26 February 2026
EMADOC-1829012207-19045
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tuyory

International non-proprietary name: Tocilizumab

Procedure No. EMEA/H/C/006416/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell mediated cytotoxicity
ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
AUC	Area under the serum concentration time curve
AUC0-inf	Area under the serum concentration curve (from time zero to infinity)
AUC0-last	Area under the concentration-time curve from time zero to the time of last quantifiable concentration
AUC0-tau	Area under the serum concentration curve (from time zero to the end of dosing interval)
AUC0-144	AUC from 0 hours (immediately before administration) to 144 hours after administration
AUC144-t	AUC from 144 hours (immediately before administration) to the time of the last quantifiable concentration
AUEC	Area under the effect-time curve
AUS	Australia
BLA	Biologics license application
BLI	Biolayer interferometry
BMI	Body mass index
BUN	Blood urea nitrogen
CAR	Chimeric antigen receptor
CAR-T	Chimeric antigen receptor T cell
CDAI	Clinical disease activity index
CDC	Complement dependent cytotoxicity
CDER	Center for Drug Evaluation and Research
CDR	Complementarity-determining region
CfB	Change from baseline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
cIEF	Capillary isoelectric focusing
CL	Clearance
CL/F	Apparent total clearance
Cmax	Maximum observed serum concentration
Cmin	Minimum observed serum concentration
COVID-19	Coronavirus disease 2019
CPB	Carboxypeptidase B
CRES	Chimeric antigen receptor T cell-related encephalopathy syndrome
CRP	C-Reactive Protein
CRS	Cytokine release syndrome
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CTD	Common technical document
CTx / CTX	Carboxyl-terminal telopeptide of type I collagen
CV	Coefficient of variation
CYP	Cytochrome P450
DMARD	Disease-modifying anti-rheumatic drug

DNA	Desoxyribonucleic acid
DP	Drug product
DS	Drug substance
DSC	Differential scanning calorimetry
ECG	Electrocardiogram
ECLIA	Electrochemiluminescent immunoassay
EGA	Evaluator's global assessment
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	End of treatment
EPAR	European Public Assessment Report
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism (old) European Alliance of Associations for Rheumatology
F	Fraction absorbed (bioavailability)
FAS	Full analysis set
Fc	Fragment crystallizable
FcRn	Neonatal Fc Receptor
FCS	Fully conditional specification
FDA	Food and Drug Administration
FR4	Framework region-4
GCP	Good Clinical Practice
GCV	Geometric coefficient of variation
γ-GTP (GGT)	γ-Glutamyl transpeptidase (gamma-glutamyl transpeptidase)
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GMR	Geometric mean ratio
gp-130	Signaling transducer molecule glycoprotein 130 dimer
h	Hour
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBV-DNA	Hepatitis B virus DNA
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
hsCRP	high-sensitivity C-Reactive Protein
ICE	Intercurrent event
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IFN-γ	Interferon-γ
Ig	Immunoglobulin
IgG	Immunoglobulin G
IL-6	Interleukin-6
ILAR	International League of Associations for Rheumatology
IP	Investigational product
IRB	Institutional review board
ISR	Injection site reaction
IV	Intravenous
JAK	Janus kinase
JAK-STAT	Janus kinases-signal transducer and activator of transcription
JCR	Japan College of Rheumatology
JRA	Juvenile rheumatoid arthritis
kel	Elimination rate constant
kg	Kilogram
L	Liter
LC-MS	Liquid chromatography-mass spectrometry
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LLoQ	Lower limit of quantification

LOCF	Last observation carried forward
LoQ	Limit of quantification
LOQ	List of questions
LS	Least squares
MAA	Marketing authorization application
MAPK/NF-kB	Mitogen-activated protein kinase/nuclear factor 'kappa-light-chain-enhancer' of activated B-cells
MAR	Missing at Random
MAS	Macrophage activation syndrome
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Japanese translation of the Medical Dictionary for Regulatory Activities
mg	Milligram
MHC	Mahor histocompatibility complex
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Multiple imputation
mL	Milliliter
mIL-6R	Membrane-bound IL-6 receptor
min	Minute
mL	Milliliter
MMRM	Mixed Model Repeated Measurement
MNAR	Missing not at random
MRT	Mean residence time
MTX	Methotrexate
NAb	Neutralizing antibody
NANA	N-Acetyneuraminic acid
NGNA	N-Glycolylneuraminic acid
NK	Natural killer (cells)
NMR	Nuclear magnetic resonance
NSAID	Non-steroidal anti-inflammatory drug
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PDGF	Platelet-derived growth factor
PFS	Pre-filled syringe
PGA	Patient global assessment
PI	Prescribing information
pJIA	Polyarticular juvenile idiopathic arthritis
PK	Pharmacokinetics
PKS	Pharmacokinetic analysis set
PMDA	Pharmaceuticals and Medical Devices Agency, Japan
PPS	Per Protocol Set
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term
PtGA	Patient’s global assessment of disease activity on a VAS of 100 mm
Q	Quartile
QOL	Quality of life
RA	Rheumatoid arthritis
Ref.	Reference
RF	Rheumatoid factor
RMP	Reference medicinal product
SAE	Serious adverse event
SAF	Safety analysis set
SAWP	Scientific Advice Working Party
SC	Subcutaneous
SD	Standard deviation
SDAI	Simple disease activity index
sIL-6R	Soluble interleukin-6 receptor
sJIA	Systemic juvenile idiopathic arthritis
SJC	Swollen joint count
SmPC	Summary of product characteristics
SOC	System organ class

SSc-ILD	Systemic sclerosis-associated interstitial lung disease
STAT3	Signal transducer and activator of transcription 3
TEAE	Treatment emergent adverse event
TJC	Tender joint count
TLR	Toll-like receptor
tmax	Time to maximum serum concentration
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
t1/2	Terminal elimination half-life
ULN	Upper limit of normal
US	United States
V	Visit
VAS	Visual analog scale
Vd/F	Apparent volume of distribution
VEGF	Vascular endothelial growth factor
vs.	Versus
WBC	White blood cell
WMA	World Medical Association
µg	Microgram

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Product data	
Product name	Tuyory
Active substance	Tocilizumab
INN or common name	Tocilizumab
Applicant	Chemical Works of Gedeon Richter Plc. (Gedeon Richter Plc.) Gyomroi Ut 19-21 1103 Budapest X HUNGARY
EMA product number	EMEA/H/C/006416
ATC code and pharmacotherapeutic group	L04AC Immunosuppressants, interleukin inhibitors
Pharmaceutical form(s) and strength (s)	Concentrate for solution for infusion 20 mg/ml; Solution for injection 162 mg
Packaging	pre-filled syringe (glass), pre-filled pen (glass), Vial (glass)
Package size(s)	12 (3 x 4) pre-filled pens (multipack), 4 pre-filled pens, 12 (3 x 4) pre-filled syringes (multipack), 4 pre-filled syringes, 1 vial and 4 vials
Route of administration	Intravenous use and Subcutaneous use
Device or diagnostic	Class IIa device pre-filled syringe (single-use, disposable pre-filled syringe) Class IIb Pre-filled syringe in single use autoinjector (Single use disposable needle-based injection system with automated functions)
Orphan designation	No
Orphan indication status confirmed	Not applicable
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	Standard
Legal basis	Article 10(4) of Directive 2001/83/EC
Final indication	The full indication for Tuyory 20 mg/ml concentrate for solution for infusion is: <u>Rheumatoid arthritis (RA)</u>

Product data	
	Tuyory, in combination with methotrexate (MTX), is indicated for: • the treatment of severe, active and progressive RA in adults not previously treated with MTX. • the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tocilizumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with MTX. Coronavirus disease 2019 (COVID-19) Tuyory is indicated for the treatment of COVID-19 in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. Systemic juvenile idiopathic arthritis (sJIA) Tuyory is indicated for the treatment of active sJIA in patients 2 years of age and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Tuyory can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX. Polyarticular juvenile idiopathic arthritis (pJIA) Tuyory in combination with MTX is indicated for the treatment of pJIA (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Cytokine release syndrome (CRS) Tuyory is indicated for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening CRS in adults and paediatric patients 2 years of age and older. The full indication for Tuyory 162 mg solution for injection in pre-filled syringe is: Rheumatoid arthritis (RA)

Product data	
	Tuyory, in combination with methotrexate (MTX), is indicated for: • the treatment of severe, active and progressive RA in adults not previously treated with MTX. • the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tocilizumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate. <u>Systemic juvenile idiopathic arthritis (sJIA)</u> Tuyory is indicated for the treatment of active sJIA in patients 1 year of age and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Tuyory can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX. <u>Polyarticular juvenile idiopathic arthritis (pJIA)</u> Tuyory in combination with MTX is indicated for the treatment of pJIA (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. <u>Giant cell arteritis (GCA)</u> Tuyory is indicated for the treatment of GCA in adult patients.
The full indication for Tuyory 162 mg solution for injection in pre-filled pen is:	<u>Rheumatoid arthritis (RA)</u> Tuyory, in combination with methotrexate (MTX), is indicated for • the treatment of severe, active and progressive RA in adults not previously treated with MTX.

Product data	
	• the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tocilizumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate. <u>Systemic juvenile idiopathic arthritis (sJIA)</u> Tuyory is indicated for the treatment of active sJIA in patients 12 years of age and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Tuyory can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX. <u>Polyarticular juvenile idiopathic arthritis (pJIA)</u> Tuyory in combination with methotrexate (MTX) is indicated for the treatment of pJIA (rheumatoid factor positive or negative and extended oligoarthritis) in patients 12 years of age and older, who have responded inadequately to previous therapy with MTX. Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. <u>Giant cell arteritis (GCA)</u> Tuyory is indicated for the treatment of GCA in adult patients.
New active substance status	Not applied for

1.2. Scientific advice

Table 1: Scientific advice and protocol assistance

Date	*Topic (quality/ non-clinical / clinical*	*Reference number / Coordinator(s)*	*Brief summary of the advice*

	)		
4 August 2016	Quality, Non-clinical and Clinical	MHRA: 1311/	The Scientific advice pertained to the following quality, non-clinical and clinical aspects: - Strategy to ascertain comparability between the proposed biosimilar and the reference product (Ro-Actemra) - DS and DP development - Design of the phase I study to demonstrate the PK biosimilarity, and of the Phase III study to demonstrate efficacy similarity
14 December 2017	Quality, Non-clinical and Clinical	EMEA/H/SA/3704/1/2017/SME/III Dr Andreas Kirisits and Dr Jan Mueller-Berghaus	The Scientific advice pertained to the following quality, non-clinical and clinical aspects: - Physicochemical and functional comparability of the proposed biosimilar and the reference product RoActemra - Adequacy of the in vitro and *in vivo* non-clinical development programme. - Design of the clinical development programme (PK and phase III studies) - Extrapolation of clinical study data to all authorized indications of the reference product
29 May 2019	Quality and Clinical	EMEA/H/SA/3704/1/FU/1/2019/SME/III Dr Elena Wolff-Holz and Mr Christian Gartner	This is a follow-up advice of the above 2017 procedure. It pertained to the following quality and clinical aspects: - Physicochemical and functional comparability of the proposed biosimilar and the reference product drug substance following changes to the manufacturing process - QTTP revision - Product characterization - DS and DP specifications - Design of a comparative, randomized, double-blind efficacy, safety, and immunogenicity study in patients with rheumatoid arthritis - Adequacy of the overall clinical development programme - Extrapolation of clinical study data to all authorized indications of the reference product
27 February 2020	Clinical	EMEA/H/SA/3704/1/FU/2/2020/SME/II Dr Elina Rönnemaa and Dr Linda Trauffler	This is a second follow-up advice of the above 2017 procedure. It pertained to the following clinical aspects: - Design of a PK, safety, and tolerability study comparing subcutaneous administration of Tuyory and EU-sourced RoActemra in healthy Japanese volunteers - Design of an efficacy, safety, and

			immunogenicity study comparing intravenous administration of the proposed biosimilar product and EU-sourced RoActemra in Japanese patients with moderate to severe rheumatoid arthritis with inadequate response to methotrexate - Adequacy of the overall clinical development programme
15 December 2021	Clinical	Scientific Advice Paul Ehrlich Institut	The Scientific advice pertained to the following clinical aspects: - identified sequence variants and their potential impact on the biosimilarity assessment of RGB-19 (Tuyory) - relevance and clinical relevance of differences in sequence variants in the clinical programme of RGB-19 (Tuyory)
21 November 2023	Quality, Non-clinical and Clinical	MHRA 6022/RGB-19 (Tocilizumab)	The Scientific advice pertained to the following quality, non-clinical and clinical aspects: - assessment of comparability of Tuyory (tocilizumab) as a biosimilar to RoActemra, - Validation and criteria of the bioanalytical methods - Adequacy of the clinical development program
25 January 2024	Quality	EMA/SA/0000157362 Vilma Petrikaite and Andrea Laslop	The Scientific advice pertained to the following quality aspects: - Acceptability of the proposed quality comparability approach between the pre-filled syringe and autoinjector presentations.

1.3. Eligibility to the centralised procedure

The applicant Chemical Works of Gedeon Richter Plc. (Gedeon Richter Plc.) submitted on 28 February 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for Tuyory (Tocilizumab), through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indications:

Tuyory, 20 mg/ml, Concentrate for solution for infusion

Rheumatoid arthritis (RA)

Tuyory, in combination with methotrexate (MTX), is indicated for:

- the treatment of severe, active and progressive RA in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Tuyory has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with MTX.

Coronavirus disease 2019 (COVID-19)

Tuyory is indicated for the treatment of COVID-19 in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

Systemic juvenile idiopathic arthritis (sJIA)

Tuyory is indicated for the treatment of active sJIA in patients 2 years of age and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Tuyory can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Polyarticular juvenile idiopathic arthritis (pJIA)

Tuyory in combination with MTX is indicated for the treatment of pJIA (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Cytokine release syndrome (CRS)

Tuyory is indicated for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening CRS in adults and paediatric patients 2 years of age and older.

Tuyory, 162 mg, Solution for injection in pre-filled syringe (glass)

Rheumatoid arthritis (RA)

Tuyory, in combination with methotrexate (MTX), is indicated for:

- the treatment of severe, active and progressive RA in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Tocilizumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

Systemic juvenile idiopathic arthritis (sJIA)

Tuyory is indicated for the treatment of active sJIA in patients 1 year of age and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Tuyory can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Polyarticular juvenile idiopathic arthritis (pJIA)

Tuyory in combination with MTX is indicated for the treatment of pJIA (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Giant cell arteritis (GCA)

Tuyory is indicated for the treatment of GCA in adult patients.

Tuyory, 162 mg, Solution for injection in pre-filled pen

Rheumatoid arthritis (RA)

Tuyory, in combination with methotrexate (MTX), is indicated for

- the treatment of severe, active and progressive RA in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Tocilizumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

Systemic juvenile idiopathic arthritis (sJIA)

Tuyory is indicated for the treatment of active sJIA in patients 12 years of age and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids (see section 4.2).

Tuyory can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Polyarticular juvenile idiopathic arthritis (pJIA)

Tuyory in combination with methotrexate (MTX) is indicated for the treatment of pJIA (rheumatoid factor positive or negative and extended oligoarthritis) in patients 12 years of age and older, who have responded inadequately to previous therapy with MTX (see section 4.2).

Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Giant cell arteritis (GCA)

Tuyory is indicated for the treatment of GCA in adult patients.

1.4. Legal basis and dossier content

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for biosimilar medicinal products

The application submitted is composed administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with European Union provisions in force for not less than 8 years in the EEA:

Product name, strength, pharmaceutical form:	RoActemra (EU) - 20 mg/ml, Concentrate for solution for infusion - 162 mg, Solution for injection in pre-filled syringe (glass)
Marketing authorisation holder:	Roche Registration GmbH
Date of authorisation:	- 16-01-2009 for the 20 mg/ml, Concentrate for solution for infusion - 23-04-2014 for the 162 mg, Solution for injection in pre-filled syringe (glass)
Marketing authorisation granted by:	European Union
Marketing authorisation number:	20 mg/ml, Concentrate for solution for infusion: EU/1/08/492/001 EU/1/08/492/002 EU/1/08/492/003 EU/1/08/492/004 EU/1/08/492/005 EU/1/08/492/006 Solution for injection in pre-filled syringe (glass): EU/1/08/492/007 EU/1/08/492/008

Medicinal product authorised in the European Union/Member States where the application is made for European reference medicinal product:

Product name, strength, pharmaceutical form:	RoActemra (EU) - 20 mg/ml, Concentrate for solution for infusion - 162 mg, Solution for injection in pre-filled syringe (glass) - 162 mg, Solution for injection in pre-filled pen
Marketing authorisation holder:	Roche Registration GmbH
Date of authorisation:	- 16-01-2009 for the 20 mg/ml, Concentrate for solution for infusion - 23-04-2014 for the 162 mg, Solution for injection in pre-filled syringe (glass) - 12-04-2018 for the 162 mg, Solution for injection in pre-filled pen
Marketing authorisation granted by:	European Union
Marketing authorisation number:	20 mg/ml, Concentrate for solution for infusion:

	EU/1/08/492/001 EU/1/08/492/002 EU/1/08/492/003 EU/1/08/492/004 EU/1/08/492/005 EU/1/08/492/006 Solution for injection in pre-filled syringe (glass): EU/1/08/492/007 EU/1/08/492/008 162 mg, Solution for injection in pre-filled pen: EU/1/08/492/009 EU/1/08/492/010

Medicinal product which is or has been authorised in accordance with European Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

Product name, strength, pharmaceutical form:	RoActemra (EU) - 20 mg/ml, Concentrate for solution for infusion - 162 mg, Solution for injection in pre-filled syringe (glass)
Marketing authorisation holder:	Roche Registration GmbH
Date of authorisation:	- 16-01-2009 for the 20 mg/ml, Concentrate for solution for infusion - 23-04-2014 for the 162 mg, Solution for injection in pre-filled syringe (glass)
Marketing authorisation granted by:	European Union
Marketing authorisation number:	20 mg/ml, Concentrate for solution for infusion: EU/1/08/492/003 EU/1/08/492/004 Solution for injection in pre-filled syringe (glass): EU/1/08/492/008
Bioavailability studies numbers:	**- RGB-19-101** for the Concentrate for solution for infusion (Phase III. efficacy/safety study) **- RGB-19-2101** for the Solution for injection in pre-filled syringe (glass) (Phase I. PK/PD study)

1.5. Information on paediatrics

Not applicable

1.6. Information on orphan market exclusivity

1.6.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the procedure because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.7. Steps taken for the assessment of the product

The rapporteur and Co-rapporteur appointed by the CHMP were:

Rapporteur:	Kristina Dunder
Co-rapporteur:	Hjalti Kristinsson

The application was received by the EMA on	28 February 2025
The procedure started on	27 March 2025
The CHMP rapporteur's first assessment report was received on	16 June 2025
The CHMP Co-rapporteur's first assessment report was added to the rapporteur's report on	20 June 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	24 June 2025
The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	24 July 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	02 October 2025
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	17 November 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 November 2025
The CHMP agreed on a list of outstanding issues (LoOI) to be sent to the applicant on	11 December 2025
The applicant submitted the responses to the CHMP list of outstanding issues on	23 January 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs Joint assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on	20 February 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tuyory on	26 February 2026

1.8. CHMP outcome

1.8.1. Considerations related to paediatrics

Not applicable.

1.8.2. Considerations related to orphan market exclusivity

Not applicable

1.8.3. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tuyory is favourable in the following indication(s):

The full indication for Tuyory 20 mg/ml concentrate for solution for infusion is:

Rheumatoid arthritis (RA)

Tuyory, in combination with methotrexate (MTX), is indicated for:

- the treatment of severe, active and progressive RA in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Tocilizumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with MTX.

Coronavirus disease 2019 (COVID-19)

Tuyory is indicated for the treatment of COVID-19 in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

Systemic juvenile idiopathic arthritis (sJIA)

Tuyory is indicated for the treatment of active sJIA in patients 2 years of age and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Tuyory can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Polyarticular juvenile idiopathic arthritis (pJIA)

Tuyory in combination with MTX is indicated for the treatment of pJIA (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Cytokine release syndrome (CRS)

Tuyory is indicated for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening CRS in adults and paediatric patients 2 years of age and older.

The full indication for Tuyory 162 mg solution for injection in pre-filled syringe is:

Rheumatoid arthritis (RA)

Tuyory, in combination with methotrexate (MTX), is indicated for:

- the treatment of severe, active and progressive RA in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Tocilizumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

Systemic juvenile idiopathic arthritis (sJIA)

Tuyory is indicated for the treatment of active sJIA in patients 1 year of age and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Tuyory can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Polyarticular juvenile idiopathic arthritis (pJIA)

Tuyory in combination with MTX is indicated for the treatment of pJIA (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Giant cell arteritis (GCA)

Tuyory is indicated for the treatment of GCA in adult patients.

The full indication for Tuyory 162 mg solution for injection in pre-filled pen is:

Rheumatoid arthritis (RA)

Tuyory, in combination with methotrexate (MTX), is indicated for

- the treatment of severe, active and progressive RA in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Tocilizumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

Systemic juvenile idiopathic arthritis (sJIA)

Tuyory is indicated for the treatment of active sJIA in patients 12 years of age and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids.

Tuyory can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Polyarticular juvenile idiopathic arthritis (pJIA)

Tuyory in combination with methotrexate (MTX) is indicated for the treatment of pJIA (rheumatoid factor positive or negative and extended oligoarthritis) in patients 12 years of age and older, who have responded inadequately to previous therapy with MTX.

Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Giant cell arteritis (GCA)

Tuyory is indicated for the treatment of GCA in adult patients.

The CHMP, therefore, recommends the granting of the marketing authorisation subject to the conditions described in the following sections.

1.8.4. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Tuyory is considered biosimilar to RoActemra (tocilizumab). Therefore, a benefit/risk balance comparable to the reference product can be concluded.

1.8.5. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

1.8.6. Other conditions and requirements of the marketing authorisation

1.8.6.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

1.8.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.8.7.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or

as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

1.8.7.2. Additional risk minimisation measures

The proposed additional risk minimisation measures include a patient (alert) card.

Key messages of the additional risk minimisation measures are described below:

Patient Card

- To address the risk of getting infections which can become serious if not treated. In addition, some previous infections may reappear. Patients should seek guidance from their healthcare professional in case they develop an infection of any kind (even a head cold) at the time of their scheduled treatment with Tuyory.
- To address the risk that patients using Tuyory may develop complications of diverticulitis which can become serious if not treated. Patients should inform their doctor immediately if they experience signs and symptoms of stomach pain, or colic with a change in bowel habits, or notice blood in their stool. The patient should inform the healthcare professional if they have or have had intestinal ulceration or diverticulitis (inflammation in parts of the large intestine).
- To address the risk that patients using Tuyory may develop serious hepatic injury. Patients' liver function would be monitored for changes in the level of liver enzymes through liver function tests during treatment with Tuyory. Patients should inform their doctor immediately if they experience signs and symptoms of liver toxicity including tiredness, confusion, abdominal pain, pain or swelling in the upper right side of the stomach area and jaundice (yellowing of the skin and eyes, and have dark brown coloured urine).

1.8.8. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

1.8.9. Proposed list of recommendations

Table 2: Proposed list of recommendations

Description of recommendation
The applicant is recommended to continue the leachable study and to provide the data of the study when available.

2. Introduction

2.1. Therapeutic context

This section is not relevant for a biosimilar.

2.2. Aspects of development

Tuyory (company code RGB-19) has been developed as a biosimilar to originator RoActemra (tocilizumab), for the same use with respect of administration and therapeutic indications as for the EU-approved Reference Medicinal Product (RMP) RoActemra 20 mg/mL concentrate for solution for infusion, 162 mg solution for injection in pre-filled syringe, 162 mg solution for injection in pre-filled pen. Tuyory contains no novel excipients.

In the EU, tocilizumab is marketed by Roche Registration GmbH (RoActemra) since 2009.

The clinical development of RGB-19 comprised two pivotal clinical studies: One phase 1 single dose, cross over study in healthy males, and one phase 3 study in RA-patients.

Scientific advice was obtained from the Medicines and Healthcare products Regulatory Agency (MHRA) in 2016 and 2023 and from the European Medicines Agency (EMA) between 2017-2024. Advice given regarding the clinical development of biosimilar tocilizumab is a historical part of the clinical development strategy for RGB-19. Within the time span, important changes in the planning of clinical studies were noted. According to the applicant, scientific advice procedures supported the clinical development of RGB-19, resulting in two pivotal clinical studies and critical design and evaluation features of these studies are based on scientific advice received. However, as the applicant states, the clinical development strategy changed several times, not all recommendations by EMA have been accepted, i.e., first time point of submission: After initial submission of 6-month data, the long-term one year data will be submitted along with the response to the Day 120 LOQ assessment.

2.3. Description of the product

Tocilizumab is a recombinant humanised Immunoglobulin G1 (IgG1) monoclonal antibody against human interleukin-6 (IL-6) receptor produced in Chinese hamster ovary cells by recombinant DNA technology. Tocilizumab is used to treat inflammatory and autoimmune conditions. It belongs to the pharmacotherapeutic group of immunosuppressants, interleukin inhibitors; ATC code: L04AC07.

The indication and posology of Tuyory are the same as the reference product. The composition of the intravenous (IV) formulation is almost identical to the reference product and the subcutaneous (SC) formulation is different from the reference product. Based on the EU Summary of Product Characteristics (SmPC) the intended indications are: Rheumatoid arthritis (IV and SC formulation), Giant cell arteritis (SC formulations only), Coronavirus disease 2019 (COVID-19) (IV formulation only), Juvenile Idiopathic Arthritis (IV and SC formulations), Cytokine Release Syndrome (IV formulation only).

2.4. Inspection issues

2.4.1. Good manufacturing practice (GMP) inspection

No inspection required.

2.4.2. Good laboratory practice (GLP) inspection

No inspection required.

2.4.3. Good clinical practice (GCP) inspections

No issues regarding GCP have been identified. The clinical and bioanalytical sites in study RGB192101 have not undergone inspection by an EU/EEA inspectorate. However, the clinical study site has been inspected by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), most recently in October 2019. The bioanalytical laboratory is GLP certified, that undergoes regular GLP inspections by the PMDA. In 2022, the bioanalytical laboratory underwent a remote regulatory assessment by the FDA. In addition, audits by independent GCP/GLP consultants have been conducted and the corresponding audit certificates have been submitted. No inspection was required.

A GCP inspection of the phase 3 study (RGB19101) has been conducted by the PMDA in the context of the Tocilizumab dossier submission to PMDA. The notification has been received.

3. Quality aspects

3.1. Introduction

Tuyory is a proposed biosimilar to the reference medicinal product (RMP) RoActemra (EMEA/H/C/000955). The active substance tocilizumab, also referred to as RGB-19, is a humanised IgG1 monoclonal antibody (MAb) produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

The finished product is presented as:

- A concentrate for solution for infusion in 4 mL, 10 mL or 20 mL vial containing 20 mg/mL of tocilizumab;

- A solution for subcutaneous (SC) injection in either a single use pre-filled syringe (PFS) or a single use pre-filled pen (PFP) containing one dose of 162 mg tocilizumab.

The finished product for the vial presentations is formulated with sucrose, polysorbate 80 (PS80), disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, phosphoric acid concentrated (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

The finished product for the PFS and PFP presentations is formulated with L-Histidine, L-Histidine monohydrochloride monohydrate, L-Valine, L-Methionine, PS80, phosphoric acid concentrated (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

3.2. Active substance

3.2.1. General information

RGB-19 is a recombinant humanised immunoglobulin G subclass 1 (IgG1) type MAb, composed of two covalently linked heterodimers, each of which consists of a heavy and a light polypeptide chain. One N-glycosylation site is present at Asn299 of the heavy chain. The amino acid sequence and the properties of the antibody are acceptably presented in the dossier. The molecular weight (MW) is 148 kDa.

The proposed mechanism of action is inhibition of IL-6-mediated signalling, through binding to membrane-bound IL-6 receptor (mIL-6R) and soluble IL-6 receptor (sIL-6R).

The information provided in this section is found acceptable.

3.2.2. Manufacture, characterisation, and process controls

Description of manufacturing process and process controls

The active substance is manufactured at Gedeon Richter Plc. (Chemical Works of Gedeon Richter Plc.), Richter Gedeon Utca 20, Debrecen, 4031 Hungary. All sites involved in manufacturing and control of the active substance operate in accordance with EU GMP.

RGB-19 is manufactured at production scale. Chinese hamster ovary (CHO) cells are used for expression. The manufacturing process consists of three main stages:

1) Upstream cell culture process (USP)) with thawing working cell bank (WCB) vial, inoculum I phases for shake flask expansions, inoculum II phases for bioreactor, resp., and fed-batch production phase in bioreactor.

2) Midstream process (MSP) including depth filtration and microfiltration.

3) Downstream process (DSP) including chromatography and , virus removal steps. Following ultrafiltration/diafiltration and formulation, the last step with bulk filtration and filling is reached. The active substance is then stored at ≤-70 ºC.

One active substance batch is defined as the amount that is harvested, filtered, and purified from a singleproduction bioreactor run. The batch numbering system is adequately described in the dossier. Batch size is indicated as per the volume of the production bioreactor. This is acceptable.

Reprocessing is not performed in the tocilizumab active substance manufacturing process.

Lifetime studies for membrane and chromatographic columns are addressed.

The active substance manufacturing process is acceptably described.

Control of materials

Raw materials

Descriptions of raw materials used in master cell bank (MCB) / WCB preparation and active substance manufacturing are provided. Compendial and non-compendial raw materials are listed and specifications for all non-compendial raw materials are provided.

All buffers and solutions used in the process are listed with corresponding specifications. Resins, membranes and filters used are listed and the manufacturer of each consumable is stated. In conclusion, the raw materials used are sufficiently described.

The culture medium is stated to be a proprietary protein-and animal-free, chemically defined cell culture medium formulation for the cultivation of CHO cells. The composition of the cell culture media and feed solutions are provided. In case of the Cell culture production medium, (Feed medium A), and (Feed medium B) the composition is not specified. This is found acceptable and the quality agreement between the applicant and the supplier ensures that the applicant is informed about any changes in the proprietary media to assess potential impact on the product.

No components in the commercial manufacturing process for the active substance are directly derived from animal or human sources. This is acknowledged.

Detailed information has been provided regarding source, history, and generation of the cell substrate. Sufficient information has been provided.

The generation of the cell banking system has been described in acceptable detail. The characterisation and virus testing of the parental cell line, MCB, WCB1 and WCB2 are in accordance with ICH Q5A and ICH Q5D. The WCB2 is used for commercial production only. An extensive analytic assessment of RGB-

19 active substance batches produced using WCB1 and WCB2 has been performed and is provided in 3.2.R. WCB1 and WCB2 show a high level of comparability in terms of identity, purity, structure-function-relationship and biological activity.

In conclusion, comparability between WCB1 and WCB2 in the manufacturing of RGB-19 active substance has been demonstrated. Based on overall high degree of comparability no clinically meaningful impact is expected on the performance of the product. This is accepted.

New WCB

The materials used in the culture and cryo-preservation of future WCB have been specified and listed. Additionally, description of cultivation and establishment of future WCB has been provided. A general protocol for the establishment of future WCBs has been submitted concerning the maintenance of the safety, genetic stability, cell viability after thaw, cell growth, protein production, and product quality. It also includes the respective analytical methods and acceptance criteria. Since this is in the dossier and upon approval of MAA this allows that any newly qualified WCB will be implemented without the need of further communication with the health authority.

End of production cell bank production and characterisation

Sufficiently detailed descriptions have been presented for the establishing of limit of *in vitro* cell age (LIVCA) and end-of-production cell bank (EOPCB). The results from testing of the EOPCB confirm CHO identity and the results from virus testing is as expected for CHO cells (some reverse transcriptase (RT) activity detected and presence of A-type and C-type retrovirus-like particles). The results are acceptable.

In addition, acceptable information on monitoring of MCB and WCB stability has also been provided. Also, the data presented from studies of genetic stability is deemed acceptable.

For overall conclusion on virus strategy and testing, please refer to section A.2. adventitious agents' safety.

Control of critical steps and intermediates

Manufacture of the RGB-19 active substance is controlled by process parameters for each stage of the manufacturing process. In this section, definitions are provided for in-process controls (IPCs) and critical process parameters (CPPs). There are no IPCs or CPPs defined for the midstream process. Proven acceptable ranges (PARs) are established in S.2.6. The CPPs and IPCs for the active substance manufacturing process are acceptably presented and harmonised with what is described in the Process Description. Regarding the CPPs, it is presented how they are defined and controlled for the upstream and downstream process steps, it is clear how the criticality was assigned and what distinguishes a critical parameter from a non-critical. Furthermore, a complete list of the abbreviations and definitions of all different input parameters (CPP, process performance parameter (PPP), general process parameter (GPP)) and output attributes (IPC, process performance indicator (PPI), in-process monitoring (IPM)) has been provided in the dossier. This is acceptable.

Acceptance criteria are provided for individual steps of the upstream and downstream processes, respectively. Additional information on the justification for the IPC limits for active substance manufacturing, specifically IPC limits for charge variant fraction analysis, was acceptably provided upon request.

Description of test methods used for in-process testing have been provided. The methods include determination of cell concentration, purity and titre. Related validation report summaries, submitted as separate files to section 3.2.S.2.4, support the claim they are fit for purpose. This is agreed.

Consequences of an IPC or CPP deviation are acceptably described in this section.

The unprocessed bulk has been identified as a critical intermediate in the RGB-19 active substance manufacturing process. Test results with respect to product titre, microbial and viral contamination are assessed in A.2. Endotoxin, bioburden, mycoplasma, adventitious viruses and viruses like particles were tested on three individual commercial scale batches. Summary of the results are included in section 3.2.A.2. According to ICH Q5A, routine testing for adventitious viruses in production batches is recommended. Therefore, these tests are also included as IPCs reflecting the criticality of the quality attribute.

The indicator cell lines used are stated in S.2.4, and a 28-day in vitro assay is used routinely.

Description of process intermediates are presented with validated hold times and storage conditions. This is found acceptable.

Process validation and/or evaluation

Process validation of the RGB-19 active substance manufacturing process was executed at the proposed commercial manufacturing site. The validation study included consecutive process performance qualification (PPQ) batches produced. In addition, results from commercial-scale GMP batches produced were used in some of the process validation studies. Validation activities undertaken by the applicant included process consistency validation, impurity clearance, hold time studies, resin and membrane lifetime studies and transport validation.

Process consistency validation

Batch data results from the PPQ batches demonstrated that the process input parameters (CPPs) and process output attributes (IPCs) met their corresponding acceptance criteria. This was demonstrated for the upstream, midstream (IPC only) and downstream processes. Additional tests on the PPQs covering all individual process steps with non-critical process control elements demonstrated that their target acceptance ranges were met.

For the upstream process, process consistency was shown by plotting selected results (e.g. culture pH and temp, dissolved oxygen, agitation speed) against cultivation time for the PPQ batches as well as for two engineering batches. Overall, data were at target set points within accepted ranges. The occurrence of a few deviations is explained.

Furthermore, batch homogeneity and batch-to-batch consistency for the PPQs was demonstrated and all release specifications limits met. Process consistency is further supported by batch data in S.4.4. Testing for sialic acid is not part of the release specification but was included during the validation. This is acknowledged.

Protocol for ongoing process verification is not mentioned in the dossier. However, this is considered a GMP matter and should follow the principles of GMP and is therefore acceptable.

Impurity clearance

As part of the process validation, removal of impurities associated with RGB-19 active substance manufacturing was evaluated. The evaluation included product-related impurities (charge variants and molecular mass variants) and process-related impurities (host-cell DNA, host-cell protein, leached Protein A and sequence variants observed during process development). Testing results from different stages of manufacturing, supportive of effective removal, is presented. Removal of anti-foam is evaluated in S.3.2. This is acknowledged.

Hold time studies

Microbial hold time studies for all media, buffer solutions and process intermediates of the RGB-19 active substance manufacturing process were outlined to establish hold time limits under specified conditions, including the storage vessel type and temperature. The hold time for each component was

determined by the longest duration that a batch continued to meet acceptance criteria. Extensive set of data is presented in the dossier. The approach is found acceptable and the microbial and biochemical hold times are found justified.

Resin and membrane lifetimes

Lifetime studies have been conducted at small scale to establish the maximum number of product-contacting cycles for each chromatography resin used during the different steps of the manufacturing process. In addition, the lifetime for the membranes used tangential flow filtration (TFF) was established. Number of cycles were validated at small scale for the chromatography. For TFF the number of cycles were determined. Resin and membrane performance studies are further outlined in section S.2.6. The resin and membrane lifetime validation study will also be verified during commercial processing. Protocols have been added to the dossier. The lifetime studies are found acceptable.

Active substance transport validation study

Adequate information concerning the transport validation study was provided in the dossier.

To conclude, it is agreed that process validation activities undertaken by the applicant sufficiently demonstrate that the intended commercial manufacturing process at Debrecen performs as expected. The RGB-19 active substance manufacturing process is considered validated.

Manufacturing process development

Manufacturing Process History

Following acquisition of the initially developed product, Gedeon Richter Plc. changed its name to RGB-19 and implemented a number of changes to the manufacturing process. Those changes are outlined in this section.

Gedeon Richter modified the active substance process significantly during three development stages before the final manufacturing process. In brief, USP development was performed using microbioreactors pilot scale batches, and commercial scale batches. The MSP and DSP steps were also evaluated and improved upon, in order for RGB-19 to meet the RMP's quality target product profile (QTPP) ranges.

GMP batches, including the engineering batches, batches for process validation and the PPQ batches have since been produced at the Debrecen site using the final manufacturing process. The use of the batches post PPQ production have mainly been to finalise glucose control strategy, critical quality attributes (CQA) process capability analysis, hold time studies, long-term and accelerated stability studies. Results are presented in the dossier, and changes are detailed in the dossier. Thus, the description of the manufacturing process history is found acceptable.

Comparability

Batches produced at commercial scale were used for clinical trials. Given the final manufacturing process was used to provide material for these clinical studies, no comparability exercise is required for this purpose.

An extensive study report is though presented for active substance batches produced with the final manufacturing process versus the initial process at commercial scale (from development stage III). Importantly, a main reason for development of the final process was to optimise (i.e. reduce) the presence of tocilizumab sequence variants, in particular asparagine to serine sequence variants, to acceptable levels for the applicant to claim biosimilarity (refer to Scientific Advice EMA/CHMP/SAWP/278572/2019). The final process was optimised at upstream level, thereby reducing the proportion of asparagine to serine sequence variants in the produced RGB-19 active substance.

Mass spectrometry (MS)-based structural characterisation data (presented in S.2.6) proved that the asparagine to serine sequence variants in RGB-19 active substance produced with the final process indeed were successfully reduced compared to RGB-19 active substance produced with the previous, initial process. Furthermore, extensive side-by-side data on physicochemical properties and biological functionality for RGB-19 active substance produced with the final versus initial process is summarised in a separate quality comparability report. This report covers a large number of analyses conducted to address identity, higher order structure, post translational modifications, purity, structure-function-relationship and potency. The applicant concludes that presence of sequence variants in the RGB-19 active substance batches was reduced to an acceptable level in terms of the efficiency and safety, while none of the other analysed CQAs were affected substantially. Based on the comprehensive set of analytical data presented, this conclusion is supported. The comparability study undertaken for the optimised upstream process change is acknowledged and acceptable.

It can be noted that all batches of RGB-19 finished product SC and IV included in the Phase I and Phase III clinical trials, process validation, comparability and stability studies as well as in the biosimilarity exercise, were manufactured according to the same proposed commercial scale process of both active substance and finished product.

Process development and control strategy

A control strategy was developed to assure the consistency of the process performance of RGB-19 active substance manufacturing, as well as the quality of the finished product. The identification of CQAs was accomplished by a risk-based analysis approach using the QTPP, experimental data on RGB-19 as well as the reference medicinal product (RMP), and published knowledge including available authorisation documents of the RMP. The establishment of QTPP ranges for RGB19 active substance and finished product from RMP, i.e. RoActemra and Actemra, is presented in 3.2.S.2.6. This assessed to be in accordance with ICH Q8 and EMA/CHMP/BWP/247713/2012 guidelines and therefore acceptable.

The CQAs were categorised into three main groups: obligatory CQAs (composition and strength, contaminants of bacterial origin, drug specific QAs), leachables and product variants. The overall risk of a given quality attribute for the product variants and process related impurities, that may affect bioactivity, pharmacokinetics (PK) /pharmacodynamics (PD), immunogenicity and safety of the product, was established on basis of its uncertainty and impact. The scoring system for uncertainty and impact is presented in the dossier. Considering the CQAs of the active substance have been listed, the rationale for designating these characteristics as CQAs have been provided and that CQAs selected for process characterisation studies have been presented, the CQA assessment is deemed acceptable.

Upstream process development included optimisation of product glycation. The applicant explains that glycation generates structural heterogeneity in the product that can potentially affect potency and safety by blocking the biologically functional site or by further degradation that induces aggregation. Therefore, the mono-glycated ratio is a CQA with a target QTPP range of established from the RMP. For RGB-19, a low glucose control strategy was first developed at microscale to reduce product glycation. Further optimisation of product glycation was performed. The process improvements implemented have succeeded in reducing the upstream levels of product glycation. This optimisation work is acknowledged. Upon request, the applicant confirmed that the glucose control strategy was changed and remained unchanged in all subsequent RGB-19 active substance batches including the PPQ batches. The glucose control strategy related to a minor fine-tuning of daily glucose setpoints with no impact on cell culture performance or product quality. Consequently, the claim that engineering batches are representative of the final manufacturing process is agreed.

Importantly, the applicant has also confirmed that no additional process changes was undertaken after the manufacturing of the PPQ batches had started.

A cause and effects (C&E) analysis based on criticality calculations was performed to understand the impact of mid- and downstream process steps on quality attributes (QAs). Results from pilot scale batches and production batches were evaluated. Protein A chromatography, MMAEX chromatography, and CEX chromatography steps were identified as the most critical steps in midstream and downstream processing. Considering the Protein A column removes process-related impurities, the MMAEX column removes high molecular weight species (HMWs), leached Protein A (LPA), and HCP glutamine variants are reduced to acceptable levels during the incubation and CEX chromatography steps, this can be agreed.

