up)
NRA	**Clinical data. Efficacy data assessment outcome**
	The efficacy and safety trial in RA patients achieved its primary endpoint since the 95% confidence interval for the difference in the ACR20 response rate at Week 24 was contained within the **predefined equivalence margin (± 15%)** in the Per Protocol populations **(95% CI: -7.83, 8.13)**. At week 24 and 52, the results of the secondary endpoints (in particular ACR50 and ACR70, ACR-N, AUC of ACR-N up to week 24, DAS28, EURAR response) were all consistent with the results of the primary endpoint. These data were further supported by comparable response rates at Week 52.

Treatment	n/N	(%)	Estimated Difference in Proportions	95% CI
SB5	173/239	(72.4%)	0.1%	(-7.83, 8.13)
EU Humira	171/227	(72.2%)		

* N: number of patients in the per-protocol set, n: number of responder
* Nonparametric randomisation-based analysis of covariance was used with region as a stratification factor and baseline C-reactive protein (CRP) value as a covariate.

MAH	**Clinical data. Safety/ Immunogenicity studies** (specify population, dose used, length of the study and comparability margins)
	Safety and immunogenicity data were collected from all clinical study: SB5-G11-NHV and SB5-G31-RA
NRA	**Clinical data. Safety/ Immunogenicity data assessment outcome**
	Safety. Overall incidence of TEAEs and SAE were comparable across all treatment group both up to Week 24 and 52. And safety profile was similar between SB5 and EU Humira. Both SAEs were assessed to be unrelated to the IP.

Treatment	SB5 N=268	Humira N=273

Number of subject experiencing	n	(%)	E	n	(%)	E
TEAE	140	(52.2)	325	154	(56.4)	402

* E: frequency of treatment-emergent adverse events

Immunogenicity. There was a significant (p-value =0.816) difference in overall ADA formation at week 24. Antibody formation in SB5 was considered to be comparable to that in the ECL, using appropriately validated methods.

Timepoint	ADA result	SB5 N=268			Humira N=273			p-value[a]
		n	n'	(%)	n	N'	(%)	
Week 24	Positive	246	79	(32.1)	260	81	(31.2)	0.816
Week 52	Positive	246	88	(35.8)	260	97	(37.3)	

[a] p-value is based on Chi-squared test if number of subjects with positive ADA within group is at least 5, otherwise Fisher's exact test
N: number of patients in the Safety Set 1 (all subjects who received at least 1 dose of IP during the study)
n: number of patients with event of interest
n': number of patients with available ADA results at each timepoint

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: 20 September 2017~ 19 December 2021
NRA	**Post-authorization risk measures: assessment outcome.**
	Post-marketing surveillance study (re-examination study) plan was considered to be acceptable. Number of subjects of Hadlima for re-examination study met the MFDS criteria (over 400).
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.
<The data provided by the Applicant were in line with the local legislation, guidelines and international 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 Hadlima were comparable to those of the reference biotherapeutic product Humira

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

Clinical Studies
The PK and efficacy studies to demonstrate biosimilarity conducted in healthy subjects and Rheumatoid Arthritis patients provided robust evidence there are no clinically meaningful differences Hadlima versus the reference biotherapeutic product Humira.

Safety: Overall incidence of TEAEs and SAEs were comparable across all treatment group both up to Week 24 and 52. And safety profile was similar between Hadlima and EU Humira.

Immunogenicity: The proportion of patients who developed anti-drug antibodies (ADA) with SB5 was generally similar to that of patients who developed ADAs with EU Humira in the reference biotherapeutic prdocut Humira.

Risk Management
The risk management plan (or equivalent) was considered to be acceptable.

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