

Avtozma S.C Inj.
Ministry of Food and Drug Safety

APPROVED

PART A - ADMINISTRATIVE INFORMATION		
Entered by:	Biosimilar Product Information	
MAH	Name of the biosimilar medicinal product	Avtozma S.C Inj. 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 / 29
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	162 mg/0.9mL/1 pen
MAH	Route of administration	SC (Subcutaneous)
MAH	Packaging/material	Glass auto-injector
MAH	Package size(s)	1 AI/pack
MAH	Local legal basis	Pharmaceutical Affairs Act article 31 and Enforcement for drug safety article 4

**IPRP – PASIB TEMPLATE Public
Assessment Summary Information for
Biosimilar IPRP Biosimilars WG**

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MAH	Local biosimilar guidelines	Guidelines on the Evaluation of Biosimilar Products (MFDS 2021)
MAH	Date of authorisation/licensing of biosimilar	12 February 25
	Reference Biotherapeutic Product (RBP) Information	
MAH	Name of the RBP	Actemra
MAH	Authorised indications for RBP	Rheumatoid arthritis Giant cell arteritis
MAH	Pharmaceutical form	colorless to pale yellow solution
MAH	Quantitative composition	162 mg/0.9mL/1 PFS 162 mg/0.9mL/1 AI
MAH	Route of administration	SC (Subcutaneous)
MAH	Packaging/material	Glass pre-filled syringe Plastic pre-filled syringe Glass auto-injector Plastic auto-injector
MAH	Package size(s)	1 PFS/pack 1 Auto-injector/pack
MAH	Authorisation (Licence) number (of RBP)	JW Pharmaceutical / 113
MAH	Date of authorisation (of RBP)	31 July 14
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,

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		<i>in vitro, in vivo</i> 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 RBP)
NRA	Authorised indications for biosimilar	Rheumatoid 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)
	Tocilizumab L-Histidine L-Histidine HCl Monohydrate L-Methionine L-Threonine Polysorbate 80 Water for Injection
MAH	Quality data. State-of-the-art methods
	<p>Structural Characteristics</p> <ul style="list-style-type: none"> - Primary Structure: Peptide mapping, Reduced/Non-reduced intact mass by LC/MS - High order structure analysis : Free thiol analysis, Disulfide bonds, Circular dichroism (CD), Differential scanning calorimetry (DSC), FTIR <p>Physicochemical Test</p> <ul style="list-style-type: none"> - Purity and impurities, Charge variants, Glycosylation, Protein concentration <p>Biological properties</p> <ul style="list-style-type: none"> - 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 <p>Immunochemical properties</p> <ul style="list-style-type: none"> - C1q Binding Assay (ELISA), FcγRIIIa (V-type) binding affinity (SPR), FcγRIIIa (F-type) binding affinity (SPR), FcγRIIIb binding affinity (SPR), FcγRIIa binding affinity

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	(SPR), FcγRIIb binding affinity (SPR), FcγRI binding affinity (SPR), FcRn binding affinity (SPR)
NRA	Quality data assessment outcome
	<p>. 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.</p> <p>There were slight differences in PTM, glycosylation and Fc binding. The differences were appropriately justified with comparability on the biological activity of Avtozma</p> <p>Comparative forced degradation studies including heat stress, exposure to basic/acidic condition, oxidation and photostress demonstrated similar degradation profiles for Avtozma and RoActemra</p> <p>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.</p>
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. <i>In vitro</i> studies
	<ul style="list-style-type: none"> - 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. <i>In vivo</i> studies
	<p>Pharmacokinetics Multiple dose pharmacokinetics (PK)/toxicokinetics (TK) were evaluated as part of the 4-week repeat-dose toxicity study in cynomolgus monkeys.</p> <p>Toxicity Study (including TK) A 4-week Once Weekly Subcutaneous Injection Toxicity and Toxicokinetics Study in Cynomolgus Monkeys</p>
NRA	Nonclinical data assessment outcome
	<p>1. <i>In vitro</i> studies In vitro PD studies demonstrated the similarity between Avtozma and RoActemra.</p>

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	<p>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.</p>
	<p>CLINICAL STUDIES - include relevant study data from the following (not all may be required) which have been included to demonstrate biosimilarity.</p> <ul style="list-style-type: none"> • Pharmacokinetic (PK) • Efficacy • Safety • Immunogenicity
MAH	<p>Clinical data. PK studies</p>
	<p>Study Number : CT-P47 1.1</p> <ul style="list-style-type: none"> • 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 <p>Study Number : CT-P47 1.2</p> <ul style="list-style-type: none"> • 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

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- 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 (AUC_{0-inf}) and maximum serum concentration (C_{max}) 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-P47 or 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 (AUC_{0-inf}, AUC_{0-last}, and C_{max}) 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		
	n	Results	n	Results	
AUC _{0-inf} (day·µg/mL)	138	79.37	136	73.54	107.92 (98.04, 118.80)
AUC _{0-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 (AUC_{0-inf}, AUC_{0-last}, C_{max}) 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-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-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 (AUC_{0-inf} and C_{max}) 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-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**

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	Not applicable																																														
MAH	Clinical data. Efficacy studies																																														
	<p>Study Number : CT-P47 3.1</p> <ul style="list-style-type: none"> 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) : <ul style="list-style-type: none"> - 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 : <p>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</p> <ul style="list-style-type: none"> Secondary objective: <p>The secondary objective of this study was to evaluate additional efficacy, pharmacokinetics (PK), and overall safety, including immunogenicity.</p> <ul style="list-style-type: none"> Dose used: 8 mg/kg, not exceeding 800 mg/dose 																																														
NRA	Clinical data. Efficacy data assessment outcome																																														
	<p>Study Number : CT-P47 3.1</p> <p>The primary efficacy endpoint was the mean change from baseline in DAS28(ESR) at Week 12. It is summarised for the ITT and PPS in the table.</p> <p>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.</p> <p>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%].</p> <table border="1"> <thead> <tr> <th>Analysis set</th> <th>n</th> <th>LS mean (SE)</th> <th>Estimate of</th> <th>95% CI of</th> </tr> <tr> <th>Parameter</th> <th></th> <th></th> <th>Treatment Difference</th> <th>Treatment Difference</th> </tr> </thead> <tbody> <tr> <td colspan="5">ITT Set</td> </tr> <tr> <td colspan="5">DAS28 (ESR) at Week 12</td> </tr> <tr> <td>CT-P47</td> <td>221</td> <td>-3.01 (0.121)</td> <td rowspan="2">-0.01</td> <td rowspan="2">(-0.26, 0.24)</td> </tr> <tr> <td>RoActemra</td> <td>225</td> <td>-3.00 (0.120)</td> </tr> <tr> <td colspan="5">PPS</td> </tr> <tr> <td colspan="5">DAS28 (ESR) at Week 12</td> </tr> <tr> <td>CT-P47</td> <td>213</td> <td>-3.05 (0.121)</td> <td rowspan="2">0.04</td> <td rowspan="2">(-0.20, 0.29)</td> </tr> <tr> <td>RoActemra</td> <td>207</td> <td>-3.09 (0.119)</td> </tr> </tbody> </table>	Analysis set	n	LS mean (SE)	Estimate of	95% CI of	Parameter			Treatment Difference	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)
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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	
	<u>Safety.</u> The overall safety profiles were similar between Avtozma and RoActemra treatment groups. <u>Immunogenicity.</u> 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 3 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 Adverse 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.