Yuflyma

Ministry of Food and Drug Safety

APPROVED

PART A - ADMINISTRATIVE INFORMATION		
Entered by:	**Biosimilar Product Information**	
MAH	**Name of the biosimilar medicinal product**	Yuflyma
MAH	**MAH**	Celltrion Co. Ltd., 20, Academy-ro 51beon-gil, Yeonsu-gu, Incheon, Republic of Korea
NRA	**Authorisation / Licence number**	Celltrion Co. Ltd., / 3 (pre-filled syringe), 4 (pre-filled pen)
MAH / NRA	**API manufacturing facilities and batch release site for the finished product** (if applicable)	Not Released
MAH	**Name of the active substance**	Adalimumab (INN)
MAH	**Pharmaco-therapeutic group**	ATC code: L04AB04
MAH	**Substance category**	Monoclonal antibodies
MAH	**Pharmaceutical form**	Clear to slighthly opalescent, colorless to pale brown solution
MAH	**Quantitative composition**	40 mg/syringe 40 mg/pen
MAH	**Route of administration**	subcutaneous infusion
MAH	**Packaging/material**	Pre-filled syringe Pen
MAH	**Package size(s)**	1 pre-filled syringe/box 2 pre-filled syringe/box 4 pre-filled syringe/box 6 pre-filled syringe/box 1 pre-filled pen/box 2 pre-filled pen/box 4 pre-filled pen/box 6 pre-filled pen/box

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 2014)
MAH	**Date of authorisation/licensing of biosimilar**	15 Oct 2021
	Reference Biotherapeutic Product (RBP) Information	
MAH	**Name of the RBP**	Humira
MAH	**Authorised indications for RBP**	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*
MAH	**Pharmaceutical form**	Clear to slighthly opalescent, colorless to pale brown solution
MAH	**Quantitative composition**	40 mg/syringe 40 mg/pen
MAH	**Route of administration**	subcutaneous infusion
MAH	**Packaging/material**	Pre-filled syringe Pen
MAH	**Package size(s)**	1 pre-filled syringe/box 1 pre-filled pen/box
MAH	**Authorisation (Licence) number (of RBP)**	Abbie Korea / 30, 31
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 European Union
MAH / NRA	**Availability of the RBP** **assessment report** (language)/**link**	https://nedrug.mfds.go.kr/pbp/CCBAC02/getItem?itemName=%ED%9C%B4%EB%AF%B8%EB%9D%BC&totalPages=4&limit=10&page=1&&jdgmnResultInfoSeq=33417
	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*, PK, efficacy, safety and immunogenicity studies
NRA	**Availability of full assessment** **report** (language)/**link**	https://nedrug.mfds.go.kr/pbp/CCBAC02/getItem?searchYn=true&title=%EC%9C%A0%ED%94%8C%EB%9D%BC%EC%9D%B4%EB%A7%88&totalPages=1&limit=10&page=1&jdgmnResultInfoSeq=20220000190
MAH	**Indications applied for** (if different to RBP)	The indications applied for were all authorized for RBP (see section Authorised indications for RBP).
NRA	**Authorised indications for biosimilar**	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*

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 40 mg Sodium acetate trihydrate

	Acetic acid Glycine Polysorbate 80 Water for injection
MAH	**Quality data. State-of-the-art methods**
	Structural Chracteristics - Primary structure : Molecular weight, N-terminal sequence analysis, C-terminal sequence analysis, Peptide mapping - High order structure analysis : Disulfide bond analysis, Free thiol analysis, FTIR, CD, DSC **Physicochemical Test** - Purity and Impurities, Charge variants, Post-translational forms, Oligosaccharide profile, N-linked glycan analysis, Protein concentration **Biological properties** - hTNFα neutralization assay, ADCC assay, CDC assay, Apoptosis **Immunochemial properties** - TNFα binding assay (ELISA), tmTNFα binding assay (CELISA), FcRn binding assay, Fc gamma Receptor(FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa-V, FcγRIIIa-F, FcγRIIIb) binding assay, C1q binding assay
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 Yuflyma 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 EU Humira, and the bridging data demonstrated the equivalence of EU Humira, US Humira and KR Humira. There were slight differences in N-glycan profiles. The differences were appropriately justified with comparability on the biological activity of Adalimumab. Comparative forced degradation studies including heat stress, exposure to akaline/acidic condition, oxidation and UV stress demonstrated similar degradation profiles for Yuflyma and Humira. Overall, based on the totality of evidence with respect to all quality characteristics and global clinical studies, the biosimilarity of Yuflyma to Hurima was concluded.

