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Avtozma Inj. 80mg

Ministry of Food and Drug Safety

APPROVED

PART A - ADMINISTRATIVE INFORMATION		
Entered by:	**Biosimilar Product Information**	
MAH	**Name of the biosimilar medicinal product**	Avtozma Inj. 80mg CT-P47(Company code)
MAH	**MAH**	Celltrion Inc. 20, Academy-ro 51 beon-gil, Yeonsu-gu, Incheon, Republic of Korea
NRA	**Authorisation / Licence number**	Celltrion /28
MAH / NRA	**API manufacturing facilities and batch release site for the finished product** (if applicable)	Confidential
MAH	**Name of the active substance**	Tocilizumab (INN)
MAH	**Pharmaco-therapeutic group**	ATC code: L04AC07
MAH	**Substance category**	Monoclonal antibodies
MAH	**Pharmaceutical form**	A clear to slightly opalescent, colorless to pale yellow solution
MAH	**Quantitative composition**	80 mg/4 mL/1 vial
MAH	**Route of administration**	IV (Intravenous)
MAH	**Packaging/material**	Glass vial
MAH	**Package size(s)**	1 vial/pack
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**	80 mg IV vial: 12 February 25
	Reference Biotherapeutic Product (RBP) Information	
MAH	**Name of the RBP**	Actemra
MAH	**Authorised indications for RBP**	Rheumatoid arthritis Juvenile idiopathic arthritis Juvenile idiopathic polyarthritis Giant cell arteritis
MAH	**Pharmaceutical form**	colorless to pale yellow solution
MAH	**Quantitative composition**	80 mg/4 mL/1 vial 200 mg/10 mL/1 vial 400 mg/20 mL/1 vial
MAH	**Route of administration**	IV (Intravenous)
MAH	**Packaging/material**	Glass vial
MAH	**Package size(s)**	1 vial/pack
MAH	**Authorisation (Licence) number (of RBP)**	JW Pharmaceutical / 111
MAH	**Date of authorisation (of RBP)**	IV vial: 06 April 12
MAH	**Authorisation (Licence) Holder (of RBP)**	JW Pharmaceutical
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**	https://nedrug.mfds.go.kr/pbp/CCBAC02/getList?totalPages=1&page=1&limit=10&sort=&sortOrder=&searchYn=true&targetGb=&title=&entpName=&itemName=&mainIngrName=%ED%86%A0%EC%8B%A4%EB%A6%AC%EC%A3%BC%EB%A7%99&mainIngrEngName=&btnSearch=
	Summary of outcomes	
MAH	**Comparability exercise to demonstrate similarity to RBP**	Extensive comparability exercise including data from : physicochemical, biological characterization,

		in vitro, in vivo non-clinical studies, PK, efficacy, safety and immunogenicity studies
NRA	**Availability of full assessment report** (language)/**link**	Not yet available
MAH	**Indications applied for** (if different to RBP)	The indications except giant cell arteritis applied for were all authorized for RBP (see section Authorised indications for RP)
NRA	**Authorised indications for biosimilar**	Rheumatoid arthritis Juvenile idiopathic arthritis Juvenile idiopathic polyarthritis

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)**
	Tocilizumab L-Hitidine L-Histidine HCl Monohydrate L-Methionine L-Threonine Polysorbate 80 Water for Injection
MAH	**Quality data. State-of-the-art methods**
	Structural Chracteristics - Primary Structure: Peptide mapping, Non-reduced intact mass by LC/MS, PTM - High order structure analysis : Free thiol analysis, Disulfide bonds, Circular dichroism (CD), Differential scanning calorimetry (DSC), FTIR **Physicochemical Test** - Purity and impurities, Charge variants, Glycosylation, Protein concentration **Biological properties** - sIL-6R Binding Assay (ELISA), Cell-based mIL-6R Binding Assay (CELISA), Inhibition of IL-6-Mediated Cell Proliferation Assay, Competition Assay of IL-6 and CT-P47 Binding to IL-6R, Dissociation Assay of IL-6 from IL-6/sIL-6R Complex by CT-P47 **Immunochemial properties** - C1q Binding Assay (ELISA), FcγRIIIa (V-type) binding affinity (SPR), FcγRIIIa (F-

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type) binding affinity (SPR), FcγRIIIb binding affinity (SPR), FcγRIIa binding affinity (SPR), FcγRIIb binding affinity (SPR), FcγRI binding affinity (SPR), FcRn binding affinity (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 Avtozma were comparable to those of RoActemra with respect to physiochemical, biological and immunochemical properties. The similarity range was determined using the sufficient characterization data from EU RoActemra, and the bridging data demonstrated the equivalence of EU RoActemra and KR Actemra.
There were slight differences in PTM, glycosylation and Fc binding. The differences were appropriately justified with comparability on the biological activity of Avtozma
Comparative forced degradation studies including heat stress, exposure to basic/acidic condition, oxidation and photostress demonstrated similar degradation profiles for Avtozma and RoActemra
Overall, based on the totality of evidence with respect to all quality characteristics and global clinical studies, the biosimilarity of Avtozma to Actemra was concluded.