Process Characterisation Studies

A separate set of studies was performed to establish PARs for the up-, mid-and downstream process. It is claimed that studies were performed on scale-down models from the commercial scale process. A list of studies performed with the purpose of determining PAR is shown. A description of the scale-down models used to establish proven acceptable ranges (PARs) has been provided upon request. In addition, detailed information on the qualification and evaluation of these scale-down models as well as the experimental and statistical analyses carried out have been provided as Annexes. The applicant justifies the relevance of the scale-down models based on statistical analyses including equivalency test and multi variate data analysis based on commercial scale data. Results obtained were found significantly comparable and showed a good level of agreement regarding all the investigated process parameters and quality attributes. Thus, the justification of the scale-down models as valid models for the RGB-19 manufacturing process is found acceptable.

Parameter characterisation studies were carried out to define the PARs. Details have been provided and the applicant has acceptably described and justified the use of scale-down models for these studies. Results and conclusions are found supportive of the proposed ranges. Hence, the PARs are found acceptable.

Several process parameters were identified as critical for the USP production phase and for most of the DSP steps. The USP production phase is controlled by different CPPs. For example, culture glucose concentration was monitored with individual PAR set points for PAR

The DSP chromatography steps were investigated according to a design of experiments (DoE) approach with 3 input parameters (protein load, conductivity and pH of the load), respectively. For (Protein A chromatography), the operating ranges were determined using worst-case and one factor at a time (OFAT) approaches. The established PARs, including PAR set points, for the identified critical process parameters are presented.

For the membrane and chromatography column performance studies, the applicant describes that validations of the small-scale models are presented**.** The acceptance criteria were defined through statistical evaluation of data derived from commercial-scale batches. The setting of the acceptance criteria and the validity of the scale-down models are found acceptable.

Extractables and leachables, contact materials

An evaluation of extractables and leachables and from contact materials was performed on the materials with product contact during the active substance manufacturing process with an acceptable conclusion that the safety concern was negligible. All calculated permitted daily exposure (PDE) levels were below the permitted levels indicating that there are no safety concerns due to potential leachables of primary contact materials (PCMs) in the manufacture and storage of RGB-19 active substance. Mutagenic/genotoxic potential of extractable compounds were discussed in detail. In conclusion, the applicant has addressed the development history of the RGB-19 active substance manufacturing process.

In conclusion, the process development and characterisation, including development of the control strategy, is considered adequately described and justified. The information provided in section 3.2.S.2.6 is acceptable.

Characterisation

Tocilizumab is a recombinant humanised mAb of the IgG1 subclass with a molecular weight of approximate 148 kDa. It contains 16 disulfide bridges and an asparagine residue at position 299 (Asn 299) in each heavy chain, that is amenable to glycosylation.

Characterisation of RGB-19 active substance was performed with respect to structural, physicochemical and biological functions and activities. The main batch used for characterisation was the primary reference standard PRS-RGB19-02. The choice of PRS-RGB19-02 is endorsed since it originates from PPQ1 produced with the final manufacturing process. In addition, material from its preceding development reference standard, PRS-RGB19-01 and three RMPs sourced from EU, and non-EU market were included in the structural studies since the majority of the characterisation studies was conducted as part of the comparative analytical similarity assessment (section 3.2.R).

The methods used are qualified, state-of-the-art and the use of orthogonal methods is acknowledged.

Structural characterisation

The primary structure characterisation included intact and subunit (light chain and two different heavy chains fragment; aa 1-238 and aa 239-448, resp.) mass analyses by RP-HPLC-ESI-MS. To confirm the amino acid sequence of the heavy and light chains, peptide mapping was performed under reducing conditions. Three combinations of enzymes were used for protein cleavage, to fully cover the primary structure. Representative base peak and total ion chromatograms (including overlay with RMPs), lists of peptides identified (all mass accuracy within ±5 ppm) and sequence coverage of heavy and light chain are included in the dossier. A sequence coverage of 100% is demonstrated for RGB-19 tocilizumab. In conclusion, it is agreed that the primary sequence is sufficiently verified.

The predicted disulfide bond structure, with 12 intrachain and 4 interchain bridges, was confirmed by a non-reducing Lys-C+ trypsin peptide mapping after protection with N-ethylmaleimide (NEM) to avoid formation of mismatches during sample preparation. Besides the major disulfide bridge containing peptides identified by MS, some minor cysteine variants such as free thiol groups were detected and presented. The amount of free thiol groups was further determined quantitatively by Ellman's assay in 3.2.R. The obtained results showed free thiol content in RGB-19 below the reporting limit of the analytical method. This is endorsed.

Higher order structure was analysed by 2D nuclear magnetic resonance (NMR), micro-differential scanning calorimetry (DSC) and far UV circular dichroism (CD) spectroscopy. Taken together, results from these methods were indicative of an immunoglobulin molecule with proper folding. This is found acceptable.

Physiochemical characterisation

Verification of the conserved glycosylation site at Asn299 was performed by enzymatic treatment (Lys-C and trypsin) of PNGase F glycosidase digested tocilizumab samples. The N-glycan pattern was investigated by InstantPC labelling with Hydrophilic interaction chromatography (HILIC), ultra-high performance liquid chromatography (UHPLC), flow injection electrospray ionisation tandem mass spectrometry (FL/ESI-MS/MS) during the similarity assessment. The six dominating glycoforms were presented in this section as G0F, G1F, G1F', G2F, G0 and Man5 and the composition data could be found in S.3.2. Assignment of peaks from peptide mapping of intact RBG-19 samples also shows the presence of the major glycoforms. Subunit peptide mapping following IdEs protease digestion further located the glycosylation to the Fc/2 fragment.

Sialic acid content was quantified by reverse phase HPLC (RP-HPLC) method with fluorescence detection. The levels of the potential immunogenic form N-glycolylneuraminic acid (NGNA) were below limit of detection.

A LC-MS/MS based approach under reducing conditions was used to determine N- and C-terminal heterogeneity as well as oxidation, deamidation and isomerisation sites. The glycation sites were also investigated by this method while the level was determined by an intact glycation method. The higher level of glycation in RGB-19 compared to RMPs was subject for process optimisation studies and is discussed in S.2.6. It is stated by the applicant that this difference is not considered critical, since it has no effect on bioassay results.

The N-glycan structures of RGB-19 are found sufficiently characterised.

Quantitative information about charge variants in RGB-19 active substance was provided by cIEF and IEX-HPLC. Further characterisation of enriched charge variants by MS-methods revealed various aspartic acid isomerisation variants (LC_D167, HC_D282; none located in the CDR-regions); C-terminal Lysine variants; a C-terminal Proline amidation variant in the basic fraction. In the acidic fraction, N-terminal carbamylated variant and glycated variants (none localised in the CDRs of RGB-19) were identified.

For size variants, a representative SEC-HPLC chromatogram of a RGB-19 active substance batch is presented showing a dominating monomeric form of RGB-19 and HMWs. The low molecular weight (LMW) species were quantified by NR-CS-SDS and further characterised by HILIC-MS identification under partially reduced conditions after deglycosylation to identify different antibody fragments. Isolation and further analysis of the HMW species is presented in the analytical similarity assessment (CTD 3.2.R) where SEC-MALLS was used to evaluate the molecular weights of the HMWs in RGB-19 finished product batches. HMW weights were around 300 kDa indicating dimer formation. Furthermore, monomer Mw and HMW Mw data show that RGB-19 batches are similar to RoActemra. Batches of different presentation also show similarity. Size distribution data by analytical ultracentrifugation showed that the monomeric content was dominant in RGB-19 finished product batches. This is acceptable.

Biological functions and activities

Tocilizumab binds to both the transmembrane and soluble IL-6 receptors (mIL-6R and sIL-6R, respectively), thereby inhibiting cell proliferation. Relative antigen binding for RGB 19 active substance was evaluated by two methods, sIL-6R binding by ELISA and mIL-6R binding by flow cytometry. Thus, Fab binding to both the soluble and the membrane bound receptor were investigated. It was demonstrated that Fab binding was consistent between batches (see 3.2.R). Dose-response curves for both the antigen assays are presented. Moreover, ligand binding data by biolayer interferometry (BLI) generated a K_D value proving a specific, high affinity interaction. The sIL-6R binding ELISA method is included in the RGB-19 active substance specification to test for antigen binding at release. This is acceptable from a characterization point of view.

Effector functions in terms of Fc-receptor binding and binding to C1q were evaluated by BLI using a receptor capture approach for each assay. Representative sensorgrams and kinetic data are presented for each receptor showing K_D-values in the expected nM and µM ranges. The specific Fc receptors characterised were FcRn, FcγRI, FcγRIIa R131, FcγRIIIa V158. It's noted that only one polymorphism variant of FcγRIIa and FcγRIIIa was studied, respectively. The biosimilarity exercise should include binding to both polymorphic receptor in cases where binding to FcγRIIa and FcγRIIIa is a relevant quality parameter, respectively. However, considering RGB-19 has been shown to not induce any ADCC and CDC activity, the panel of Fc-receptors studied here can be deemed acceptable.

The RGB active substance was further characterised with respect to functional activities. These included anti-proliferation, inhibition of tocilizumab STAT3 phosphorylation, dissociation activity of the IL-6/sIL6R complex and inhibition of sIL-6R mediated trans signaling. In conclusion, the repertoire of cell-based and ligand-based assays developed to characterise the biological functions and activities of RGB -19 active substance is acknowledged. It is noted that the same methods were applied and that the results are further evaluated in the biosimilarity assessment exercise with consistent results. This is acceptable.

Impurities

Presence, identity and risk assessments of product- and process related impurities arising from e.g., raw materials, manufacturing process and product-related degradation, were discussed in section 3.2.S.3.2 and Appendices thereof.

Product-related impurities of RGB-19 active substance include, N-glycoforms, charge variants, oxidised forms, HMW and LMW species and non-glycosylated heavy chain (NgHC). Biological functional characterisation results have been submitted for the charge variants and degradation products (oxidation, HMW and LMW, deamidated, and isomerisation variants). Generally, no significant difference in biological activity or target binding of the charge variants was detected, when compared to the RMP. Only the binding activity of the A1 acidic variant (measured by ELISA) showed slightly below the RMP, and in case of the A2 acidic variant slightly decreased antiproliferation activity in TF-1 was detected. The characterisation of the product-related variants is found acceptable.

The process-related impurities addressed in section 3.2.S.3.2. included residual host cell proteins (HCPs), residual host cell DNA (hcDNA), LPA, bacterial endotoxins (BET) and microbial contaminants. Media components were also discussed. Safety assessments and calculation of PDE limits are outlined in separate Appendixes for Protein A and for media components: Batch results presented in this section confirm efficient removal of all the process-related impurities. The applicant concluded that simethicone in the active substance is evaluated as a minimal safety risk and that the clearance potential does not need to be demonstrated by analytical measurements. This is acceptable.

Robust clearance of raw materials is shown in section S.2.3. Contaminants are thoroughly controlled during the manufacturing process and the capability of the active substance process for virus removal is discussed in section A.2. Furthermore, based on the results of a risk assessment report, the risk of presence of nitrosamine impurities in RGB-19 active substance is considered low. This is agreed. The characterisation of impurities in RGB-19 active substance is found acceptable.

3.2.3. Specifications

Specifications

The specification of RGB-19 active substance includes tests for general pharmaceutical quality (appearance, colour, opalescence, pH, osmolality, visible particles), for purity (size and charge variants), for N-glycosylation, for process related impurities (HCP, HCDNA), for biological activity, for microbiological control (bacterial endotoxin, bioburden) and protein content. The inclusion of two highly specific tests (capillary isoelectric focusing (cIEF) and peptide mapping) to establish the identity of RGB-19 active substance is endorsed. Regarding biological activity, it is noted that different tests are included in the specifications for active substance and finished products, respectively. Quality control of active substance with respect to biological activity is performed using the in house sIL-6R binding ELISA method to test for relative antigen binding. For the finished product presentations, the in-house antiproliferation assay is used as the biological activity test to monitor cell-based potency. In principle, different tests for biological activity at active substance versus finished product level is acceptable provided the validation and justification of these methods have been acceptably performed.

For compendial methods, references are made to the corresponding Ph. Eur. chapters. For non-compendial method, the type of method used for analysis is stated.

The applicant confirmed that active substance specification is used for release and stability testing with the same proposed acceptance criteria.

To provide a clear link between the active substance specifications, the method descriptions and the validation summaries, in-house method numbers have been defined and provided for all non-compendial test methods.

Regarding BET testing, the compendial LAL test based on the Limulus Amebocyte lysate (Ph. Eur. 2.6.14) is used. Whilst this is acceptable, the applicant has laid down a tentative plan for transitioning from compendial LAL test to Ph. Eur. 2.6.32 Test for BET using recombinant factor C. This is endorsed.

Justification of specification

To set the specification limits for the quality control of the RGB-19 tocilizumab active substance, the applicant has used a strategy based on statistical calculations (on release and long-term stability data of representative active substance batches), extrapolation to the end of shelf-life, process capability analysis and the QTPP range. Results from characterisation, qualification of analytical methods and compendial requirements have also been taken into account. This strategy is acceptable.

The proposed acceptance criteria at release and end of shelf life are identical for all specification tests that are stability indicating. Tests that are not stability indicating, that is identification tests by cIEF and peptide mapping, purity tests for N-glycan patterns and high mannose glycan as well as impurity tests for HCP and hcDNA, are not included for end of shelf-life testing. Overall, the active substance specification criteria are aligned with the limits at release of the three finished product specifications, where applicable. This is acceptable.

For compendial tests, the specification limits, as defined, are considered acceptable. For the two identity tests, peptide mapping and IEX-HPLC, the acceptance criteria are based on that the profile of the test sample conforms to the reference standard, which is found acceptable. The limits for protein content are found reasonable.

The proposed upper limit for HCP by the process specific ELISA is based on variance of the method and commercial scale batch data, including batches for clinical material, showing consistent low levels . Thus, the upper limit for HCP is assessed to be justified based on obtained batch data.

Dose calculations based on the 10ng/dose WHO limit and a worst-case scenario (maximum dose) was used to derive the upper limit for host cell DNA (hcDNA). All data from active substance release batches were under the LLOQ. The proposed limit for hcDNA, tested at active substance release, is agreed.

The acceptance criterion for BET by turbidimetric kinetic method was based on the calculation formula presented in compendial monographs that takes into account the daily dose of the finished product. Details of the endotoxin limit calculation of RGB-19 active substance is presented in the dossier along with calculations on maximum dose of the finished product (both finished product IV and finished product SC) based on the clinical studies. This is found acceptable.

The specifications for RGB-19 were amended during development. A justification for each method included in the development specification but excluded from the proposed specification is provided. The following methods were excluded from the proposed active substance specification: N-glycan pattern (i.e. afucosylated glycans), oxidised forms, sialic acid content, size variants (i.e. non-glycosylated heavy chain) and cell-based potency assay (antiproliferation assay). As mentioned above, the antiprolifiration is proposed as potency assay for finished product release while the antigen-binding

assay is proposed for active substance release.

The proposed specification for the antigen-binding assay (80-125%) is supported by process capability, development data and GMP batch data including clinical and process validation batches (. According to the applicant, the limits have been set to be slightly wider, than the mean ± 3SD calculation, to have a safety margin for manufacture and stability studies; the wider limits applied for the marketed RMP ensures that this causes no efficacy or safety issues. This is acceptable.

Testing for residual Protein A is not mentioned in this section but the clearance ability of the active substance process for impurities including leached Protein A (LPA) was demonstrated in S.3.2 for the PPQ batches. This is acceptable.

In conclusion, a rationale has been given for including the proposed set of test methods, with acceptance criteria, in the active substance specification out of a wider range of test methods used during development. This is found acceptable.

In conclusion, the proposed specifications of the RGB 19 active substance are found acceptable.

Analytical procedures

Test for Appearance is in line with Ph. Eur 2031. The tests for degree of coloration, opalescence (using visual method), visible particles, pH, osmolarity, bioburden/microbiological purity (microbial enumeration using membrane filtration) and BET are stated to comply with methods in Ph. Eur. This is found acceptable.

Method descriptions of all non-compendial procedures are provided. For all these in-house methods, the method principle is described, and the equipment, preparation of standards and samples and method parameters are listed. System suitability criteria are also listed, and the calculation and reporting of results are sufficiently described. The results of robustness testing are included. Examples of typical chromatograms and electropherograms are provided. A representative dose-response curve of the sIL-6R binding ELISA is shown. The description of the in-house UV spectroscopy method does not include any information on the origin of the extinction coefficient (theoretically or experimentally derived). However, this information is present in the characterisation section (S.3.1). Representative UV spectra of high quality for all three relevant test samples have been provided. This is acknowledged. The method descriptions of the non-compendial procedures are found adequate and sufficient.

Four analytical methods used during development but not part of the commercial active substance specification, are described along with their validations. These methods concern oxidised forms () by RP-UHPLC-UV, size variants by non-glycosylated heavy chain by reduced capillary electrophoresis-sodium dodecyl sulfate with UV detection (R-CE-SDS-UV), sialic acid content by RP-UHPLC-FL and the cell-based, antiproliferation assay (potency assay used for finished product release).

Validation of analytical procedures

Validation summaries are provided including descriptions of validation approaches and parameters. Relevant validation parameters have been evaluated for both active substance and finished product samples. Relevant calculations and results obtained for individual samples are presented. Chromatograms and representative dose response curves are presented in this section or under Analytical procedures. Some of the analytical procedures (identification by cIEF and peptide mapping, purity by SEC and NR-CE, charge variants by IEX, protein content by UV and antigen binding by ELISA) were validated in different steps to conduct a bridging validation for finished product samples with old and new formulation (with respect to L-methionine). This approach is found acceptable.

Residual testing of HCPs is routinely performed during IPM and at release of active substance. For tocilizumab, the applicant has developed a process specific ELISA for detection of CHO HCPs. The method and the validation are described in the dossier. Furthermore, demonstration of the HCP coverage for the antiserum used in the validation of the HCP method has been provided. The coverage of RGB-19 process-related HCPs was determined by immunoaffinity chromatography combined with 2D DIGE. The HCP coverage was calculated by dividing the number of matched spots with total spots of the RGB-19 mock antigen. Thus, the process specific HCP assay is assessed to be suitable for intended use according to the recommendations given in Ph. Eur. general chapter 2.6.34.

Batch analyses

Results from several batch analyses of RGB-19 active substance batches are presented, all of which have been manufactured with the commercial process. All results complied with the proposed specification limits in place at the time of testing. The provided release data from the commercial process is in support of a consistent manufacture of active substance.

Reference standards or materials

For the commercial process, a two-tiered reference standard system is used. The current primary (PRS-RGB19-02) and working (SRS-RGB19-02) reference standards was produced from commercial active substance batches. SRS-RGB-01, the first working standard established from PRS-RGB19-02, was replaced by SRS-RGB19-02. The SRS must always be calibrated against the PRS. All reference standards are stored at the same conditions, -70ºC. It is explained that homogeneity of the PRS and SRS aliquots will be controlled by protein content determination of the vials at the beginning, middle and end of aliquoting. The preparation of the current reference standards is found acceptably described.

The qualification protocols of historical, current, as well as future RGB-19 reference standards, are well described. The methods used for qualification and the acceptance criteria are provided as well as results from QC testing and extended characterisation. Bridging of potency during qualification of new PRS and SRS against the current reference is presented including calculation of acceptance criteria used for potency qualification for the anti-proliferation assay and calculation of number of replicates needed for the bioassay methods (for the anti-proliferation assay. The calibration of the biological activity against the previous standard is sufficiently described and the increased number of measurements as well as the more stringent acceptance criteria applied (compared to acceptance criteria for QC release) is endorsed. Certificate of analysis are provided as separate Appendices for the current primary and working standards. This is acknowledged.

Stability studies at the proposed storage conditions are on-going for both the primary and secondary (working) reference standards and results from up to 24 and 3 months, respectively, are provided in the dossier. All results comply with the acceptance criteria, and no degradation trends were observed.

In conclusion, the reference standards are found sufficiently characterised and the information provided is found acceptable.

Container closure system

RGB-19 tocilizumab active substance is stored frozen in single use, sterile and pre-assembled bags. Specifications for all three bags including fill volumes and schematic drawings are provided. The bags consist of a five-layer film and the layer that contacts the active substance is made of ultralow density polyethylene (PE). Certificate of analysis (CoA) for the three sizes of bags are provided, demonstrating compliance of the contact films with Ph. Eur. 3.2.2.1 (*Plastic containers for aqueous solutions for parenteral infusion*) and that USP Class VI (*biological reactivity in vivo*) is met. Inspection requirements for incoming containers are outlined. This is acknowledged.

An evaluation of extractables and leachables was performed in S.2.6 on the materials with product contact during the active substance manufacturing process and storage. All calculated PDE levels were below the permitted levels, indicating that there are no safety concerns due to potential leachables.

Stability samples are stored in reduced size bags which are representative of the bags for the bulk frozen storage, of active substance.

Stability samples are further assessed in section 3.2.S.7. Potential difference in fill volumes that could result in some localised differences with impact on product quality were evaluated in S.2.6 in a 2-step approach consisting of first a bulk-scale freeze and thaw, followed by bulk-scale frozen storage. Testing performed over six freeze-thaw cycles demonstrated that results for physical parameters and product quality attributes were highly comparable. Longer-term stability testing also demonstrated comparability between the two frozen storage configurations.

The information in this section is deemed acceptable.

3.2.4. Stability

A shelf life for RGB-19 tocilizumab active substance of 24 months, when stored at the recommended temperature of -70 °C in its container closure system () with protection from light, was initially claimed.