MAH	**Mechanism of action**
	Yuflyma(Adalimumab) is a recombinant human monoclonal antibody that selectively binds directly to human tumor necrosis factor α (TNFα), a cytokine that is involved in normal inflammatory and immune responses but dysregulated in inflammatory diseases.
MAH	**Nonclinical data. *In vitro* studies**
	hTNF-α neutralization, TNF-α affinity (ELISA), apoptosis (FACS), ADCC reporter assay, PBMC ADCC, CDC, Fc gamma Receptor(FcγRIIIa-V type, FcγRIIIa-F type, FcγRIIIb, FcγRIIa, FcγRIIb, FcγRI, FcRn), C1q (ELISA)
MAH	**Nonclinical data. *In vivo* studies**
	Multiple dose pharmacokinetics (PK)/toxicokinetics (TK)/immunotoxicity/immunogenicity/local tolerance were evaluated as part of the 4-week repeat-dose toxicity study in cynomolgus monkeys 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 Yuflyma and EU-Humira. **2. *In vivo* studies** Pharmacokinetic studies showed similar PK profiles between Yuflyma and EU-Humira groups. In a 4-week repeat-dose toxicity study using cynomolgus monkeys, all animals treated Yuflyma or EU-Humira were well tolerated at a dose level of 157 mg/kg 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**
	Study Number : CT-P17 1.1 • Summary of design : a randomized, double-blind, three-arm, parallel group, single-dose study to compare the pharmacokinetics and safety of CT-P17 and Humira (US-licensed Humira and EU-approved Humira) in healthy subjects • Randomized subjects (N=312): 103 or 106 healthy subjects in each group -CT-P17(Yuflyma), EU sourced Humira, US sourced Humira

	• Objective and primary endpoints : Demonstration of Pharmacokinetic (PK) similarity in terms of AUC_{0-inf}, AUC_{0-last}, C_{max} of CT-P17 PFS(Yuflyma), US-Humira PFS, and EU-Humira PFS in healthy subjects • Dose used: 40mg • Length of the study : 10 weeks (EOS visit at Day 71) **Study Number : CT-P17 1.2** • Summary of design : a randomized, double-blind, two-arm, parallel group, single-dose study to evaluate the safety and pharmacokinetics of CT-P17 and EU Humira in healthy male subjects • Randomized subjects (N=30) : 15 healthy male subjects in each group • Objective and primary endpoints : Evaluation of safety in terms of TEAEs of CT-P17 PFS (Yuflyma), compared to that of EU-approved Humira PFS in healthy male subjects. • Dose used : 40mg • Length of the study : 17 weeks (EOS visit at Day 120) **Study Number : CT-P17 1.3** • Summary of design : a randomized, open-label, two-arm, parallel group, single-dose study to compare the pharmacokinetics and safety of the auto-injector and pre-filled syringe of CT-P17 (Yuflyma) in healthy subjects • Randomized subjects (N=30) • Objective and primary endpoints : Demonstration of Pharmacokinetic (PK) similarity in terms of AUC_{0-inf}, AUC_{0-last}, C_{max} of CT-P17 (Yuflyma) subcutaneous (SC) administration via auto-injector (AI) versus pre-filled syringe (PFS) in healthy subjects. • Dose used : 40mg • Length of the study : 10 weeks (EOS visit at Day 71)
NRA	**Clinical data. PK data assessment outcome**
	Study Number : CT-P17 1.1 The primary PK results: The 90% Confidence Interval(CI) of the geometric least squares means(LSMeans) ratios of Yuflyma to EU/US Humira for the PK parameters (AUC_{0-inf}, AUC_{0-last} and C_{max}) were comparable between the Yuflyma and EU/US Avastin treatment groups. Yuflyma and EU Hurima showed comparability between the two products as the 90% CIs of the geometric mean ratios for AUC_{inf}, AUC_{last} and C_{max} were 0.980, 1.008 and 1.001, respectively, and these were all within the acceptance range of 80-125%. Yuflyma and US Humira showed comparability between the two products as the 90% CIs of geometric mean ratios for AUC_{inf}, AUC_{last} and C_{max} were 1.058, 1.073, 1.019, respectively, and these were all within the acceptance range of 80-125%. **Study Number : CT-P17 1.2** The secondary PK results: Pharmacokinetic parameters were comparable between the two treatment groups. (Median T_{max} occurred at 144 hours for the CT-P17 (Yuflyma) treatment group and at 169 hours for the EU-approved Humira treatment group) **Study Number : CT-P17 1.3** The primary PK results: Statistical analysis using an ANCOVA model including covariates for gender, study center, and body weight demonstrated that the mean peak and total systemic exposure (Cmax, AUC0-inf, and AUC0-last) to CT-P17 were equivalent between CT-P17 AI and PFS. The 90% CIs of the geometric LSM ratios were within the predefined 80% to 125% equivalence margin in all instances. Mean serum concentrations measured at Day 71 were generally lower in subjects with positive ADA status compared with subjects with negative ADA status for both CT-P17 AI and CT-P17 PFS treatment groups.