MAH | **Mechanism of action**

Tocilizumab is a recombinant immunoglobulin (IgG1) monoclonal antibody (mAb) that binds to soluble and membrane-bound interleukin-6 receptor (IL-6R)

MAH | **Nonclinical data. *In vitro* studies**

- sIL-6R Binding Assay (ELISA), Cell-based mIL-6R Binding Assay (CELISA), Inhibition of IL-6-Mediated Cell Proliferation Assay, Competition Assay of IL-6 and CT-P47 Binding to IL-6R, Dissociation Assay of IL-6 from IL-6/sIL-6R Complex by CT-P47, C1q Binding Assay (ELISA), FcγRIIIa (V-type) binding affinity (SPR), FcγRIIIa (F-type) binding affinity (SPR), FcγRIIIb binding affinity (SPR), FcγRIIa binding affinity (SPR), FcγRIIb binding affinity (SPR), FcγRI binding affinity (SPR), FcRn binding affinity (SPR)

MAH | **Nonclinical data. *In vivo* studies**

Pharmacokinetics
Multiple dose pharmacokinetics (PK)/toxicokinetics (TK) were evaluated as part of the 4-week repeat-dose toxicity study in cynomolgus monkeys.

Toxicity Study (including TK)
A 4-week Once Weekly Subcutaneous Injection Toxicity and Toxicokinetics Study in Cynomolgus Monkeys

NRA | **Nonclinical data assessment outcome**

1. ***In vitro* studies**
   In vitro PD studies demonstrated the similarity between Avtozma and RoAcemra.

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	2. *In vivo* studies In a 4-week repeat-dose toxicity study using cynomolgus monkeys, all animals treated Avtozma or RoActemra were well tolerated at a dose level of 45mg/kg and there were no differences in toxicity profile between two groups. Pharmacokinetic studies showed similar PK profiles between Avtozma and RoActemra groups.

	CLINICAL STUDIES **- include relevant study data from the following (not all may be required) which have been included to demonstrate biosimilarity.** • **Pharmacokinetic (PK)** • **Efficacy** • **Safety** • **Immunogenicity**
MAH	**Clinical data. PK studies**
	Study Number : CT-P47 1.1 • Summary of design : A Phase 1, Randomized, Double-blind, Two-arm, Parallel Group, Singledose Study to Compare the Pharmacokinetics and Safety of Two Subcutaneous Injection Formulations of Tocilizumab (CT-P47 and EUapproved RoActemra) in Healthy Subjects • Randomized subjects (Part 1 –29 / Part 2 - 289) : Part 1 – 14 subjects for CT-P47 and 15 subjects for EU-Actemra Part 2 – 146 subjects for CT-P47, 143 subjects for EU-Actemra • Objective and primary endpoints : To demonstrate the PK similarity in terms of area under the concentration-time curve (AUC) from time zero to infinity (AUC0-inf), AUC from time zero to the last quantifiable concentration (AUC0-last), and maximum serum concentration (Cmax) of CT-P47 and EUapproved RoActemra in healthy subjects up to Day 43. • Dose used: 162 mg (162 mg/0.9 ml), a single PFS SC injection of study drug • Length of the study : up to day 43 **Study Number : CT-P47 1.2** • Summary of design : A Phase 1, Randomized, Double-blind, Three-arm, Parallel Group, Single-dose Study to Compare the Pharmacokinetics and Safety of Three Intravenous Infusion Formulations of Tocilizumab (CT-P47, EU-approved RoActemra, and US-licensed Actemra) in Healthy Japanese Subjects • Randomized subjects (N=132) : -Treatment Group 1 (N=45): CT-P47 -Treatment Group 2 (N=44): EU-approved RoActemra -Treatment Group 3 (N=44): US-licensed Actemra • Objective and primary endpoints : To demonstrate PK similarity in terms of area under the concentration-time curve (AUC) from time zero to infinity (AUC0-inf), AUC from time zero to the last quantifiable concentration (AUC0-last), and maximum serum concentration (Cmax) of CT-P47, EU-approved RoActemra, and US-licensed Actemra in healthy Japanese subjects up to Day 56 (CT-P47 to EU-approved RoActemra, CT-P47 to US-licensed Actemra, and EU-approved RoActemra to US-licensed Actemra) • Dose used: - Treatment Group 1: CT-P47, 8 mg/kg by IV infusion administered over a 1-hour (+15 minutes) as a single dose -Treatment Group 2: EU-approved RoActemra, 8 mg/kg by IV infusion administered over a 1-hour (+15 minutes) as a single dose