To support the shelf-life claim, an ongoing stability program has been designed in accordance to ICH guidelines, Q5C and Q1A. The studies are conducted in scaled-down containers of the same product contact material as for the full-size bags. Stability data is provided for long-term conditions (-70 ± 10°C), accelerated conditions (5 ± 3°C) and stressed (25 ± 2°C / 60 ± 5% RH) conditions. The quality is monitored using multiple, stability indicating, analytical procedures with acceptance criteria as described in the active substance specification (S.4.1). Information on what test methods that are considered stability indicating can be found in S.4.5.

Real-time data to support the shelf-life claim has been provided from recommended storage in containers representative of commercial scale storage which is endorsed. Specifically, stability data is available in the dossier from -70 °C for 36 months for engineering batches and PPQ batches. All batches have been assessed to be representative of the commercial manufacturing process (see section S.2.6).

Long-term microbiological (BET and bioburden) results have been submitted for two batches according to the stability protocol.

Supporting stability data obtained from accelerated (5 °C) and stressed (25 °C) storage conditions were also presented, indicating shelf-lives of 12 months and 6 months at 5 °C and 25 °C, respectively.

All available stability results met the acceptance criteria for the tested CQAs (including potency and purity) through the proposed shelf life without any observed trends. Only slight trends well within the specification limits were observed for HMW and acidic variants following storage at 12 months at 5 °C.

A brief freeze-thaw study carried out with a full-scale container proved that RGB-19 active substance can withstand the storage conditions of the RGB finished product at 5 ± 3°C after thawing (≤-70°C).

A photostability study revealed impact of light exposure on the content of monomers, HMW, LMW, charge variants (main, acidic, basic) and oxidation variants. Importantly, no impact on the parameters tested were observed for the non-exposed and dark control samples. These results are supportive of the recommendation to protect RGB-19 active substance from light during storage.

To conclude, the stability data provided support a shelf life for RGB-19 active substance of 36 months at the recommended storage condition (≤-70 °C), in its container closure system with protection from light.

Ongoing stability studies and post-approval stability studies will be performed according to the protocols described in the dossier. The applicant commits to continue these studies through the proposed shelf-life. This is found acceptable.

3.3. Finished product

This part describes two formulations resulting in different pharmaceutical forms, routes of administration and strengths:

- Finished product for intravenous administration (FP-IV) in vial, 20 mg/mL, concentrate for solution for infusion;

- Finished product for subcutaneous administration (FP-SC), 162 mg, solution for injection in pre-filled syringe and pre-filled pen.

3.3.1. Finished medicinal product IV

3.3.1.1. Description of the product and pharmaceutical development

Description of the product

RGB-19 20 mg/mL concentrate for solution for infusion is a clear to opalescent colourless to pale-yellow liquid, free from visible particles, presented in three fill volumes: 80 mg in 4 mL, 200 mg in 10 mL and 400 mg in 20 mL vials.

RGB-19 20 mg/mL is presented in a 6R (for 80 mg/4 mL), or a 20R (for 200 mg/10 mL and 400 mg/20 mL) clear, Type I glass vial, sealed with bromobutyl rubber stopper covered with a fluorinated coating, and a green (for 80 mg/4 mL), yellow (for 200 mg/10 mL) or red (for 400 mg/20 mL) plastic flip cap with aluminium sealing.

RGB19 20 mg/mL finished product is formulated with sucrose, PS80, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, phosphoric acid concentrated (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

There are no formula overages applied to the formulation of finished product-IV.

The overfills in the three presentations have been sufficiently justified.

The three presentations share the same composition and differ only in the size of the vial and the fill volume applied.

The vial, stopper and seal components are compliant with appropriate Ph. Eur. monographs for primary containers and closures and are further addressed in section P.7.

The section on description and composition of the finished product is found acceptable.

Pharmaceutical development

Formulation development

The formulation of the biosimilar candidate finished product-vial is practically identical to the EU-authorised RMP RoActemra. As mentioned by the applicant, there is a slight difference between the

two formulations regarding the hydrate form of the dibasic sodium phosphate. However, the phosphate buffer is present at the same concentration in both RGB-19 finished product IV and the RMP and therefore the difference is considered negligible.

The formulation development section in 3.2.P.2.2 describes and justifies the chosen formulation and is sufficiently described.

Manufacturing process development

The manufacturing process of finished product RGB-19 IV 20 mg/mL concentrate for solution for infusion involves the dilution of the active substance solution with prefiltered PS 80 buffer solution and prefiltered formulation buffer, bioburden reduction filtration and sterile filtration with 0.2-micron sterilising-grade filter and subsequent filling into 6R or 20R glass vials. These are sealed with a rubber stopper and flip caps. The manufacturing process development activities consisted of the identification of CQAs and characterisation of CPPs as well as the corresponding PARs. Risk assessments and the history of analytical methods and specification are presented. These activities provide the basis for the development of the process control strategy. An overview of all finished product batches and their use are provided.

Upon request, the applicant performed an evaluation of the criticality of unit operations and process parameters based on risk analysis using the Failure Mode and Effect Analysis (FMEA). The risk analysis was based on the potential impact on finished product-related quality attributes. The summary of non-CPPs and unit operations were presented in tabular format. This is endorsed.

It is noted that manufacturing batches were tested and a number of relevant CQAs (12) have been identified for the finished product-IV process.

Microbiological attributes

The information given on microbiological attributes is found sufficient.

Extractables /Leachables and Compatibility

Acceptable data is presented by the applicant on extractables and leachables as well as elemental impurities for the product containing glass container and rubber stopper.

The leachables study is currently ongoing and will not be finished within the regular procedural timeline. None of the target leachables were detected in the finished product above the respective AET for these compounds. Semi quantitative non-target evaluation on samples stored for 18 months at 2-8°C revealed the presence of tentatively assigned fatty acid related compounds as well as isomers of these fatty acid related compounds.

The applicant is recommended to continue the leachable study and to provide the data of the study (Recommendation). The study on elemental impurities is in line with ICHQ3D(R2).

Upon request, the detection limits of the analytical methods, gas chromatography mass spectrometry (GC-MS), LC-UV-MS and inductively-coupled plasma mass spectrometry (ICP-MS) have been provided and the used analytical methods have been accordingly qualified.

The compatibility of RGB-19 finished product-IV with the components of the container closure system is assessed in the stability evaluation on vials stored in the inverted position, where the finished product comes into contact with both the glass vial and the rubber stopper. The applicant submitted stability studies results that demonstrate that there is no adsorption of RGB-19 finished product to the inner surface of the container closure system and the container closure system is non-reactive relative to the strength, potency, and purity of the finished product. Therefore, the Type I clear borosilicate tubing glass vial and the fluoropolymer-laminated bromobutyl rubber stopper were found to be capable

of maintaining the finished product quality during storage.

In-use stability has been studied to simulate in-use conditions and verify the chemical and physical stability of the finished product-IV as well as to confirm the compatibility upon in-use administration with the ancillaries (i.e. infusion container, infusion tube, in-line filter or injection needle). The studies have been performed using finished product-IV batches. Two dilutions were studied, , concerning the lowest and highest concentration level in the infusion.

The information provided in sections P.2.2.4-P.2.2.6 is found acceptable.

3.3.1.2. Manufacture of the product and process controls

Manufacture

EU batch release is performed at Gedeon Richter Plc. (Chemical Works of Gedeon Richter Plc.), Gyömrői Út 19-21, Budapest, 1103 Hungary. All sites involved in manufacturing and control of the finished product operate in accordance with EU GMP.

Minimal and maximum batch sizes for finished product-IV are provided. Quality standards and quantities are given.

Description of manufacturing process and process controls

The manufacturing process for the RGB-19 finished product-IV consists of preparation of buffer solutions, thawing of active substance, pooling and dilution of active substance followed by bioburden reduction filtration and sterile filtration, filling, stoppering and capping.

The applicant has defined the maximum number of active substance batches included in a single finished product-IV batch (two RGB-19 active substance batches may be used to produce one RGB-19 finished product batch). This is endorsed.

The finished product-IV is manufactured by aseptic technique and the solution is passed through a 0.2 µm filter for bioburden reduction and a second 0.2 µm pore-sized filter as the sterile filtration. Filter integrity testing is performed both pre- and post-use for the second filter during the sterile filtration.

Bioburden testing is performed prior to the sterile filtration according to Ph. Eur. 2.6.12 with an acceptance criterion of 10 CFU/100 mL.

The filling speed is defined.

Reprocessing

No reprocessing has been described in the dossier and is consequently not allowed for the steps up to an including filling, stoppering and capping.

Control of critical steps and intermediates

The information provided on control of critical steps and intermediates is considered sufficient and acceptable.

It is noted that stability data for 1 batch freeze-thaw study was submitted by the applicant for a three-month period vid 5 ± 3°C after thawing (⩽ −70°C) in the commercial storage container. This is found sufficient and acceptable.

Process validation

Consecutive 80 mg/4 mL PPQ batches were manufactured. In case of 200 mg/10 mL and 400 mg/20 mL presentations the validation combined the two presentations consisting of consecutive PPQ batches.

. Each PPQ batch was manufactured from a single active substance batch except for one batch where two active substance batches were mixed. This is found acceptable.

All finished product-IV validation batches complied with the established validation acceptance criteria for all process parameters and in-process controls as well as with the proposed finished product-IV specifications. The validation was run at set points while the ranges of process parameters were challenged during the manufacturing process development as described in section P.2.3.

Validation of the aseptic process

According to the applicant media fill tests and results supporting the process validation were performed and are available for review upon agency request. It is agreed that media fill studies fall under GMP. As requested by the Agency, the applicant has provided a detailed description of the media fill studies supporting the process validation. The results of the media fills tests show that the acceptance criteria were met. Section 3.2.P.3.5 has been appropriately updated. This is endorsed.

Filter validation

Filter validation comprises of compatibility study of the filter with RGB-19 finished product-IV, filter wetting studies for pre- and post-use integrity testing as well as viability and bacterial retention study. Information is also included in the report regarding the filter material, pore size and surface area. The provided results demonstrate that the 0.2 µm filters used are fit for purpose and justify the use of these filters in commercial manufacturing of the finished product-IV.

Hold times validation

Process steps durations and hold times in the finished product-IV manufacturing process have been mentioned in section P.3.3. According to the applicant hold time studies were performed on the finished product-IV manufacturing process. PPQ batches were tested: 80mg/4 ml and 200 mg/4 ml and 400 mg/4 ml respectively. Supportive data regarding validation of hold times for all steps in the manufacturing process have been submitted. This is accepted.

Upon Agency request, the applicant has clarified the concept regarding hold times for the RGB-19 finished product-IV manufacturing process by adding relevant information in section 3.2.P.3.5. The hold times are presented separately in tabular format as in-process holds and process times and time out of fridge (TOR), respectively. This is acceptable.

Transport validation

Adequate information was provided.

In conclusion, the process validation data presented in section P.3.5 demonstrate at large that the process is robust and performs as intended, giving a finished product which meets the quality requirements when run within the defined operating ranges.

3.3.1.3. Product specification

Specifications

The specifications for RGB-19 20 mg/mL finished product include control of identity, purity and impurity, potency and other general tests. The specifications include a large and comprehensive set of relevant tests for the finished product-IV covering limits for both release and end-of-shelf-life (EOSL) of the various attributes. Separate limits are proposed at release and EOSL for all purity/impurities and product related substances, i.e. nrCE-SDS, SE-HPLC, IEX-HPLC and RP-UPLC.

The proposed acceptance criteria and are found acceptable and clinically qualified for protein content, potency and purity tests for aggregates HMW.

The charge heterogeneity profile of finished product-IV is monitored by IEX-HPLC.. The proposed acceptance criteria are found acceptable compared to the levels found in clinical batches of finished product-IV and/or EU-RMP (Ro-Actemra) and non-EU reference product (Actemra).

In addition, the proposed acceptance criteria for the general tests (appearance, clarity and degree of opalescence, degree of coloration, pH, osmolality, particulate matter: subvisible particles and extractable volume), identification tests (identification by peptide mapping and identification by IEX-HPLC) and microbiological tests (sterility and BET) are found acceptable as well.

It is noted that the evaluation of appearance is based on the results of colour and opalescence tests. This is found acceptable.

The acceptance criteria for the LMW content of RGB-19 finished product-IV have been tightened both at release and end-of-shelf-life. This is found sufficient and acceptable.

Upon request, the limit for RGB-19 finished product-IV protein content is tightened. Tightening is acceptable.

Upon request, the limit for RGB-19 finished product-IV PS80 content will be tightened at release and at shelf-life. Tightening is acceptable.

Analytical procedures

Many tests used for release and stability testing of RGB-19 finished product IV and finished product SC are also used for release and stability testing of active substance. These methods and validation results are presented, discussed and assessed in sections S.4.2 and S.4.3 and cover both active substance, finished product IV and finished product SC. The analytical methods have been validated in accordance with ICH Q2 and the compendial methods have in general been verified according to the appropriate compendia chapters and been determined to be suitable for use.

The method description and validation summary of the method "Antiproliferation assay" (cell-based potency assay in TF-1 cell), that is the potency assay used for release and stability testing of both the finished product IV and finished product SC in sections 3.2.P.5.1, are provided in section 3.2.S.4.4 with links directly from sections 3.2.P.5.2 and 3.2.P.5.3. The method description and the validation summary of the "Antiproliferation assay" are both found adequate and acceptable. Furthermore, it can also be noted that the sIL-6R binding assay by ELISA is included in the active substance specification in section 3.2.S.4.1.

Batch analysis

Batch analysis data has been provided for finished product-IV batches used for development, clinical studies, stability, process validation (PPQ-batches) as well as used in the biosimilarity exercise. Information for the batches include batch number, manufacturing date, batch size, active substance batch number as well as the use of each finished product-batch. The batch analysis data complies with the limits in the proposed finished product-vial release specification in place at the time of testing and confirm process and product batch-to-batch consistency. In conclusion, the batch data provided demonstrate a reproducible manufacturing of finished product-vial.

Reference standard

The same product-specific methods and reference materials, that are being used for testing of the RGB-19 active substance, are also being used for testing of RGB-19 20 mg/mL finished product.

Impurities

Potential process and product-related impurities are sufficiently addressed in section S.3.2. It has been shown that no new impurities/product-related substances are generated during manufacture of the finished product-IV. Leachables and extractables are discussed in section P.2.4.

Furthermore, a risk assessment of N-nitrosamine contamination in the finished product-IV has been performed and a report has been provided in section P.5.5. It is agreed that the risk of formation and entry of N-nitrosamine impurities is negligible in the finished product-IV.

A risk assessment of elemental impurities in the finished product-IV has been performed and results are provided in section P.5.5. It is agreed that the residual quantity of elemental impurities is very low, and all meet the requirements specified in ICH Q3D. This is found acceptable.

Container closure

The development of the container closure system is sufficiently presented. The vial, stopper and seal components are compliant with appropriate Ph. Eur. monographs for primary containers and closures.

The finished product-IV is available in three presentations: 80 mg/4 mL in 6R vials, 200 mg/10 mL in 20R vials and 400 mg/20 mL in 20R vial. The three presentations share the same composition and differ only in the size of the vial and the fill volume applied.

The development of the container closure system has been sufficiently described in section P.2.4. It is presented at a concentration of 20 mg/mL in single dose type I glass vial closed with a fluoropolymer-laminated bromobutyl rubber stopper and sealed with an aluminium seal with flip cap and secondary packaged in a paper folded carton.

The applicant has submitted specifications, certificate of analysis, conformity statements and technical drawings for the vials as well as information on the supplier of the primary packaging material. The vials and stoppers are in compliance with the Ph. Eur. monographs for primary containers (Ph. Eur. 3.2.1) and closures (Ph. Eur. 3.2.9, Ph Eur 2.6.1). The primary packaging material has been described in detail and the information is found acceptable.

As states by the applicant the containers proposed for storage are those which have been used in the stability studies in section P.8.

Sterilisation

The vials are washed, sterilised and depyrogenated at the finished product-IV manufacturing site. The sterilisation and depyrogenation is performed by dry heat sterilisation by depyrogenation tunnel qualified according to the requirements of Ph. Eur. 5.1.1. The rubber stoppers are received ready to sterilise and are sterilised by steam at the finished product-IV manufacturing site. the steam sterilisation is performed by autoclave qualified according to the requirements of Ph. Eur. 5.1.1.

3.3.1.4. Stability of the product

The applicant, based on the evaluation of the stability data obtained and their trends, initially proposed a shelf-life of 24 months for RGB-19 20 mg/mL (80 mg/4mL, 200 mg/10 mL and 400 mg/20 mL) concentrate for solution for infusion.

The applicant presented a stability program according to ICH Q5C and Q1A, and 3 finished product stability batches for each concentration (finished product batches manufactured from various active substance batches). Batches included the PPQ batches, engineering and small-scale batches.

A stability data evaluation (long-term and accelerated) including graphical trends for the batches across quality attributes, reveals similar trends for all batches, strengths and container closure system (6R and 20R vials). The applicant notes, for long-term stability, trends within specifications for HMW, acidic variants and main peak charge variants. Regarding accelerated and stress stability additional trends are noted and that not all acceptance criteria were met. The applicant concludes that the degradation profiles of the stability batches are similar. This conclusion is supported.

The stability section is in general adequately described. Upon request, the applicant updated the dossier with available stability data and additional data has been submitted.

Shelf-life claim of 80 mg/4 mL RGB-19 finished product-IV vial

The shelf-life claim of RGB-19 finished product-IV 80 mg/4 mL is based on real time real condition stability data of 24 months obtained with commercial scale batches under long-term storage in an upright or inverted position, respectively. An increase of acidic variants and concomitant decrease in the main charge variant is observed under long-term storage condition with moderate trends within 24 months and stability data being well within the acceptance criteria for charge variants. Therefore**, a shelf-life of 24 months for the RGB-19 finished product-IV 80 mg/4 mL vial** presentation is justified and supported by real-time real storage condition data obtained with large scale batches representative of the intended commercial product.

Shelf-life claim of 200 mg/10 mL and 400 mg/20 mL RGB-19 finished product-IV vial

The shelf-life claim of RGB-19 finished product-IV 200 mg/10 mL and RGB-19 finished product-IV 400 mg/20 mL is based on a matrixing approach with RGB-19 finished product-IV 200 mg/10 mL representing the worst-case 20R vial scenario for the RGB-19 finished product-IV 400 mg/20 mL vial presentation. Real time real condition stability data of 30 months were obtained with commercial scale batches under long-term storage in an upright or inverted position, respectively. An increase of acidic variants and concomitant decrease in the main charge variant is observed under long-term storage condition with moderate trends within 30 months and stability data being well within the acceptance criteria for charge variants. Therefore, a **shelf-life of 30 months for the RGB-19 finished product-IV 200 mg/10 mL and RGB-19 finished product-IV 400 mg/20 mL vial** presentation is justified and supported by real-time real storage condition data obtained in a matrixing stability study design with large scale batches representative of the intended commercial products.

The applicant commits to complete ongoing stability studies, inform competent authorities of OOS and place a minimum of one commercial batch of RGB-19 finished product IV per year (if manufactured) on stability and test according to the presented stability protocol.

Photostability

The photostability study was executed on one batch (200 mg/10 mL) and matched overall illumination conditions described in ICH Q1B. Changes were observed and not all tested parameters met the set long-term stability criteria, the specifications. The product is light sensitive.

The applicant confirmed that the secondary packaging / cardboard box used in the photostability study is representative of the commercial secondary packaging of the vial and PFS presentations. This is acceptable.

In-use stability

The applicant provided in-use stability data, which do not indicate any issue. After dilution, the prepared solution for infusion is physically and chemically stable in sodium chloride 9 mg/mL (0.9%) solution for injection. It can be stored for 50 hours at 30ºC and for up to 4 weeks in a refrigerator at 2°C-8°C.

From a microbiological point of view, the prepared solution for infusion must be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

For infusion administration, preferably DEHP-free PVC, polypropylene (PP) or polyethylene (PE) infusion bags shall be used.

3.3.2. Finished medicinal product SC

3.3.2.1. Description of the product and pharmaceutical development

Description of the product

The finished product for the PFS and PFP presentations is formulated with L-Histidine, L-Histidine monohydrochloride monohydrate, L-Valine, L-Methionine, PS80, phosphoric acid concentrated (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

The finished product for subcutaneous administration (FP-SC) is presented as a sterile, ready to use, single dose solution for injection at a nominal concentration of 180 mg/mL in a 1 mL Type I glass syringe combined with a 27G ½ inch (12.7 mm) staked stainless steel needle protected by a rigid needle shield, stoppered with a fluorinated bromobutyl plunger stopper. The product is further assembled with a single-use needle safety device (NSD) and with built-in finger flange and polycarbonate resin plunger rod for administration of the finished product solution.

Each PFS contains 0.965 mL formulated product. The overfill in the PFS has been sufficiently justified.

The pre-fillable syringe and plunger stopper are compliant with appropriate Ph. Eur. monographs for primary containers and closures and are further addressed in section P.7.

The PFS is further permanently assembled with either a single use needle safety device or an auto-injector device. Further details on these devices are provided in the Notified Body Opinions provided by the applicant which confirm full compliance with the relevant general safety and Performance

Pharmaceutical development

The formulation development section in 3.2.P.2.2 describes and justifies the chosen formulation and is found comprehensive and well described.

Formulation development

The formulation of the biosimilar candidate finished product-SC is similar but not identical to the EU-authorised RMP RoActemra. Differences are in levels of histidine buffer and methionine, as well as the use of valine instead of arginine in the RGB-19 SC formulation.