	Of note, a majority of the subjects in the PK population (82 out of 84 subjects in the CT-P17 AI treatment group and 78 out of 80 subjects in the CT-P17 PFS treatment group) had at least 1 ADA positive post-treatment result and thus, mean serum parameters of CT-P17 for ADA negative subjects should be viewed with caution due to the small number of subjects.
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: CT-P17 3.1 • Summary of design: A randomized, Active-controlled, double-blind, Phase III study to compare efficacy, safety of CT-P17 (Yuflyma) with EU-approved Humira when co-administered with Methotrexate in Patients with Moderate to severe Active Rheumatoid Arthritis. Eligible patients were randomized in a 1:1 ratio to receive either CT-P17(Yuflyma) or EU-approved Humira. Prior to dosing at Week 26, all patients underwent the second randomization process. Patients who were initially randomly assigned to EU-approved were randomized again in a ratio of 1:1 to either continue EU-approved Humira or undergo transition to CT-P17. All patients who were initially randomly assigned to CT-P17 at Day 1 (week 0) continued their treatment with CT-P17. The patients were received either CT-P17 or EU-approved Humira, as per the first and second randomizations, 40 mg (100 mg/mL) by SC injection via PFS EOW. Patients were dosed at specific time points. (Randomized patients (N=648): 324 patients in CT-P17 (Yuflyma) treatment group and 324 patients in EU-approved Humira treatment group for Treatment Period I) • Objective and primary endpoint: Demonstration of comparable clinical efficacy between CT-P17 PFS and EU-approved Humira PFS at determined by clinical response according to the American College of Rheumatology definition of a 20% improvement (ACR20) at Week 24. • Secondary objective: Evaluation of additional efficacy, pharmacokinetics (PK), pharmacodynamics (PD), usability (Bulgaria and Poland only), and overall safety, including immunogenicity and biomarker. • Dose used: 40 mg (100 mg/mL) every other week for Treatment Period I
NRA	**Clinical data. Efficacy data assessment outcome**
	The number of patients who achieved ACR20 response at Week 24 was equal between the CT-P17 and EU-Humira treatment group in the ITT population. A total of 268 (82.72%) patients achieved ACR20 response at Week 24 in each of the treatment groups. The 95% CI of the treatment difference was [-5.94, 5.94], which was within the pre-defined equivalence margin of [-15%, 15%]. A similar result was observed in the PP population: the difference between the 2 treatment groups in ACR20 response rate at Week 24 was 0.06%, and the 95% CI of the treatment difference was [-5.60, 5.78], which was within the pre-defined margin of [-15%, 15%].