-Treatment Group 3: US-licensed Actemra, 8 mg/kg by IV infusion administered over a 1-
hour (+15 minutes) as a single dose
- Length of the study : up to day 56

Study Number : CT-P47 1.3

- Summary of design : A Phase 1, 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-P47 in Healthy Subjects
- Randomized subjects (N=314) :
  - CT-P47 AI (N=155)
  - CT-P47 PFS (N=159)
- Objective and primary endpoints : To demonstrate Pharmacokinetic (PK) similarity in terms of area under the concentration-time curve (AUC) from time zero to infinity (AUC0-inf) and maximum serum concentration (Cmax) of CT-P47 Subcutaneous (SC) administration via Auto-injector (AI) versus Pre-filled syringe (PFS) in healthy subjects up to Day 43
- Dose used:
  - CT-P47, 162 mg in 0.9 mL by SC injection to the outer upper arm via AI as a single dose
  -CT-P47, 162 mg in 0.9 mL by SC injection to the outer upper arm via PFS as a single dose
- Length of the study : up to day 43

NRA

Clinical data. PK data assessment outcome

Study Number : CT-P47 1.1

- In the CT-P47 1.1, subjects received a single dose of CT-P47or EU-RoActemra by SC injection.
  The 90% Confidence Interval(CI) of the geometric least squares means(LSMeans) ratios of CT-P47 to EU-RoActemra for the PK primary endpoints (AUC0-inf, AUC0-last, and Cmax) were contained within the predefined bioequivalence margin of 80-125%.

Statistical Analysis of Serum Pharmacokinetic Parameters (ANCOVA) (PK set)

PK parameter (unit)	Geometric LS Mean				%Ratio (90% CI)
	CT-P47 N=144		EU-approved RoActemra N=140		CT-P47/ EU-approved RoActemra
	n	Results	n	Results	
$AUC_{0\text{-}inf}$ (day·μg/mL)	138	79.37	136	73.54	107.92 (98.04, 118.80)
$AUC_{0\text{-}last}$ (day·μg/mL)	144	77.55	139	72.52	106.93 (97.36, 117.43)
C_{max} (μg/mL)	144	8.89	140	8.63	103.00 (94.67, 112.06)

Study Number : CT-P47 1.2

- In the CT-P47 1.2, subjects received a single dose of CT-P47, EU-RoActemra, or US-Actemra by IV infusion. The 90% confidence intervals (CIs) of the geometric least squares means (LSMeans) ratios of CT-P47 to EU-RoActemra/US-Actemra for the primary endpoints (AUC0-inf, AUC0-last, Cmax) were within the predefined bioequivalence margin of 80%-125%.

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PK Parameter (unit)	Comparison	Treatment	n	Geometric LS Means	Ratio of Geometric LS Means (Test/Reference)	90% CI
$AUC_{0\text{-inf}}$ (hour•µg/mL)[a]	CT-P47	Test	45	26735.00	96.65	(92.09, 101.43
	EU-approved RoActemra	Reference	42	27663.04		
	CT-P47	Test	45	26735.00	92.61	(88.30, 97.12)
	US-licensed Actemra	Reference	44	28869.86		
	EU-approved RoActemra	Test	42	27663.04	95.82	(91.30, 100.57
	US-licensed Actemra	Reference	44	28869.86		
$AUC_{0\text{-last}}$ (hour·µg/mL)	CT-P47	Test	45	26637.45	96.41	(91.85, 101.19
	EU-approved RoActemra	Reference	43	27630.43		
	CT-P47	Test	45	26637.45	92.99	(88.63, 97.57)
	US-licensed Actemra	Reference	44	28644.65		
	EU-approved RoActemra	Test	43	27630.43	96.46	(91.89, 101.25
	US-licensed Actemra	Reference	44	28644.65		
C_{max} (µg/mL)	CT-P47	Test	45	154.15	97.51	(93.41, 101.79
	EU-approved RoActemra	Reference	43	158.09		
	CT-P47	Test	45	154.15	96.44	(92.41, 100.64
	US-licensed Actemra	Reference	44	159.84		
	EU-approved RoActemra	Test	43	158.09	98.90	(94.73, 103.25
	US-licensed Actemra	Reference	44	159.84		

Study Number : CT-P47 1.3

- The primary objective of CT-P47 1.3 was to demonstrate PK similarity of CT-P47 SC administration by AI vs. PFS. In the PK set, the 90% CIs of the ratio of the geometric means for all PK primary endpoints (AUC0-inf and Cmax) were entirely contained within the equivalence margin of 80% to 125%.