The formulation development for RGB-19 finished product-SC consisted of selection of the composition and primary packaging components, evaluation of the compatibility of the active substance with the excipients, as well as compatibility with the primary packaging components. Selection of the composition and primary packaging components of RGB-19 SC finished product were initially carried out with small plant scale adaptation batches, before being scaled up for optimisation batches. The planned batch size for commercial production is found acceptable.

Upon request, section 3.2.P.2.2 has been updated with the detailed results of the formulation development and robustness studies as requested. The results demonstrated that that the quality attributes of the selected formulation are maintained during storage.

Overages and Physicochemical and biological properties

There are no formula overages applied to the formulation of finished product-SC. The information given on physicochemical and biological properties is found sufficient.

The information provided in sections P.2.2.1-P.2.2.3 is found acceptable.

Manufacturing process development

The section on manufacturing process development for the finished product-SC has been sufficiently described and justifies the commercial manufacturing process.

The manufacturing process of finished product includes preparation and filtration of buffer solutions, thawing of active substance, pooling and dilution of active substance followed by compounding of final finished product in concentrated excipient solution and sterile filtration, aseptic filling in the syringes and insertion of the plunger stoppers. The filled syringes are then assembled with a needle safety device or auto-injector device.

The manufacturing process development activities consisted of the definition of a QTPP, identification of CQAs, establishing the linkage between CQAs and potential CPPs and characterisation of CPPs as well as the corresponding PARs. These activities provide the basis for the development of the process control strategy.

It can be noted that a number of relevant CQAs have been identified for the finished product-SC. As stated by the applicant the product CQAs have been derived from the QTPP, reference is made to Annex 1 section 3.2.S.2.6.

Upon request, the applicant performed an evaluation of the criticality of unit operations and process parameters based on risk analysis using FMEA. The risk analysis was based on the potential impact on finished product-related quality attributes. The summary of non-critical process parameters and unit operations were presented in tabular format. This is sufficient.

The commercial manufacturing process has been characterised through process characterisation studies of each process step and details for these studies are provided in the dossier. The criticality of the process parameters was investigated using a combination of small-scale/laboratory scale and commercial scale.

Furthermore, it can also be noted that the manufacturing process for both finished product-SC and finished product-IV is similar except for the dilution to the required tocilizumab concentration and filling. Due to these similarities a number of process characterisation studies are applicable to both finished product-SC and finished product-IV.

The process characterisation studies demonstrate that the finished product-SC manufacturing process is robust and can deliver the required product quality and process consistency when the manufacturing process is conducted within the prescribed operating ranges.

Control strategy

The development of the control strategy for the finished product has been sufficiently described in section P.2.3. The CPPs and IPCs for the commercial manufacturing process are provided in section P.3.4 and the specifications in section P.5.1.

The information provided on manufacturing process development for the finished product-SC is found sufficient and acceptable.

Microbiological attributes

The information given on microbiological attributes is found sufficient.

Compatibility

Compatibility of finished product-SC with the container closure system has been demonstrated by development studies presented in sections P.2.6 and stability data in P.8.1. The finished product-SC is not in direct contact with the NSD and AI devices.

No reconstitution diluents are being used to administer finished product-SC.

The information provided with respect to container closure system, microbiological attributes and compatibility is found sufficient and acceptable.

3.3.2.2. Manufacture of the product and process controls

Manufacture

EU batch release is performed at Gedeon Richter Plc. (Chemical Works of Gedeon Richter Plc.), Gyömrői Út 19-21, Budapest, 1103 Hungary. All sites involved in manufacturing and control of the finished product operate in accordance with EU GMP.

Description of manufacturing process and process control

The manufacturing process for the RGB-19 finished product-SC consists of preparation of buffer solutions, thawing of active substance, pooling, diafiltration and concentration of active substance, dilution of active substance followed by preparation of bulk finished product solution and bioburden reduction filtration, sterile filtration, aseptic filling in the syringes and insertion of the plunger stoppers. The filled syringes are then assembled with a needle safety device (PFS) or auto-injector device (PFP).

The finished product-SC is manufactured by aseptic technique and the solution is passed through two sequential 0.2 µm filters at the two sterile filtration steps. Filter integrity testing is performed both pre- and post-use for both the two filters used during the sterile filtration.

Bioburden testing is performed in accordance with Ph Eur 2.6.12 (acceptance criterion of 10 CFU/100 mL) as well as testing for bacterial endotoxins in accordance with Ph Eur 2.6.14 (acceptance criterion of NMT 10 EU/mL) prior to the first sterile filtration step.

The applicant has defined the maximum number of active substance batches included in a single finished product-SC batch. This is accepted.

Control of critical steps and intermediates

An overall manufacturing process time of for the PFS presentation was calculated based on the provided data. Upon request, the overall manufacturing process time has been clarified. The total time of RGB-19 (hold time and process time) out of refrigeration (TOR) has been provided .

Acceptable ranges are provided for process parameters and IPCs and brief process flow diagrams are provided for the manufacturing process of the finished product-SC.

The IPCs and for the PFS assembly into the NSD and in the auto-injector device have also been defined and they also include acceptable acceptance criteria.

For the microbial control of the process alert and action limits are established. This found acceptable.

The description of manufacturing process and process controls and control of critical steps and intermediates of the finished product-SC is considered sufficiently described.

In general, the information provided in sections P.3.3 and P.3.4 in the dossier is found sufficiently detailed. In addition, the IPCs performed during PFS assembly into the autoinjector include cap

removal force, activation force, needle extension, injection time, override force and container closure integrity testing. The parameters for device functionality for the autoinjector are included in the specifications document in P.5.1 for the finished product-SC. This is found acceptable.

Reprocessing

No reprocessing has been described in the dossier and is consequently not allowed for the manufacturing of finished product-SC.

Hold times

Process steps durations and hold times in the finished product-SC manufacturing process have been mentioned in section P.3.3. According to the applicant hold time studies were performed on the finished product-SC manufacturing process. Two PPQ batches were tested.

Upon request, the results of the hold times and process times/TOR times applicable to the RGB-19 SC PFS manufacturing process have been added in tabulated format to dossier section 3.2.P.3.5 RGB-19 SC PFS. In addition, the dossier has been updated with hold times regarding the PFS assembly into the NSD and in the auto-injector device. This is accepted.

Process validation

Commercial scale PPQ-batches of the finished product-SC were manufactured and they all complied with the established validation acceptance criteria for all process parameters and in-process controls as well as with the proposed finished product-SC specifications. These batches have been manufactured at the extremes of the batch size range (). Batch data are provided in section P.5.4 for all finished product-SC validation batches. Furthermore, stability studies are currently ongoing on all these validation batches on long-term (2-8 °C) and accelerated/stressed storage conditions.

Process validation for assembly of NSD device and auto-injector device

Validation results have been provided in section P.3.5 from validation studies of the assembly of the NSD and auto-injector device that successfully demonstrates that the assembly process does not compromise the finished product integrity and is capable to deliver combination products fulfilling all the quality, safety and functional requirements.

Transport validation

As mentioned by the applicant, transport validation studies are planned for commercial production for to demonstrate that the RGB-19 SC product quality could be maintained when transported under refrigerated conditions (5 ± 3 °C) on the longest air- or/and land-based route.

Upon request, the applicant amended Section 3.2.P.3.5 with parameters and release data regarding the transport validation studies for shipping of RGB-19 SC product between relevant manufacturing, test and storage sites of the manufacturer. This is accepted.

Filter validation

The filter validation report submitted by the applicant includes studies that confirm the compatibility of the filter with RGB-19 PFS as well as pre-and post-use integrity testing. The data is found acceptable. Information is also included in the report describing the filter material, pore size and surface area. The provided results demonstrate that the 0.2 µm-filters used are fit for the purpose and justify the use of these filters in commercial manufacturing of the finished product-SC batches in line with the requirements in the guideline EMA/CHMP/CVMP/QWP/850374/2015.

Validation of the aseptic filling process

Media fills were used to validate the aseptic filling process. According to the applicant media fill tests and results supporting the process validation were performed.

Upon request**,** the applicant provided a detailed description of the media fill studies supporting the process validation. The results of the media fills tests show the acceptance criteria were met. This is endorsed.

In conclusion, the process validation data demonstrate at large that the process is robust and performs as intended, giving a finished product-SC which meets the quality requirements when run within the defined operating ranges.

The data presented in section 3.2.P.3 is considered acceptable.

3.3.2.3. Product specification

Specifications

The specifications for RGB-19 162 mg finished product-SC include control of identity, purity and impurities, potency and other general tests. They include a large and comprehensive set of relevant tests for the finished product-SC covering limits for both release and end-of-shelf-life (EOSL) of the various attributes. Separate limits are proposed at release and EOSL for all purity/impurities and product related substances, i.e. nrCE-SDS, SE-HPLC, IEX-HPLC and RP-UPLC.

The proposed acceptance criteria and are found acceptable and clinically qualified for protein content, potency and purity tests for aggregates HMW.

The charge heterogeneity profile of finished product-SC is monitored by IEX-HPLC. The proposed acceptance criteria at release and at EOSL are found acceptable compared to the levels found in clinical batches of finished product-SC and/or EU-RMP (Ro-Actemra) and non EU reference product (Actemra).

In addition, the proposed acceptance criteria for the general tests (appearance, clarity and degree of opalescence, degree of coloration, pH, osmolality, particulate matter: subvisible particles and extractable volume), identification tests (identification by peptide mapping and identification by IEX-HPLC) and microbiological tests (sterility and bacterial endotoxins) are found acceptable as well.

The LMW content is controlled by NR-CE-SDS-UV. Upon request, the acceptance criteria for the LMW content of RGB-19 finished product-SC was tightened both at release and end-of-shelf-life. This is found sufficient and acceptable.

PS80 is a critical excipient by preventing the surface related aggregation events. The applicant provided acceptable data to support the proposed specification.

Analytical procedures

Many tests used for release and stability testing of RGB-19 finished product IV and finished product SC are also used for release and stability testing of active substance. These methods and validation results are presented, discussed and assessed in sections S.4.2 and S.4.3 and cover both active substance, finished product IV and finished product SC. The analytical methods have been validated in accordance with ICH Q2 and the compendial methods have in general been verified according to the appropriate compendia chapters and been determined to be suitable for use.

Upon request, unequivocal identifiers for in-house analytical methods have been included in the specification table and the method descriptions and the method validation summaries have been updated to include these in-house method identifiers for the non-compendial methods. This is acceptable.

Batch analyses

Batch analysis data) has been provided for finished product-SC batches used for development, clinical studies, stability, process validation (PPQ-batches) as well as used in the biosimilarity exercise. Information for the batches include batch number, manufacturing date, batch size, active substance batch number as well as the use of each finished product-batch. The batch analysis data complies with the limits in the proposed finished product-SC release specification in place at the time of testing and confirm process and product batch-to-batch consistency. In conclusion, the batch data provided demonstrate a reproducible manufacturing of RGB-19 finished product-SC.

Reference standard

The same product-specific methods and reference materials, that are being used for testing of the RGB-19 active substance, are also being used for testing of RGB-19 20 mg/mL finished product.

Impurities

Potential process- and product-related impurities are sufficiently addressed in section S.3.2. It has been shown that no new impurities/product-related substances are generated during manufacture of the finished product-IV. Leachables and extractables are discussed in section P.2.4.

Furthermore, a risk assessment of N-nitrosamine contamination in the finished product-IV has been performed and a report has been provided in section P.5.5. It is agreed that the risk of formation and entry of N-nitrosamine impurities is negligible in the finished product-IV.

A risk assessment of elemental impurities in the finished product-IV has been performed and results are provided in section P.5.5. It is agreed that the residual quantity of elemental impurities is very low, and all meet the requirements specified in ICH Q3D. This is found acceptable.

Container closure

The finished product for subcutaneous administration is presented as a sterile, ready to use, single dose solution for injection in a 1mL glass syringe (Type I glass) with staked-in needle and rigid needle shield (elastomer + polypropylene rigid shell) and sealed with a FluroTec plunger stopper. The development of the container closure system has been sufficiently described in section P.2.4. Each prefilled syringe contains 0.9 mL formulated product.

The applicant has provided dimensional drawings and specifications for the glass syringe barrel with staked needle and rigid needle shield and the rubber plunger stopper as well as information on the supplier of primary packaging material. Compliance with the requirements in the Ph. Eur. monographs 3.2.1 (Glass containers for Pharmaceutical use) and 3.2.9 (Rubber closures) has been demonstrated. This is acceptable.

The sterilisation of the glass syringe barrel and the rubber plunger stopper are performed at standard conditions by ethylene oxide using a validated method in accordance to ISO 11135 for the glass syringe barrel and gamma irradiation using a validated method in accordance to ISO 11135 for the rubber plunger stoppers. The specifications for both the glass syringe barrel and the rubber plunger stopper include testing for sterility (Ph. Eur. 2.6.19 and 2.6.1) and bacterial endotoxins (Ph. Eur. 2.6.14).The tests for residual ethylene oxide and ethylene chlorohydrin with acceptance criteria according to the guideline EMA/CHMP/CVMP/QWP/850374/2015 are included in the specification for the glass syringe barrel (Appendix in section P.7). The information is found acceptable.

The PFS is further permanently assembled with either a needle safety device or an auto-injector device. The PFS and the auto-injector forms two combination products and integral medicinal devices. Further details on these two combination products and integral devices as well as their corresponding

Notified Body Opinions (NBOp), confirming full compliance with the relevant GSPRs, have been provided.

The suitability of the container closure system was confirmed by the results of the extractables and leachables testing in section P.2.

A comparative analysis report for RGB-19 162 mg/0.9 ml solution for injection in PFS, PFS-NSD and prefilled pen is submitted by the applicant in section P.5.6. The test results for critical and stability indicating attributes confirm that the quality of the RGB-19 PFS, PFS-NSD and PFS-AI are comparable and that the assembly of the PFS with NSD and auto-injector has no impact on the quality of RGB-19 finished product-SC.

3.3.2.4. Stability of the product

The applicant presents a stability program according to ICH Q5C and Q1A, and stability batches across RGB-19 finished product batches; PFS, PFS-NSD and PFP (unassembled commercial scale PFS batches, NSD assembled PFSs in secondary packaging, and PFP assembled in secondary packaging). Of the total number of batches in the program some have no data reported.

The applicant initially presented up to 24 months long-term, real-time data for PFS, 18 months for PFS with NSD and 12 months for PFP. In the long-term stability studies, no trends were noted for PFS, PFS with NSD or PFP. For accelerated conditions significant trends are noted (charge variant profile, HMWs, LMWs, oxidation) and functional failures for PFP. The stress studies as expected show further changes.

The applicant compared stability of the different presentations and concludes: "There is no significant difference in the quality attributes between pre-filled syringe (PFS), pre-filled syringe assembled with needle-safety device (PFS-NSD) and pre-filled pen (PFS assembled into autoinjector)" based on quality attributes not including device functional testing. The conclusion is acceptable.

The applicant proposed 30 months of shelf life at a storage condition of 2-8°C with the submission of 30 months data for one PFS-NSD batch. Data includes the specified functional parameters, and all are within specifications, supporting the applicant's claim of 30 months shelf-life for PFS-NSD. 18 months data for the PFP presentation is available. The injection time has an increasing trend and is just within specification at 18 months. Currently there is no real-time data for the PFP presentation supporting the applicant's claim of 30 months shelf-life.

Upon request, the applicant has provided real-time data to support the 30 months shelf-life claim for RGB-19 SC PFS-NSD and the 24 months (2 years) shelf-life claim for PFP.

Considering the totality of the data, the acceptable shelf-life is:

- 30 months (2°C-8°C) for the PFS-NSD;

- 24 months (2°C-8°C) for the PFP.

In-use

On the basis of the in-use stability data provided, Once removed from the refrigerator, the PFS and PFP can be stored up to 2 weeks at or below 30 °C.

Photostability

A photo stability study according to ICH Q1B on RGB-19 PFS is presented. Specifications were met for non-package and packaged PFS. However, the applicant still proposed a protect from light warning. This is acceptable.

Overall, the stability section P.8 finished product-SC is considered adequately described.

3.4. Biosimilarity

4.1. General approach

RGB-19 has been developed as a proposed biosimilar candidate to the RMP EU-approved RoActemra containing tocilizumab as active ingredient.

RGB-19 has been developed to have the same posology, route of administration and indications as for RoActemra and is available as the following presentations:

-IV presentation (vial): 20 mg/mL, concentrate for solution for infusion, vial presentation;

-SC presentation (PFS, PFP/auto-injector): 162 mg (180 mg/mL), solution for injection, PFS and PFP presentation.

Both the IV (vial) and SC (PFS, PFP/auto-injector) presentations of RGB-19 are derived from the same active substance and differ only in their formulation, final concentration and container closure system. Furthermore, it can be noted that RGB-19 IV finished product and RoActemra IV finished product have practically identical formulations while RGB-19 SC finished product and RoActemra SC finished product is similar but not identical with respect to the composition of the formulation. The similarity and differences in formulations are sufficiently described.

Two separate analytical comparability exercises have been performed between RGB-19 IV and the EU-approved RoActemra IV finished product and between RGB-19 SC and the EU-approved RoActemra SC finished product due to the differences in concentration, formulation, presentation and route of administration. In addition, two separate forced degradation studies (FDS) were conducted for these two type of presentations, finished product IV and finished product SC of both RGB-19 and RoActemra. Furthermore, it can also be noted that comparability has been successfully demonstrated for the various presentations of the RGB-19 SC finished product between the PFS, the PFS-NSD and the PFP. This is found acceptable.

Lots included in the biosimilarity assessment

The assessments of biosimilarity include a sufficient number of EU-approved RoActemra IV and SC batches. Furthermore, a sufficient number of RoActemra IV and RoActemra SC batches were tested in head-to-head manner with commercial scale RGB-19 IV and SC finished product batches in a separate comparability study campaign.

All batches of RGB-19 finished product SC and IV included in the biosimilarity exercise, Phase I and Phase III clinical trials, process validation, stability studies and comparability studies were manufactured according to the same proposed commercial scale process of both active substance and finished product. Batches of RGB-19 IV finished product and batches of RGB-19 SC finished product were produced from independent RGB-19 active substance batches and were included and analysed in the biosimilarity exercise. Additional RGB-19 IV finished product batches of the 400 mg/20 mL-presentation have also been manufactured with active substance batches, and these IV finished product batches have been used as a part of the similarity assessment at release level as well as for stability testing.

The RGB-19 and RoActemra finished product IV are manufactured in the following three presentations: 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL. It can be noted that there is a limited number of RGB-19 finished product IV batches, six batches in total for all three presentations, that were tested in the biosimilarity study. However, it is argued that since the three presentations of RGB-19 finished product IV products have the same concentration and formulation and only differ in fill volume and since the formulation is identical of RGB-19 IV finished product and RoActemra IV finished product, six

batches for RGB-19 IV finished product for all three presentations is considered sufficient and acceptable. This argumentation is agreed.

In conclusion, the selection of batches in the biosimilarity excercise as well as the number of batches of both RGB-19 IV and SC finished product and RoActemra IV and SC finished product are considered sufficiently justified and found acceptable.

The study where the batch was used, use of batch as well as the expiry/age of the batches at the time of testing are also clearly shown. The RoActemra batches were measured over several years and the age range at the time of analysis were 6-30 months for RoActemra IV batches and 7-32 months for RoActemra SC batches, respectively.

All RGB-19 finished product SC and IV batches included in the biosimilarity study were included in the stability program for long-term, accelerated and stress stability testing.

All samples were stored under prescribed conditions: in a refrigerator at 2-8 °C, in the original packaging/outer carton protected from light. In all cases, measurements were performed within the expiry date of the respective RMP batches. It can be noted that since the shelf-life of RoActemra batches has been extended, the expiry date of RoActemra batches has been extended from 30 months to 36 months (the EMA EPAR was updated on 20 March 2024) during the biosimilarity exercise. Accordingly, it is argued by the applicant that the extended shelf-life of 36 months is also applied for all RoActemra batches used in the biosimilarity reports. This is found acceptable and agreed. Evaluation of attributes that could change on storage is also included in the biosimilarity exercise such as HMWs by SE-HPLC, charge variants by IEX-UHPLC-FL, oxidised forms by RP-HPLC oxidation hotspot, fragments/LMWs by NR-CE-SDS and biological activity tests, these attributes are evaluated and discussed with a reference to section 3.2.P.8.

It should be noted that the RGB-19 SC finished product presentation (PFS-NSD) was used in the clinical Phase I (PK) study while RGB-19 IV finished product (vial) was used in the clinical Phase III (efficacy/safety) study. It is also clearly shown which RoActemra IV and SC batches that were used during the clinical Phase I and Phase III studies.

This is found acceptable.

Analytical similarity acceptance criteria and statistical approach

The applicant has a limited discussion in the Analytical similarity section (3.2.R) regarding the definition of a QTPP to identify the product quality attributes, CQAs, for the RMP RoActemra, and provide only a limited background for the risk assessment concerning the criticality ranking of the CQAs provided in the biosimilarity section. However, the discussions of QTPP and CQAs are instead given in section 3.2.S.2.6 where it is described that the CQAs and non-CQAs were determined according to the adaption of a risk-based method evaluating the impact and uncertainty of the quality attributes on biological activity/PD/efficacy, PK, immunogenicity and safety. It can be noted that sufficient number of CQAs and non-CQAs have been defined for the biosimilarity exercise between RGB-19 and Roactemra IV and SC batches. This is found sufficient and acceptable.