Treatment Group	ACR20 Response Rate (%)	Estimated Difference (%)[1]	95% CI of Treatment Difference[1]
ITT Population			
CT-P17	268/324 (82.72)	0.00	(-5.94, 5.94)
EUHumira®	268/324 (82.72)		
PP Population			
CT-P17	248/285 (87.02)	0.06	(-5.60, 5.78)
EUHumira®	240/276 (86.96)		

[1] Estimate of the difference in proportion and 95% confidence interval between the two treatment groups are estimated using the exact binomial method using a Farrington-Manning score method.

To explore the robustness of the ACR20 responses, the number of patients who achieved ACR20 response at Week 24 was also compared using logistic regression with treatment group as a fixed effect and country and disease activity by SDAI at screening as covariates in the ITT and PP populations. The 95% CI for the estimate of treatment difference estimated from the logistic regression results using covariates was entirely within the predefined equivalence margin of [-15%, 15%], which demonstrated therapeutic equivalence between the treatment groups (95% CI: [-5.75, 5.86] for the ITT population and 95% CI: [-5.07, 5.93] for the PP population). Thus, the equivalence of CT-P17 and EUHumira® in terms of ACR20 was shown in the ITT and PP populations, and the robustness of the primary efficacy analysis was supported by this sensitivity analysis.

Treatment Group	ACR20 Response Rate (%)	Estimate (%)[1]	Estimated Difference (%)[1]	95% CI of Treatment Difference (%)[2]
ITT Population				
CT-P17	268/324 (82.72)	83.63	0.06	(-5.75, 5.86)
EUHumira®	268/324 (82.72)	83.57		
PP Population				
CT-P17	248/285 (87.02)	87.90	0.43	(-5.07, 5.93)
EUHumira®	240/276 (86.96)	87.47		

[1] Estimates of the proportions and difference in proportion between the treatment groups were calculated using a logistic regression model with treatment group as a fixed effect and country and disease activity by SDAI at screening as covariates.

[2] Estimates of the 95% confidence interval were estimated from the logistic regression results using the Delta method. This method assumes independence between the treatment groups.

The proportion of patients achieving clinical response at Week 24 according to the ACR20 criteria for the ADA positive and ADA negative subgroups of ITT and PP populations was similar between the 2 treatment groups. In the EU-approved Humira treatment group, there was a slightly lower trend in the proportion of patients who achieved ACR20 at Week 24 in the ADA positive subgroup than ADA negative subgroup, but the CT-P17 treatment group showed similar results between the ADA subgroups in the ITT and PP populations.

Parameter visit	CT-P17 Number (%) of patients	EU-approved Humira Number (%) of patients
ITT Population	**N=324**	**N=324**
ADA positive subgroup		
ACR20 at Week 24	119/143 (83.2)	148/185 (80.0)
ADA negative subgroup		
ACR20 at Week 24	149/178 (83.7)	120/138 (87.0)
PP Population	**N=285**	**N=276**
ADA positive subgroup		
ACR20 at Week 24	110/124 (88.7)	128/151 (84.8)
ADA negative subgroup		
ACE20 at Week 24	138/161 (85.7)	112/125 (89.6)

MAH	**Clinical data. Safety/ Immunogenicity studies**
	Safety and immunogenicity data were collected from all clinical studies: CT-P17 1.1, CT-P17 1.2, CT-P17 1.3 and CT-P17 3.1
NRA	**Clinical data. Safety/ Immunogenicity data assessment outcome**
	Safety. The overall safety profiles were similar between CT-P17 (Yuflyma) and Humira treatment groups. Immunogenicity. The overall immunogenicity profiles were similar between CT-P17 (Yuflyma) and Humira 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: 2021.10.15. ~ 2025.10.14
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 Yuflyma were comparable to those of the reference biotherapeutic product Humira.

Nonclinical

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

Clinical Studies

The Phase I and Phase III studies to demonstrate biosimilarity conducted in healthy volunteers and RA patients provided robust evidence that there are no clinically meaningful differences between Yuflyma and the reference biotherapeutic product Humira.

Safety: The Adeverse drug reactions (ADRs) observed with Yuflyma were in the similar range as the ADRs observed with the reference biotherapeutic product Humira.

Immunogenicity: The proportion of patients who developed ADA with Yuflyma was generally similar to the reference biotherapeutic 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 Yuflyma.

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.