PK parameter (unit)	Geometric LS Mean				%Ratio (90% CI)
	CT-P47 AI N=153		CT-P47 PFS N=157		CT-P47 AI/ CT-P47 PFS
	n	Results	n	Results	
$AUC_{0\text{-inf}}$ (day·µg/mL)	140	76.90	152	81.79	94.02 (85.87, 102.94)
C_{max} (µg/mL)	150	8.61	157	9.54	90.25 (82.98, 98.16)

MAH	**Clinical data. PD studies**
	No specific PD study was conducted due to no relevant biomarker of therapeutic activity.
NRA	**Clinical data. PD data assessment outcome**

	Not applicable
MAH	**Clinical data. Efficacy studies**
	Study Number : CT-P47 3.1 • Summary of design : A Randomized, Active-Controlled, Double-Blind, Phase 3 Study to Compare Efficacy and Safety of Two Intravenous Infusion Formulations of Tocilizumab (CT-P47 and RoActemra) when Co-administered with Methotrexate in Patients with Moderate to Severe Active Rheumatoid Arthritis • Randomized subjects (N=471) : - 234 patients were randomly assigned to CT-P47 group - 237 patients were randomly assigned to European Union (EU)-approved RoActemra group • Objective and primary endpoints : The primary objective of this study was to demonstrate that CT-P47 is equivalent to RoActemra, in terms of efficacy as determined by clinical response according to the change from baseline in disease activity measured by • Secondary objective: The secondary objective of this study was to evaluate additional efficacy, pharmacokinetics (PK), and overall safety, including immunogenicity. • Dose used: 8 mg/kg, not exceeding 800 mg/dose
NRA	**Clinical data. Efficacy data assessment outcome**
	Study Number : CT-P47 3.1 The primary efficacy endpoint was the mean change from baseline in DAS28(ESR) at Week 12. It is summurised for the ITT and PPS in the table. The mean change from baseline in DAS28(ESR) at Week 12 was equivalent between the Avtozma and RoActemra treatment groups in the ITT and PPS. The adjusted difference in least square means(LSMeans)[95% CI] at Week 12 was 0.01[-0.26, 0.24] for ITT, 0.04[-0.20, 0.29] for PPS, which was entirely contained within the pre-defined equivalence margin of [−0.6%, 0.6%].

Analysis set Parameter	n	LS mean (SE)	Estimate of Treatment Difference	95% CI of Treatment Difference
ITT Set				
DAS28 (ESR) at Week 12				
CT-P47	221	-3.01 (0.121)	-0.01	(-0.26, 0.24)
RoActemra	225	-3.00 (0.120)		
PPS				
DAS28 (ESR) at Week 12				
CT-P47	213	-3.05 (0.121)	0.04	(-0.20, 0.29)
RoActemra	207	-3.09 (0.119)		

Analysis set Parameter	n	LS mean (SE)	Estimate of Treatment Difference	95% CI of Treatment Difference
ITT Set				
DAS28 (ESR) at Week 12				
CT-P47	221	-3.01 (0.121)	-0.01	(-0.26, 0.24
RoActemra	225	-3.00 (0.120)		
PPS				
DAS28 (ESR) at Week 12				
CT-P47	213	-3.05 (0.121)	0.04	(-0.20, 0.29
RoActemra	207	-3.09 (0.119)		

MAH	**Clinical data. Safety/ Immunogenicity studies**	
	Safety and immunogenicity data were collected from all clinical studies: CT-P47 1.1, CT-P47 1.2, CT-P47 1.3, CT-P47 3.1	
NRA	**Clinical data. Safety/ Immunogenicity data assessment outcome**	
	Safety. The overall safety profiles were similar between Avtozma and RoActemra treatment groups. Immunogenicity. The overall immunogenicity profiles were similar between Avtozma and RoActemra treatment groups	
MAH	**Interchangeability data**	
	No additional data were provided	
MAH	**Additional information about the comparability exercise**	
MAH	**Post-authorization measures**	
	Re-examination study in Study: Observational, prospective cohort study to evaluate safety and efficacy of Avtozma Period: 2024.12.20 – 2028.12.19	
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

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 Avtozma were comparable to those of the reference biotherapeutic product Actemra.

Nonclinical
No major differences in non-clinical data were observed for Avtozma compared to the reference biotherapeutic product Actemra.

Clinical Studies
PK similarity of Avtozma to the reference biotherapeutic product Actemra was demonstrated in study CT-P47 1.1(sc) and CT-P47 1.2(IV).
The Phase III study to demonstrate biosimilarity conducted in Rheumatoid arthritis patients provided robust evidence that there are no clinically meaningful differences between Avtozma and the reference biotherapeutic product Actemra.

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

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

Extrapolation of indications: Based on the totality of evidence, all indications requested for Actemra were considered to be extrapolated to Avtozma.

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 Avtozma was considered approvable.