The selected set of orthogonal state-of-the-art analytical methods is considered comprehensive and adequate, covering primary and higher order structure, post-translational modifications, size and charge variants, purity and impurities, protein concentration as well as biological binding and functional activity assays. Brief descriptions of each analytical method are provided, and the corresponding results have been adequately summarised and presented in the dossier. All analytical methods used during the biosimilarity exercise were either qualified or validated at the time of measurements. The release methods which are part of the specification have been appropriately described and validated,

as described in sections 3.2.S.4.2, 3.2.S.4.3, 3.2.P.5.2 and 3.2.P.5.3, and furthermore some additional methods are provided in section 3.2.S.4.4.

The quality range was based on the RMP RoActemra IV and SC batches and calculated as mean (RMP) +/- X*SD, where X is either 3 or 2.5, where 3 is determined for the majority of the quality attributes from physical chemical and bioassay methods, and 2.5 is determined for the most critical release bioassay methods, i.e. the cell-based antiproliferation assay and sIL-6R binding ELISA that are closely related to the clinically relevant mechanism of action of the product. Separate quality ranges are defined for the RGB-19 IV and SC finished products since there are different formulations and manufacturing processes. For some quality attributes which do not depend on the formulation and manufacturing process, a combined range from RMP SC and IV is used. No multiplier is defined for identity (cIEF, LC-MS and NMR), the negative biological assays (CDC, ADCC), near UV CD, FT-IR or sub-visible particle methods (LO and RMM). This approach is considered reasonable although not fully aligned with the current guidance (EMA/CHMP/BWP/247713/2012; EMA/CHMP/138502/2017). However, since the applicant also provides graphical and tabular presentations of individual analytical results and side-by-side comparisons for both RGB-19 and Roactemra, this enables an assessment independent of the defined quality ranges of each attribute. From the graphical presentations, it was also concluded that the quality ranges were acceptably defined.

Overall, the statistical approach is found acceptable, and no objection is raised.

Reference standard

A list of the used reference standard samples over time for the RGB-19 SC and IV finished product from the development phase to the final analytical similarity assessment study has been described and provided. This is found sufficient and acceptable.

In conclusion, the information provided on the general approach to assess analytical similarity is found acceptable.

4.2. Analytical summary exercise

Protein content

This section provides data from studies to compare protein content. These studies demonstrate a high degree of similarity with respect to protein content of the biosimilar candidate RGB-19 IV finished product (vial, all three fill volumes) and RGB-19 SC finished product (PFS) to the EU approved RoActemra IV and SC finished product.

Primary structure

The primary sequence of RGB-19 SC and IV and RoActemra SC and IV finished product batches was evaluated at the intact, subunit and peptide level by peptide mapping by on-line RP-HPLC/ESI-MS intact molecular weight analysis, a LC-MS method after the proteolytic digestion of the protein by IdeS enzyme and by RP-HPLC/ESI-MS/MS with Lys-C and Chymotryptic peptide mapping experiments.

Chromatograms, data and summarizing tables have been provided for the performed tests.

These studies demonstrate a high degree of similarity with respect to the primary structure of the biosimilar candidate RGB-19 IV finished product (vial) and RGB-19 SC finished product (PFS) to the EU approved RoActemra IV and SC.

The amino acid sequence of the RGB-19 was confirmed to be identical to RoActemra reference product with a 100% sequence coverage. The profile of the deconvoluted mass spectra of the RGB-19 batches is similar to RoActemra finished product batches and the same isoforms were identified. Based on the subunit analysis the measured monoisotopic molecular mass values of the detected isoforms of the

subunits (Fc/2, LC, Fd') in all batches conform to the theoretical mass values of the specified isoforms of the subunits of tocilizumab and the profile of the deconvoluted mass spectra of the major peaks in the RGB-19 samples is also similar to that of the RoActemra finished product batches.

In conclusion, the information provided on primary structure to assess analytical similarity is found acceptable.

N-glycan pattern

Glycation of RGB-19 and RoActemra batches was analysed by LC/MS after digestion by PNGase F glycosidase and treatment with Lys-C and trypsin enzymes. N-linked glycan profiles were analysed by the HILIC-UHPLC-FLD method where the labelled glycans were separated by UHPLC and the content of the glycans determined by fluorescent detection. Sialic acid content was determined by a RP-HPLC-FL method.

Glycosylation analysis

In general, based on the LC/MS peptide mapping results, the glycan forms are found comparable in RGB-19 and RoActemra. However, a slight difference is seen in the level of galactosylated forms (G1F+G2F) of RGB-19 to the RoActemra batches. It is argued that the slightly lower level of galactosylated forms in RGB-19 do not have an impact on Fab-mediated biological activity, which is supported by the sIL-6R binding (ELISA and BLI), cell-based antiproliferation assay, and other tests of affinity of FcRn and the FcγR's binding results. Furthermore, terminal galactose might influence the MAb effector functions but ADCC and CDC are not part of the mechanism of action of tocilizumab and the absence of ADCC and CDC activity has also been shown and confirmed. This is agreed. In addition, it can also be noted that slightly lower values of sialylated forms were measured by the LC/MS peptide mapping for RGB-19 compared to RoActemra batches, that is also confirmed by the HILIC-UHPLC-FL and HILIC-UHPLC-FL-ESI-MS/MS methods. It is argued that this difference in the amount of the sialylated glycoforms does not have an impact on the efficacy, safety or immunogenicity and is not reflected in the biological functional results. Furthermore, it is also stated that the total amount of sialylated glycans are very low in both the RoActemra and RGB-19 SC and IV batches which are also below the detection and quantification limit of the analytical method (LOD and LOQ for both NANA and NGNA are provided). This is agreed.

It can be concluded that the RGB-19 has a comparable N-glycan profile to RoActemra batches.

N-glycosylation pattern

The quality ranges for the N-glycan species measured by HILIC-UHPLC-FL method were determined from the combination of both the RoActemra IV and SC batches (calculated as mean ± 3*SD) since the glycosylation profile does not depend on the formulation and the finished product manufacturing process. This argumentation is agreed.

The measurements of G0F, G1F, G2F, G1'F forms and galactosylated glycans, fucosylated glycans, afucosylated glycans and high mannose glycans of the RGB-19 and RoActemra batches show a comparable glycan profile. G0F was found to be the most abundant glycan species in RGB-19, but this glycan form is also within the quality range (only one RGB-19 batch is out of the range) and is judged as comparable to RoActemra. A minor difference is noted regarding the sialylation and the sialylated glycans are very low in RGB-19 batches and at the lower limit of the quality range calculated from the RoActemra batches, in-line with the LC/MS peptide mapping results.

Overall, the glycan profile for RGB-19 and RoActemra are considered comparable and differences in some low abundant glycoforms are not expected to have any impact on the efficacy or PK of the RGB-19 batches. Furthermore, it can also be noted that ADCC and CDC are not relevant modes of action (MoAs) for tocilizumab as further discussed below.

Sialic acid content

Sialic acid content (N-acetyl neuraminic acid (NANA) and N-glycolyl neuramiic acid (NGNA)) was also determined by fluorescent labelling of sialic acid residues and analysis by the RP-HPLC-FL method. The NANA content of RGB-19 was found to be slightly lower than in the RoActemra batches. It is argued that the absolute value of NANA content is very low in both RGB-19 and in RoActemra batches; and this difference is negligible and does not have any impact on the efficacy or immunogenicity. Furthermore, the NGNA is considered immunogenic since it is a non-human form of sialic acid and thus it may be able to trigger adverse immune reactions in higher quantities. However, it can be concluded that the NGNA level in RGB-19 is found very low in all cases, with only a low proportion of NGNA of the total acidic content as well as comparable to RoActemra therefore raising no risk for concerns with respect to immunogenicity. Furthermore, it has also been demonstrated that this difference does not affect the biological functional results. This is found acceptable, agreed to and this minor difference in sialic acid content is judged as a desirable quality characteristic in favor of the biosimilar candidate.

In conclusion, the information provided on N-glycan pattern to assess analytical similarity is found acceptable and it can be concluded that the RGB-19 has a highly comparable N-glycan profile to RoActemra batches and support the biosimilarity claim.

Size related variants

Several complementary and orthogonal analytical tests have been applied to compare batches of the biosimilar candidate RGB-19 SC and IV finished product to RoActemra SC and IV finished product with respect to size related variants. This comparison includes assessment of HMWs and LMWs species by SEC-HPLC, LMWs species by NR-CE-SDS, size distribution analysis by SEC-MALLS and AUC and determination of non-glycosylated HC species by R-CE-SDS and LC-MS.

SEC-HPLC

The chromatograms for SEC-HPLC show similar size variants profile for both RGB-19 SC and IV finished product compared to RoActemra SC and IV finished product. These studies performed have demonstrated that both products are primarily monomers. The level of HMWs as determined by SEC-HPLC is in general found low for all products studied and the RGB-19 SC and IV batches have slightly lower levels of HMWs than the RoActemra SC and IV batches and they are also well within the quality range (calculated as mean ± 3SD). As such, these slightly lower levels of HMWs in RGB-19 SC and IV batches compared to RoActemra SC and IV batches is considered as a desirable quality characteristic and positive for the biosimilar candidate.

NR-CE-SDS

RGB-19 SC and IV finished product batches contain slightly higher levels of LMWs compared to RoActemra SC and IV finished product batches. This difference noted in LMWs is similar in the SC and IV products of the biosimilar candidate and the RMP and found outside the quality range calculated as mean ± 3SD. Furthermore, it is found to be essentially driven by elevated levels of HC-HC-LC fragments with a max difference of about 1%. It is argued by the applicant that this difference in LMWs does not have an impact on FcRn or sIL-6R binding or potency by the antiproliferation assay. It is also argued by the applicant that the lack of one light chain in the HC-HC-LC variant means, from a structure-activity relationship, that one of the two antigen binding sites is not complete for antigen recognition which may reduce the biological activity of the fragment molecule. However, since the theoretical maximal reduction in activity caused by the presence of this LMWs variant in RGB-19 is minor (about 1% max difference with respect to the HC-HC-LC variant) this has unlikely any impact on the comparative biological activity of the products and, consequently, on efficacy. Thus, this difference is not expected to have any impact on efficacy, PK and immunogenicity. Further, it can also be noted that highly similar functional activities and biological bindings have been shown as measured by the

antiproliferation assay (TF-1 cell), affinity to sIL-6R, sIL-6R binding activity, cell-surface mIL-6R, inhibition of sIL-6R mediated trans signaling, C1q binding, binding to FcγRI, FcγRII and FcγRIII and affinity with FcRn, as further discussed below. All these data of functional activities and biological binding confirms that the slightly higher level of LMWs in RGB-19 compared to RoActemra is not clinically meaningful. It is also argued that the higher amount of HC-HC-LC in RGB-19 SC and IV finished product batches compared to RoActemra SC and IV batches is not expected to influence immunogenicity as this is supported by the fact that this minor difference in levels of HC-HC-LC does not lead to aggregation, as demonstrated by the highly similar data of HMWs by SEC-HPLC as well as from the comparable immunogenicity data obtained from the clinical Phase I study.

In summary, this justification for slightly higher levels of LMWs in RGB-19 batches to RoActemra batches and the conclusion drawn by the applicant that this difference is not expected to have adverse impact on clinical performance is found acceptable and agreed.

SEC-MALLS

The quality ranges for the parameters measured by SEC-MALLS were determined from the RoActemra SC and IV finished product batches calculated as mean ± 3SD.

Similar monomer molecular weight and molecular weight of HMWs (i.e. dimers) have been demonstrated for both the RGB-19 SC and IV finished product batches compared to the RoActemra SC and IV finished product batches and the results of RGB-19 SC and IV are also well within the quality ranges.

Analytical ultracentrifugation (AUC)

The quality ranges for the attributes measured by AUC were determined from the RoActemra SC and IV finished product batches calculated as mean ± 3SD for monomer content and monomer Mw values and the sedimentation coefficient. ΣHMWs and ΣLMWs contents are below the limit of quantitation (LOQ) or reporting limit of the AUC method for both RoActemra and RGB-19 IV products.

The results show that RGB-19 SC and IV finished product batches are highly comparable to RoActemra SC and IV finished product batches with similar monomer content, monomer Mw and sedimentation coefficient and these results of RGB-19 SC and IV are also well within the quality ranges.

R-CE-SDS

The quality ranges for the attributes measured by R-CE-SDS were determined from the RoActemra SC and IV finished product batches calculated as mean ± 3SD.

The results show that RGB-19 SC and IV finished product batches are highly comparable to RoActemra SC and IV finished product batches with similar level of NGHC and detected LC and HC contents and these results of RGB-19 SC and IV are also well within the quality ranges. In addition, the batches of different presentations also show similarity for both the RGB-19 SC and IV finished product.

LC-MS

The LC-MS measurements showed slightly higher level of NGHC in RGB-19 SC and IV finished product batches than in RoActemra SC and IV finished product batches. This difference is rather minor and it is argued to not pose an efficacy or safety risk since antibodies with high level of NGHC have significantly reduced Fc-related effector functions such as ADCC and CDC. Further, as ADCC and CDC are not part of the mechanism of action of tocilizumab, the level of NGHC is not critical for the function and the difference of in NGHC content between RGB-19 and RoActemra products is not considered clinically relevant. It can also be noted that the functional activities and biological binding testing, as discussed below, also confirms that the slight difference in NGHC between RGB-19 and RoActemra is not clinically meaningful. Furthermore, despite that higher level of NGHC was measured in RGB-19 SC and IV

finished product batches, no differences were found in the level of aggregate formation as demonstrated by the highly similar data of HMWs by SEC-HPLC. This justification is agreed.

In conclusion, the assessment of HMWs and LMWs species by SEC-HPLC, LMWs species by NR-CE-SDS, size distribution analysis by SEC-MALLS and AUC and determination of non-glycosylated HC species by R-CE-SDS and LC-MS all support the biosimilarity claim for RGB-19 SC and IV finished product to the RoActemra SC and IV finished product. The size related variants for the RGB-19 and RoActemra are found highly comparable and the rather small differences observed (i.e. LMW by NR-CE-SDS and NGHC by LC-MS) are appropriately discussed and sufficiently justified and are not expected to have adverse impact on clinical performance. This conclusion is also supported by the similar functional activities and biological binding testing of RGB-19 and RoActemra discussed below, and by the PK and immunogenicity data as well as from the clinical efficacy and safety data from the EU pivotal studies performed. This is found acceptable.

Charge related variants

Several complementary and orthogonal analytical tests have been applied to compare batches of the biosimilar candidate RGB-19 SC and IV finished product to RoActemra SC and IV finished product with respect to charge related variants. This section includes assessment of IEX-HPLC with and without CPB treatment, cIEF, the study of deamidation in both the CDR and non-CDR regions as well as from the intact glycation analysis and site-specific glycation.

IEX-HPLC with and without CPB digestion

The analysis of charge variants profile by IEX-HPLC with and without CPB treatment show a highly similar charge variants profile for the batches of RGB-19 and RoActemra SC and IV finished product. The level of basic variants is found slightly lower in RGB-19 compared to the RMP and this effect is found more pronounced after CPB treatment. This effect is argued to be related to slightly higher level of C-terminal lysine in RGB-19 and as C-terminal lysine is well known to be rapidly cleaved off enzymatically in serum, this difference does not affect the antigen binding and potency and is also supported by the similar and comparable bioassay results as discussed below. Furthermore, it is also described that LC-MS data have shown (structural characterisation) a somewhat higher level of proline amidation for the RoActemra batches than for the RGB-19 batches and, in addition, N-terminal glutamine peak and VHS signal peptide can be detected only in RoActemra batches. These minor differences also contribute to the slightly higher basic variants in RoActemra batches, but do not affect the efficacy and biological activity and is therefore not expected to be clinically meaningful. This conclusion is agreed.

cIEF

The cIEF results revealed that the batches of RGB-19 and RoActemra SC and IV finished product are highly similar in terms of charge variants profile and isoelectric point. Furthermore, the batches of different presentations of both the IV and SC finished product also show similarity.

Deamidation in CDR and in non-CDR

Similar deamidation sites in the CDR and non-CDR regions were qualitatively identified in both RGB-19 SC and RoActemra SC and IV finished product batches. The relative amounts of the identified deamidated species were also highly similar.

Intact glycation analysis

Intact glycation analysis by LC-MS revealed a difference in the level of mono-glycated forms in the batches of the RGB-19 and RoActemra SC and IV finished product with higher levels in RGB-19. However, it is argued that this difference does not have an impact on biological activity (i.e. binding

and potency) and on the level of aggregation and is therefore not considered to affect safety and efficacy and not expected to be clinically meaningful. This is agreed.

Site specific glycation

The results for the site specific glycation test by LC-MS Lys-C peptide mapping are in line with the results from the intact glycation analysis demonstrating a higher level of sum of site specific glycation in the batches of the RGB-19 compared to RoActemra SC and IV finished product. This difference is not considered to affect safety and efficacy and not expected to be clinically meaningful.

In conclusion, similar charge variants profile, deamidation in CDR and in non-CDR and intact and site specific glycation have at large been demonstrated for batches of RGB-19 compared to RoActemra SC and IV finished product. Some minor differences are noted in basic variants and mono-glycated forms but they have been sufficiently justified as not clinically meaningful. This is found acceptable.

Oxidated related variants

The measurement of methionine oxidation has been selected as a marker and an oxidation hotspot for both the overall level of oxidation and the highest level of oxidation observed in RGB-19 and RoActemra batches. A RP-UHPLC-UV method has been developed and qualified for the analysis of this parameter.

Heavy chain methionine oxidation determined by RP-UHPLC-UV oxidation hotspot

Highly similar levels have been demonstrated for HC methionine oxidation for batches of RGB-19 compared to RoActemra SC and IV finished product. Batches of various presentations also show similarity.

Oxidation in CDR

A single Met residue was affected by oxidation in the CDR region and a similar level was found in batches of RGB-19 compared to RoActemra SC and IV finished product.

Oxidation of non-CDR

Four additional oxidation sites were identified and studied by LC-MS in the non-CDR region. Slightly higher values were determined for batches of RGB-19 compared to RoActemra SC and IV finished product for the oxidation of two methionine oxidation sites while slightly lower values were determined for HC methionine. These minor differences are argued to not pose a stability or safety risk and do not have an impact on biological activity, FcRn binding or aggregation. This justification is agreed.

In conclusion, the information provided on oxidation related variants to assess analytical similarity is found acceptable and it can be concluded that RGB-19 has a highly comparable profile to RoActemra SC and IV finished product batches and support the biosimilarity claim.

Isomerisation, terminal variants, sequence variants and hydrophobic variants

Isomerisation

Similar levels of isomerisation were observed in batches of RGB-19 compared to RoActemra SC and IV finished product.

Terminal variants

A higher level of C-terminal lysine variant was found in RGB-19 IV finished product batches as compared to RoActemra SC and IV finished product batches. However, it is argued that since C-terminal lysine is cleaved off enzymatically in serum, this difference is not expected to affect antigen binding and potency. Furthermore, a higher level of proline amidation was determined for the

RoActemra batches than for the RGB-19 batches but as proline amidation is not expected to affect biological activity and as a comparable potency and antigen binding have been demonstrated, this difference is not considered to be critical. These justifications are agreed.

Sequence variants

No sequence variants have been identified in any of the investigated RGB-19 and RoActemra SC and IV finished product batches.

Hydrophobic variants

Based on the results from HIC chromatography, the batches of RGB-19 and RoActemra SC and IV finished product are highly similar in terms of the profile of hydrophobic variants.

Higher order structure

Several complementary and orthogonal analytical tests have been applied to compare batches of RGB-19 SC and IV finished product to RoActemra SC and IV finished product with respect to thermodynamic stability, higher order structure and study of disulfide bridges and free thiol contents. This comparison includes assessment of micro-DSC, far UV CD, near UV CD, Fourier transform infrared (FTIR), 2D-NMR and hydrogen deuterium exchange mass spectrometry (HDX MS) methods as well as peptide mapping and testing by Ellman's assay.

A high level of similarity in higher order structure and thermodynamic stability was confirmed with all techniques. Only minor differences were noted.

Micro-DSC

The micro-DSC confirmed similar thermal stability of RGB-19 SC to RoActemra SC and IV finished product batches by measurements in the enthalpy change. The Tm2 and ΔH values are on the upper limit of the RoActemra quality range. However, it is argued that as slightly higher Tm2 and ΔH values indicate a more stable product and as there are no effect on the other quality attributes, this minor difference does not cause any risk and impact on other quality attributes. This is agreed.

Far UV CD, near UV CD, FTIR

The secondary and tertiary structures of RGB-19 was demonstrated and confirmed to be similar to RoActemra as studied by far UV CD, near UV CD and FTIR.

Disulfide bridges and free thiol contents

Results have been provided from MS/MS data acquired during peptide mapping and from testing by Ellman´s assay.

All the expected disulfide bridges were identified in all the investigated RGB-19 and RoActemra SC and IV finished product batches. In addition, the positions of the disulfide bridges have been confirmed to be identical. Furthermore, the obtained results show that the RoActemra and RGB-19 SC batches are similar to each other with respect to total free thiol contents which are consistency low, below the LOQ, as tested by Ellman' assay using DTNB.

In conclusion, the analyses included in the study and the obtained results sufficiently well demonstrate that thermodynamic stability, higher order structure and disulfide bridges/free thiol contents of RGB-19 are similar to that of RoActemra, for both the SC and IV presentations. Batches of different presentations also show similarity.

This is found acceptable.

Particulate matter and sub-visible particles

Light obscuration (LO) and RMM have been applied to compare batches of the biosimilar candidate RGB-19 SC and IV finished product to the RMP RoActemra SC and IV finished product with respect to particulate matter and sub-visible particles. It is described that the measurement of sub-visible particles is not part of the formal similarity assessment and that these results are given for information only. Furthermore, it is also described that there are pharmacopoeia limits for the LO method that needs to be fulfilled (NMT 6000 per container ≥10 µm and NMT 600 per container ≥25 µm). However, it can be noted that the results for all RGB-19 SC and IV batches all meet the pharmacopoeia requirements and the RGB-19 SC and IV batches show slightly lower or similar number of subvisible particles compared to the RoActemra batches.

This is found acceptable.

Biological activity

A large and comprehensive panel of biological assays have been applied in the biosimilarity exercise to compare batches of the biosimilar candidate RGB-19 SC and IV finished product to the RMP RoActemra SC and IV finished product with respect to functional activities and biological binding testing.

The quality range applied was based on the RMP RoActemra IV and SC batches and calculated as mean (RMP) +/- X*SD, where X is either 3 or 2.5, where 3 is determined for the majority of the quality attributes from the bioassay methods, and 2.5 is determined for the most critical release bioassay methods, i.e. the cell-based antiproliferation assay and sIL-6R binding ELISA that are closely related to the clinically relevant mechanism of action of the product.

This comparison includes assessment of sIL-6R binding assay by ELISA, anti-proliferation assay in TF-1 cell, FcRn, FcγRI (CD64), FcγRIIa (CD32a_R131) and FcγRIIIa (CD16a_V158) receptor binding affinity by BLI, C1q binding affinity by BLI, inhibition of tocilizumab STAT3 phosphorylation by cell-based ELISA, sIL-6R interaction by BLI, dissociation activity to IL-6/sIL-6R complex, cell surface mIL-6R binding and inhibition of sIL-6R mediated trans signalling.

sIL-6R binding assay by ELISA and Anti-Proliferation assay in TF-1 cell

The quality ranges have been calculated as mean +/- 2.5*SD for these two biological assays. Highly similar results have been provided for batches of RGB-19 SC and IV finished product to RoActemra SC and IV finished product with respect to sIL-6R binding by ELISA and potency by the cell-based antiproliferation assay. All results for RGB-19 SC and IV finished product are also well within the quality range as well as within the min-max range of the RMP RoActemra. Batches of different presentations also show similarity.

Furthermore, it can also be noted that the sIL-6R binding assay by ELISA is included in the active substance specification (section 3.2.S.4.1) as a test of antigen binding and that the anti-proliferation assay in TF-1 cell is included in the finished product specification (section 3.2.P.5.1) as a test for cell-based potency.

FcRn, FcγRI/CD64, FcγRIIa/CD32a_R131 and FcγRIIIa/CD16a_V158 receptor binding affinity and C1q binding affinity by BLI

Several analytical tests have been applied to compare RGB-19 to RoActemra with respect to Fc-receptor binding: FcRn, FcγRI/CD64, FcγRIIa/CD32a_R131 and FcγRIIIa/CD16a_V158 receptor binding affinity and C1q binding affinity by BLI. Data from the analyses is provided both in graphical and in tabular form. Although it is well known that FcγRIIa and FcγRIIIa have polymorphisms, only testing to FcγRIIa/CD32a_R131 and FcγRIIIa/CD16a_V158 were included in the testing in the biosimilarity exercise. This is considered as a limitation in the comparison, see section 3.2.S.3.1 for further comments. However, since it is widely accepted that Fc effector functions are not included in the MOA

for tocilizumab and lack of ADCC and CDC has been appropriately demonstrated and confirmed, this is judged as a sufficient panel of Fc gamma receptors studied and found acceptable.

The quality range was calculated as mean +/- 3*SD for these tests. Based on the binding affinities as measured by the BLI method, it can be concluded that the batches of RGB-19 SC and IV finished product are highly similar to RoActemra SC and IV finished product. All results for RGB-19 SC and IV finished product are also well within the quality ranges as well as within the min-max range of the RMP RoActemra. It is also noted that a single batch for RGB-19 SC finished product is on the upper limit of the quality range for the FcγRIIIa/CD16a_V158 receptor binding affinity. However, since tocilizumab has no ADCC this finding is not considered critical and clinically meaningful. Further, the C1q binding affinity data by BLI also demonstrates similarity.

Furthermore, a high degree of similarity has also been shown for the following biological assays and the corresponding bioassay attributes: inhibition of tocilizumab STAT3 phosphorylation by cell-based ELISA, sIL-6R interaction by BLI, dissociation activity to IL-6/sIL-6R complex, cell surface mIL-6R binding and inhibition of sIL-6R mediated trans signalling.

In addition, absence of CDC and ADCC activities have been sufficiently well demonstrated and confirmed for both RGB-19 SC and IV finished product and RoActemra SC and IV finished product. Representative dose-response curves are shown for both ADCC and CDC and relevant negative and positive controls are included in the analyses.

In conclusion, all the biological binding and functional assays applied including antiproliferation assay in TF-1 cell, sIL-6R binding assay by ELISA, cell surface mIL-6R, inhibition of sIL-6R mediated trans signaling, C1q binding, affinity with FcγRI (CD64), FcγRIIa(CD32a), FcγRIIIa(CD16a) and affinity with FcRn demonstrated that the biosmilar candidate RGB-19 and the RMP RoActemra are highly similar. Furthermore, the dissociation activity to IL-6/sIL-6R complex and inhibition of STAT3 phosphorylation by ELISA assay also confirm that RGB-19 and RoActemra batches are similar. Batches of different presentations also show similarity for both the SC and IV finished product. In addition, RGB-19 and RoActemra did not show ADCC and CDC activity in-line with the published literature and prior knowledge on tocilizumab.

Overall, all data presented in the studies of similarity of biological activity between RGB-19 and RoActemra are highly comparable and support the biosimilarity claim.

Comparative forced degradation stability

A set of relevant tests and attributes have been included in the studies to compare batches of the biosimilar candidate RGB-19 SC and IV finished product to RoActemra SC and IV finished product with respect to comparative forced degradation stability. Comparative head-to-head structural, physicochemical, and biological analyses were performed on samples exposed to various stress conditions to assess the similarity between the biosimilar candidate and reference medicinal product in terms of the protein degradation profiles. The applied stress treatments were heat stress, light/UV exposure, oxidative stress, acidic and basic treatment and they all caused significant changes in the tocilizumab molecules and induced accelerated degradation processes. The analytical methods applied for analysing the stressed samples were selected taking into account the possible changes in quality parameters by the actual stress factor applied. Analytical methods included in the specification and stability indicating methods for the finished products were selected based on their sensitivity and capability to detect changes in the quality attributes. The selected analytical test methods and test attributes were: structural analysis by LC-MS/MS reduced and non-reduced peptide mapping, size variants by SEC-HPLC and NR-CE-SDS, methionine position/oxidation hotspot by RP-UHPLC-UV, charge variants by IEX-HPLC, tocilizumab content by UV, sIL-6R binding by ELISA, bioactivity by antiproliferation assay in TF-1 cell and FcRn binding by BLI. Batches of RGB-19 SC and IV finished

product were compared to batches of RoActemra SC and IV finished product and it can be noted that the batches used during the clinical Phase I (RGB-19 SC finished product) and Phase III (RGB-19 IV finished product) studies of RGB-19 SC and IV finished product were included in the comparative forced degradation stability study.

It is argued that based on a preliminary forced degradation study, the freeze-thaw and the mechanical stress did not cause significant quality change in the RGB-19 and RoActemra batches and thus these stress factors were not part of the final forced degradation study. This argumentation is agreed.

SC presentation

The quantitative and structure changes caused by the applied stress conditions (heat stress, light/UV exposure, alkaline/acidic stress) were highly similar and demonstrated comparable degradation profiles in batches of RGB-19 and RoActemra SC finished product.

Oxidative stress

Minor differences were noted with respect to chemical oxidation where a higher level of oxidation was seen for the RGB-19 batches compared to RoActemra batches at chemical oxidative stress. Even though this difference, the kinetics of the changes are similar in the two products. There is no significant change in size related variants (HMWs and LMWs) and other structural characterisation data (LC/MS, e.g. deamidation, isomerisation etc.) of RGB-19 and RoActemra batches due to the applied oxidative stress. It can also be noted that a similar decrease is found for potency by the cell-based antiproliferation assay and in sIL-6R binding ability by ELISA assay upon oxidative stress in both RGB-19 and RoActemra batches. It is argued that the difference in oxidation level due to the chemically forced oxidative stress does not mean a difference in the stability, efficacy or safety of the RGB 19 and RoActemra products. This argumentation and justification is agreed.

IV presentation

The quantitative and structure changes caused by the applied stress conditions (heat stress, light/UV exposure, alkaline/acidic stress) were highly similar and demonstrated comparable degradation profiles in batches of RGB-19 and RoActemra IV finished product.

Oxidative stress

Slight differences between the two products were only observed in the oxidation rate after light exposure, but this minor difference was only detected at strong light exposure and the bioassay results demonstrated no difference in FcRn binding, sIL-6R binding and potency by the antiproliferation assay after light-induced forced degradation. It is argued that this observation does not mean a difference in the stability, efficacy or safety of the RGB 19 and RoActemra products. This is agreed.

Conclusion on the comparative forced degradation stability study

Overall, structural analysis by LC-MS/MS Lys-C reduced and non-reduced peptide mapping, acidic and basic charged variants, disulfide isoform profile, aggregates and fragments, oxidation level and biological activities (sIL-6R binding, antiproliferation in TF-1 cell, FcRn binding) were evaluated. All the changes observed during the comparative forced degradation stability study occurred in both RGB-19 and RoActemra and at a comparable rate and degree. No specific degradation variants were detected, that were only found in either RGB-19 or RoActemra.

Hence, the results provided in the forced degradation study on the comparison of degradation profiles of RGB-19 SC and IV finished product to RoActemra SC and IV finished product under different stress conditions supports the claim for biosimilarity.

Comparative stability assessment

The stability for the biosimilar candidate RGB-19 was compared the RMP RoActemra. The stability studies were conducted according to ICH Q1A and ICH Q5C guidelines under long-term storage conditions at 5 ± 3 °C, accelerated storage conditions at 25 °C ± 2 °C, 60% ±5 % RH and stressed conditions at 40 °C ± 2°C; 75% ± 5% RH. It is described that the purpose of these reports is to present the results from the stability studies for information collection. Each analytical method was plotted and evaluated separately. These reports have been provided in section 3.2.R for both the SC and the IV presentations.

The following tests were performed: pH, osmolality, methionine oxidation by RP-HPLC-UV, HMWs by SEC-HPLC, LMWs by NR-CE-SDS, NGHC by R-CE-SDS, HC by R-CE-SDS, LC by R-CE-SDS, HC+LC by R-CE-SDS, acidic variants/Main peak/basic variants by IEX-HPLC, protein content by UV, sIL-6R binding by ELISA, cell based potency by antiproliferation assay, polysorbate 80 by IEX-MM-CAD, subvisible particles by LO.

This is found acceptable.

IV and SC presentations

According to the data provided, the overall conclusion is that the batches of RGB-19 SC and IV finished product and the batches of the RMP EU-RoActemra SC and IV finished product show comparable stability profiles for most of the attributes studied and supports the claim for biosimilarity.

4.3. Conclusions on biosimilarity

The applicant has evaluated the similarity between RGB-19 SC and IV finished product to RoActemra SC and IV finished product in a comprehensive comparability program, evaluating relevant quality attributes by a panel of state-of-the-art and standard analytical methods.

The number of batches included in the biosimilarity study are found acceptable, both with respect to RGB-19 and EU approved RoActemra. The analytical similarity assessment summarised in Table 3 has been performed with a combination of methods assessing primary and higher order structures, post-translational modifications including charge variants and glycosylation profile, purity and impurities, particles and aggregates, and product variants. In addition, biological functional activities and biological binding were measured by several methods and results from a comparative stability testing study have been presented as well.

Overall, the provided data indicates a high degree of similarity between RGB-19 SC and IV finished product to RoActemra SC and IV finished product with respect to the physicochemical and biological characterisations. In addition, further characterisation studies performed have shown comparable degradation profiles as well as similar lack of ADCC- and CDC-activity in support of the biosimilarity claim. Some minor differences are noted, and they are described in detail, for instance in LMWs, NGHC, level of basic variants, C-terminal lysine and proline amidation as well as in the levels of mono-glycated, galactosylated and sialylated forms. The applicant justifies all differences noted and provides arguments related to tocilizumab mode of action, highly similar functional activities and biological bindings, information in the literature as well as results obtained in the non-clinical and clinical studies, implying that these differences are not expected to have any impact on efficacy, safety, PK and immunogenicity and therefore not considered as clinically meaningful, hence not impacting the biosimilarity claim.

Overall, biosimilarity with EU-RoActemra is considered demonstrated from a quality point of view.

Table 3: Overview of analytical similarity exercise

Quality Attribute	Analytical method	Similarity Assessment
Primary structure	LC-MS	Identical
	RP-HPLC-UV	Identical
Molecular identity and structural integrity	Intact molecular weight analysis by LC-MS	Similar
	Subunit molecular weight analysis by LC-MS	Similar
Disulfide bridge structure	LC-MS	Identical
Cysteine-related variants		Similar
Free thiol	Ellman assay	Similar
Secondary structure & tertiary structure	CD (far UV)	Similar
	CD (near UV)	Similar
	FT-IR	Similar
	NMR	Similar
	HDX-MS	Similar
Thermodynamic stability	DSC	Similar
N-terminal integrity	LC-MS	Similar
C-terminal integrity	LC-MS	Slightly higher (Lysine variant)
		Slightly lower (Proline amidation)
High molecular weight species (HMW)	SEC-HPLC	Similar
Low molecular weight species (LMW)	NR-CE-SDS	Higher (no impact on quality and clinical performance)
Size variants	SEC-MALLS	Similar
	AUC	Similar
Hydrophobic variants	HIC-HPLC	Similar
Charge variants	IEX-HPLC	Similar
Charge variants	IEX-HPLC after CPB digestion	Similar
Glycation	Intact glycation by LC-MS	Higher (overall low glycation)
Isoelectric point	cIEF	Similar
Oxidation	RP-HPLC UV	Similar
Deamidation	LC-MS	Similar
Isomerization	LC-MS	Similar
Sub-visible particles	LO	Similar
	RMM	Similar
N-glycosylation	HILIC-HPLC	Similar (lower Galactosylation)
	LC-MS	
Sialylation	LC-MS	Similar (slightly lower)
	RP-HPLC-FL	

Quality Attribute	Analytical method	Similarity Assessment
Non-glycosylated heavy chain (NgHC)	R-CE-SDS	Similar
Protein content	UV	Similar
Potency	Cellular anti-proliferation assay	Similar
sIL-6R binding	BLI	Similar
	ELISA	Similar
IL-6/mIL-6 downstream signal neutralization (Inhibition of pSTAT3)		Similar
Dissociation activity to IL-6/sIL-6R complex		Similar
Inhibition of trans signalling mediated by sIL-6R	Reporter assay	Similar
Cell surface mIL-6R binding	Flow cytometry	Similar
FcRn binding	BLI	Similar
Affinity with FcγRI (CD64)		Similar
Affinity with FcγRIIa (CD32a)		Similar
Affinity with FcγRIIIa (CD16a)		Similar
C1q binding		Similar
ADCC	ADCC reporter assay	Similar
CDC	Cell-based assay	Similar

3.5. Adventitious agents

Raw materials

TSE statements have been provided for materials used in production such as culture media and no materials of animal or human origin is used. Information has also been provided for media components used for establishing MCB and WCB. The manufacture of RGB-19 active substance and finished products is free of animal or human tissue derived materials. The exceptions are the bovine milk derived 2-deoxy-fluoro-fucose (2-DFF) and galactose. 2-DFF is produced from bovine milk in a synthetic way. TSE/BSE statement has been provided; it is acknowledged that the risk of TSE is negligible.

Testing of cell banks

Information on virus testing of cell banks is presented in section S.2.3 Control of materials. The MCB and the initial WCB, denoted WCB1, were manufactured according to GMP. Due to a low number of remaining vials of the WCB1, a new WCB, denoted WCB2, was manufactured according to cGMP at Gedeon Richter. This is accepted.

Testing of unprocessed bulk

Analyses results of viral safety evaluation of engineering bulk unprocessed batches and validation process unprocessed bulk batches manufactured at commercial scale have been provided. The results presented are negative for mycoplasma, bioburden, endotoxin, Minute Virus of Mouse (MVM) and *in vitro* adventitious agents assay. The unprocessed bulk harvest testing is described in S.2.4 and is sufficiently described.

Initially, the applicant had provided a very short summary and significant amount of data was missing to substantiate the claim of virus reduction of the process, and a Major Objection was raised. However, the applicant provided two reports, one on small scale validation and one detailed summary report of all virus clearance studies performed. Sufficient information has been presented on the model viruses used. For Protein A, MMAEX chromatography and virus filtration all four model virus, parvovirus (PRV), reovirus type 3 (Reo-3), murine leukaemia virus (MuLV) and minute virus of mice (MVM), have adequate description. The data confirm an acceptable minimum log10 reduction factor of for the tested viruses. For protein A and MMAEX results from both new and used resins have been presented. MuLV and PRV clearance has been tested in the low pH study and results are submitted, including data of the kinetics of inactivation. Adequate description has been provided of the small-scale process. Data from comparison of performance of commercial scale and small-scale processes have also been presented in sufficient detail. The Major Objection is resolved.

Overall, adventitious agents safety is considered demonstrated.

3.6. Discussion and conclusion on chemical, pharmaceutical and biological aspects

The Tuyory dossier is of good quality. Information on development, manufacture and control of active substance and finished product has been presented in a satisfactory way. The presented documentation indicates that the active substance and finished product are manufactured in well-controlled and validated processes.

The applicant is recommended to continue the leachable study and to provide the data of the study as a post-approval measure (Recommendation).

The applicant has evaluated the similarity between the biosimilar candidate RGB-19 SC and IV finished product to RoActemra SC and IV finished product in a comprehensive comparability program. In general, RGB-19 is considered to be similar to the EU approved RoActemra at the quality level. Some minor differences are noted but the applicant justified these as being not clinically meaningful which is agreed.

In conclusion, based on the review of the quality data provided, the MAA for Tuyory is considered approvable from the quality point of view.

3.7. Recommendation(s) for future quality development

In the context of the obligation of the Marketing Authorisation Holder to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

1. The applicant is recommended to continue the leachable study and to provide the data of the study when available.

4. Non-clinical aspects

4.1. Introduction

Tocilizumab (company code: RGB-19) is a humanised IgG1 monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

A comprehensive non-clinical in vitro program to establish biosimilarity between RGB-19 and RoActemra for IV and SC administration was designed based on the principles stated in relevant guidelines. The comparability studies consisted of sIL-6R and mIL-6R binding activities and functions, inhibition of cell proliferation, and downstream signal neutralisation. In addition, comparability studies regarding different Fc-receptor binding and activation of C1q, CDC and ADCC was conducted. To establish the similarity ranges, the range was defined as average ± 3xSD, except for sIL-6R binding assay by ELISA and the anti-Proliferation assay in TF-1 cells, where average ± 2.5xSD were calculated.
Pharmacology

4.1.1. Primary pharmacodynamics

Table 4: Primary pharmacodynamics table

Functional characteristics analysis		
Attribute	**Analytical Technique**	**Results**
Target binding and functional cell-based assays	sIL-6R binding by ELISA	The relative binding activities of RGB-19 SC and IV to sIL-6R were within mean ± 2.5SD of EU-RMP RoActemra.
	sIL-6R binding by BLI	The binding affinities (K_D) of RGB-19 SC and IV to sIL-6R were within mean ± 3SD of EU-RMP RoActemra.
	Anti-Proliferation assay, TF-1 cell based assay	The biological activities of RGB-19 SC and IV were within mean ± 2.5SD of EU-RMP RoActemra.
	IL-6/mIL-6 downstream signal neutralization (Inhibition of pSTAT3 phosphorylation), by sandwich ELISA	The relative inhibition activities of RGB-19 SC and IV on STAT3 phosphorylation were within mean ± 3SD of EU-RMP RoActemra.
	Dissociation of IL-6/sIL-6R complex, ELISA	The relative dissociation abilities of IL-6/sIL-6R complex by RGB-19 SC and IV were within mean ± 3SD of EU-RMP RoActemra.
	Cell surface mIL-6R binding, human DS-1 B-cell	The relative binding activities of RGB-19 SC and IV to mIL-6R were within mean ± 3SD of EU-RMP RoActemra
	Inhibition of IL-6 induced trans signalling mediated by sIL-6R, cell-based assay	The relative inhibition activities of trans-signalling by RGB-19 SC and IV was within mean ± 3SD of EU-RMP RoActemra.
Fc binding	FcγRI/CD64 receptor binding affinity (by BLI)	The binding affinities (K_D), of RGB-19 SC and IV to FcγRI/CD64 receptor were within mean ± 3SD of EU-RMP RoActemra.
	FcγRIIa/CD32a_R131 binding affinity (by BLI)	The binding affinities (K_D) of RGB-19 SC and IV to FcγRIIa/CD32a_R131 receptor were within mean ± 3SD of EU-RMP RoActemra.
	FcγRIIIa/CD16a_V158 receptor binding by BLI	The binding affinities (K_D) of RGB-19 SC and IV to FcγRIIIa/CD16a_V158 receptor were within mean ± 3SD of EU-RMP RoActemra.
	FcRn receptor binding by BLI	The binding affinities (K_D) of RGB-19 SC and IV to FcRn receptor were within mean ± 3SD of EU-RMP RoActemra.
C1q binding	C1q binding assay (BLI)	The binding affinities (K_D) of RGB-19 SC and IV to C1q were within mean ± 3SD of EU-RMP RoActemra.
CDC binding	CDC assay	No activation of CDC was observed for the batches of RGB-19 or EU- RMP RoActemra.
ADCC binding	ADCC assay	No activation of ADCC was observed for any of the batches of RGB-19 or EU- RMP RoActemra.

4.1.1.1. Secondary pharmacodynamics, Safety pharmacology and Pharmacodynamic drug interactions

No additional studies on *in vivo* pharmacology, secondary pharmacodynamics, safety pharmacology or pharmacodynamic drug interactions were conducted and are not generally required for a biosimilar for the approval of the marketing authorisation within EU and is in line with EMA guidance documents for biosimilar development.

4.2. Pharmacokinetics

No comparative non-clinical *in vivo* pharmacokinetic/toxicokinetic studies were conducted with Tuyory and the EU-RMP product RoActemra and are not required. No differences were observed in the *in vitro* pharmacological package for similarity assessment between Tuyory and RoActemra.

4.3. Toxicology

No toxicology studies were conducted. Toxicology studies are not generally required for marketing authorisation approval of biosimilars in the EU, in line with EMA guidance documents for biosimilar development.

4.3.1. Ecotoxicity/environmental risk assessment

The applicant provided a justification for not providing an environmental risk assessment (ERA) for Tuyory: Tocilizumab is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, tocilizumab is not expected to pose a risk to the environment.

4.4. Overall discussion and conclusions on non-clinical aspects

The nonclinical data package was focused on comprehensive *in vitro* functional activity analyses. The *in vitro* comparability studies included IL-6R binding activities and functions, inhibition of cell proliferation, or downstream signal neutralization as well as FcR- and C1q binding affinities. No activation of CDC or ADCC was detected for either Tuyory or the RMP RoActemra.

The functional *in vitro* data package is adequate for demonstrating similar biological activity of Tuyory (RGB-19) and the EU approved RMP RoActemra and reflects the principal mode of action of tocilizumab. No differences were detected between Tuyory and the RMP RoActemra regarding IL-6R binding activities and functions, inhibition of cell proliferation, or downstream signal neutralization, and no differences were detected for the FcR- or C1q binding affinities. No activation of CDC or ADCC was detected for either Tuyory or the RMP RoActemra.

For establishing the similarity ranges, the range was defined as average ± 3xSD, except for sIL-6R binding assay by ELISA and the anti-Proliferation assay in TF-1 cells, where average ± 2.5xSD were calculated

No additional studies on *in vivo* pharmacology, pharmacokinetic/toxicokinetic or toxicology were conducted, and are not required.

According to the EMA guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1, Dec 2014), a stepwise approach is recommended for evaluation of the similarity of the biosimilar

and the reference product, since *in vitro* assays may often be more specific and sensitive to detect differences between the biosimilar and the reference product than studies in animals, and therefore these assays can be considered as paramount for the non-clinical biosimilar comparability exercise. Studies regarding safety pharmacology, reproduction toxicology, and carcinogenicity are not required for non-clinical testing of biosimilars, which in this case applies for studies on local tolerance as well.

The functional *in vitro* data package is adequate for demonstrating similar biological activity of Tuyory (RGB-19) and the EU approved RMP RoActemra from a non-clinical perspective.

As tocilizumab is a natural substance, a justification for absence of ERA is acceptable.

4.4.1. Conclusions

The nonclinical *in vitro* functional activity data support the biosimilarity between RGB-19 (Tuyory) and the EU reference medicinal product RoActemra.

5. Clinical aspects

5.1. Introduction

5.1.1. Good Clinical Practice (GCP) aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier (see section 2.4.3.).

5.1.2. Tabular overview of clinical trials

Table 5:Tabular overview of main clinical studies

Study No. / Description	Subjects	Number of Subjects treated	Dose, treatment period
RGB192101 Phase 1 Comparative PK/PD Randomized, Double-blind, 2-Treatment, 2-Period, 2-Sequence, Crossover Study	Healthy Japanese adult male subjects	N=110 total; N=55 per sequence	A single subcutaneous dose of 162 mg RGB-19 *or* RoActemra administered subcutaneously in the upper arm in Period 1 and Period 2, with treatment cross-over between periods. Two treatment sequences: (i) RGB-19 (Period 1) / RoActemra (Period 2) (ii) RoActemra (Period 1) / RGB-19 (Period 2)
RGB19101 Phase 3 Comparative efficacy, safety & immunogenicity using multiple IV doses	Japanese patients with Active Rheumatoid Arthritis who had an inadequate response o MTX	RGB-19=182 RoActemra=186	RGB-19 or RoActemra 8 mg/kg intravenous drip infusion (once every 4 weeks) for 48-weeks, in combination with MTX: - Primary Evaluation Period = 12 weeks - Secondary Evaluation Period = 40 weeks - Safety Follow-up = 2 weeks

IV=intravenous; MTX=methotrexate; PD=pharmacodynamic; PK=pharmacokinetic; SC=subcutaneous

5.2. Clinical pharmacology

5.2.1. Methods

Bioanalytical methods

Bioanalytical assays were developed and validated for the determination of tocilizumab serum concentration (PK), determination of sIL-6R (soluble Interleukin-6 receptor) serum concentration (PD), detection of anti-tocilizumab antibodies (ADA) and neutralising anti-tocilizumab antibodies (NAb) from serum samples.

The assays and their application in the clinical studies are summarised in Table 6.

Table 6: Summary of the bioanalytical assays

Method validation ID	Method title	Analyte	Applicable clinical studies
GB22036V	An electrochemiluminescence immunoassay for the determination of tocilizumab concentration in human serum	tocilizumab	RGB192101 RGB19101
GB22034V	An enzyme-linked immunosorbent assay for the determination of sIL-6R concentration in human serum	sIL-6R	RGB192101 RGB19101
GB22037V	An electrochemiluminescence immunoassay for the detection of anti-tocilizumab antibodies in human serum	anti-tocilizumab antibodies	RGB192101 RGB19101
GB22035V	An electrochemiluminescence immunoassay for the detection of anti-tocilizumab neutralizing antibodies in human serum	anti-tocilizumab neutralizing antibodies	RGB192101 RGB19101

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

The clinical development program of RGB-19 includes two clinical studies:

- A Randomized, Double-Blind, 2-Treatment, 2-Period, 2-sequence Crossover Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, and Immunogenicity of a Single 162 mg fixed Subcutaneous Dose of RGB-19 and RoActemra Subcutaneous Formulation in Healthy Male Volunteers (protocol number: RGB192101) in Japan
- A Randomized, Double-blind, Multicenter Comparative Clinical study to Assess the Efficacy and Safety of RGB-19 Compared to RoActemra in Patients with Active Rheumatoid Arthritis (protocol number: RGB19101) in Japan

The MAA concerns RGB-19 (tocilizumab) 20 mg/mL concentrate for solution for infusion, RGB-19 (tocilizumab) 162 mg solution for injection in pre-filled syringe (PFS) and RGB-19 (tocilizumab) 162 mg solution for injection in pre-filled pen (PFP).

Both the 20 mg/mL intravenous and the 162 mg (180 mg/mL) subcutaneous RGB-19 presentations were evaluated in comparative clinical studies using the corresponding presentation of RoActemra.

5.2.2.2. Bioequivalence/Biosimilarity

Study RGB192101 - PK similarity in healthy subjects

Study Title: A Phase I, Randomized, Double-blind, 2-Treatment, 2-Period, 2-Sequence Crossover Study to Compare the Pharmacokinetics, Pharmacodynamics, and Safety of a Single Subcutaneous Dose of RGB-19 and RoActemra 162 mg in Healthy Male Volunteers.

Methods

Study period: 26-Apr-2023 (first subject, first visit) to 19-Jan-2024 (last subject, last visit).

The study was conducted according to the protocol v1.2 (06-Apr-2023), and the three amendments, v1.3 (30-Jun-2023), v1.4 (27-Nov 2023), and v1.5 (18-Dec-2023).

The statistical analysis of the study is described in detail in the SAP v2.0, dated 15-Mar-2024.

Study Design

Subjects were randomly allocated to Sequences A or B at a 1:1 ratio to receive a single SC (upper arm) injection of investigational product – either RGB-19 162 mg or RoActemra 162 mg (assembled PFS with the needle safety device). The two-period, two-sequence crossover design of the study meant that subjects in Sequence A received RGB-19 in Period 1 and RoActemra in Period 2, whereas subjects in Sequence B received RoActemra first and then RGB-19.

Serum drug concentration was measured in each period at 24 time points: Pre-dose and 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 168, 192, 240, 288, 336, 408, 480, 576, 840, and 1008 hours after administration.

Samples for ADA / NAb testing were collected at the following timepoints: Prior to dosing on Day 1, Day 13 post-1st administration, Day 43 prior to 2nd administration, Day 55 (13 days post-2nd administration) and Day 85 (43 days post-2nd administration).

Investigational Products

RGB-19 and Tocilizumab (RoActemra)

Population Studied

In total, 110 subjects were equally randomized to Sequence A and Sequence B and received IP in Period 1 (55 subjects per sequence). In Period 2, a total of 102 subjects were administered IP; 49 subjects in Sequence A and 53 subjects in Sequence B.

A total of eight (7.3%) subjects prematurely withdrew from the study and all premature subject withdrawals occurred during Period 1. During Period 1, six (10.9%) subjects prematurely withdrew from the study in Sequence A (RGB-19); three subjects due to AEs and three subjects due to "other reasons(positive smoking test result)". In Sequence B during Period 1 (RoActemra), one subject prematurely withdrew from the study due to "a positive drug or alcohol test" the day before IP administration in Period 2 and one subject due to "other reasons (positive smoking test result)". There were no premature withdrawals from the study during Period 2.

Subjects had to be male volunteers aged 20 to 40 years (inclusive) with a body mass index (BMI) ≥18.5 kg/m^2 and <25.0 kg/m^2 and a body weight of ≥50 kg and <80 kg at screening.

Overall, mean (SD) age of subjects was 29.5 (6.2) years and all were Asian. Mean (SD) body weight and BMI was 61.91 (6.25) kg and 21.22 (1.79) kg/m^2.

Prior and Concomitant Treatments: Eleven of 110 (10.0%) subjects were in receipt of concomitant medications and one (0.9%) subject had a concomitant procedure. In all subjects, the reason for concomitant medications and the concomitant procedure was to treat or prevent adverse events.

PK Analysis Set

The population included subjects who met all of the following criteria for Periods 1 and 2:

- Subjects who received the full dose of IP

- Subjects for whom either C_{max} or AUC_{inf} could be calculated
- Subjects with no major protocol deviations that could have had an impact on PK results

Objectives and endpoints

Study Objectives

The primary objective was to demonstrate PK equivalence between RGB-19 and RoActemra 162 mg following a single SC dose in healthy adult men.

The secondary objective was to compare PK and PD parameters and safety (including immunogenicity) between RGB-19 and RoActemra following a single SC dose of 162 mg in healthy adult men.

PK parameters The primary PK parameters were maximum serum drug concentration (C_{max}) and area under the curve (AUC) from 0 hours to infinity (AUC_{inf}).

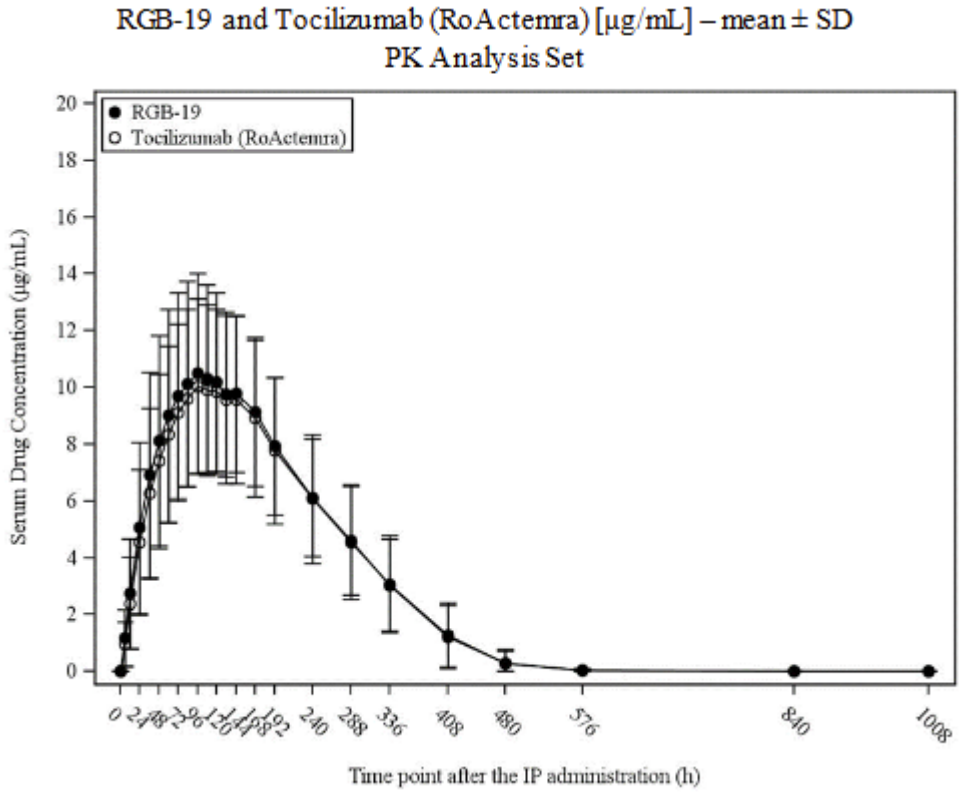
The secondary PK parameters were: AUC from 0 hours to the last quantifiable time (AUC_{last}), AUC from 0 hours to 144 hours after administration (AUC_{0-144}), AUC from 144 hours after administration to the last quantifiable time (AUC_{144-t}), time to maximum serum concentration (t_{max}), elimination half-life ($t_{1/2}$), apparent volume of distribution (V_d/F), apparent total clearance (CL/F), and elimination rate constant (k_{el}).

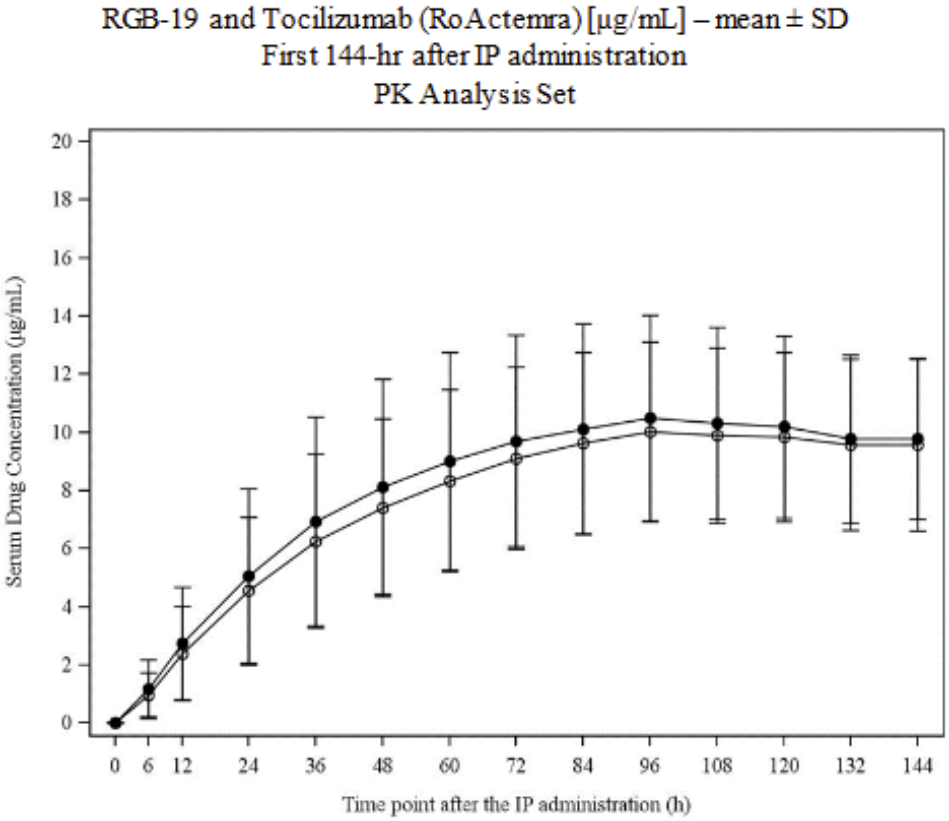
Additional PK parameters mean residence time (MRT) and the AUClast /AUCinf ratio were included in the statistical analysis plan (SAP) v2.0, dated 15-Mar-2024 per Japanese bioequivalence guidelines.

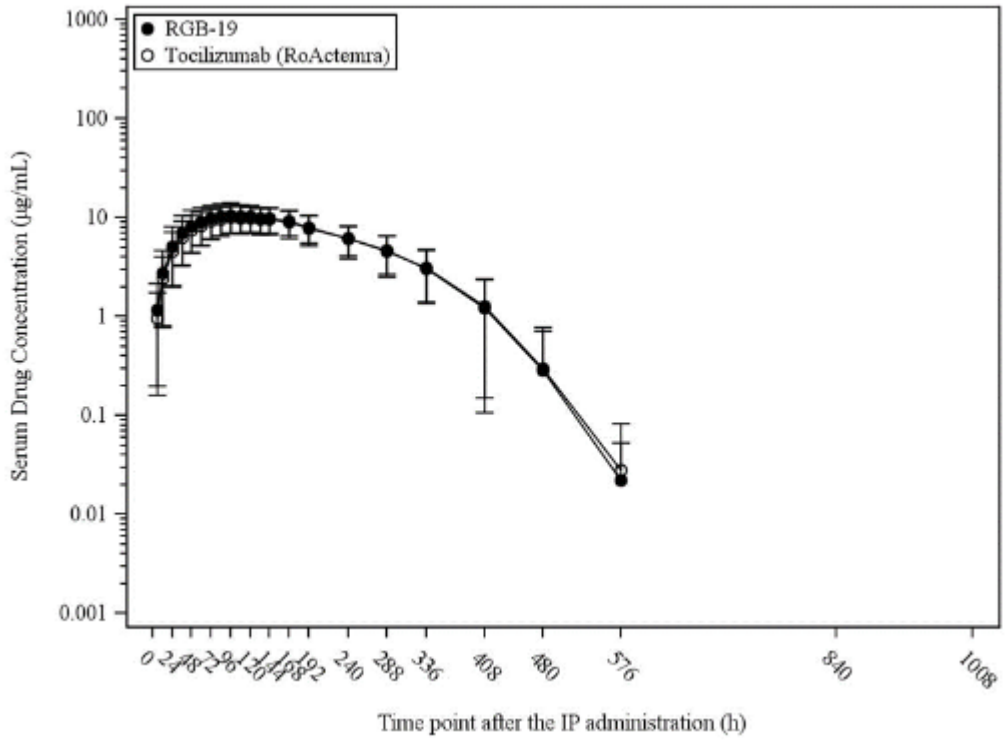
Pharmacokinetic Results

Summary data of the serum drug concentration during the study are presented graphically in Figure1. The mean serum drug concentrations of RGB-19 and RoActemra reached a maximum at 96 hours post-dose and then decreased. The mean serum drug concentration-time profiles after administration of RGB-19 and RoActemra were similar.

Figure 1: Mean Serum Drug Concentration-Time Profiles - PK Analysis Set (n=102)







IP = investigational Product; N = Number of subjects; PK = Pharmacokinetics; SD = Standard Deviation.

Descriptive statistics of the primary endpoints are summarised in Table 7. The PK parameters C_{max} and AUC_{inf} geometric means coefficient of variation (GCV%) were similar overall and for Period 1, for both treatment sequences. For Period 2, there was a difference in GCV% for AUC_{inf} between Sequence A and B of approximately 30%, which according to the applicant may be attributed to two subjects with low outlying results for this parameter.

Table 7: Descriptive Statistics of the Primary Pharmacokinetic Parameters of Serum Drug Concentration by Period - PK Analysis Set (n=102)

Period		Treatment	
		RGB-19 (N=102)	Tocilizumab (RoActemra) (N=102)
Overall			
C_{max} (µg/mL)	n	102	102
	Mean (SD)	11.11 (3.49)	10.63 (3.16)
	Median	11.20	10.75
	Min–Max	2.6-19.7	1.4-17.8
	Geo mean (GCV%)	10.51 (36.5)	10.04 (38.9)
AUC_{inf} (µg × h/mL)	n	102	102
	Mean (SD)	2586.5 (874.8)	2506.7 (853.6)
	Median	2613.3	2489.0
	Min–Max	468-4619	88-4266
	Geo mean (GCV%)	2415.9 (41.5)	2291.5 (55.1)
Period 1			
C_{max} (µg/mL)	n	49	53
	Mean (SD)	10.00 (3.26)	9.83 (3.19)
	Median	9.78	9.39
	Min–Max	2.6-17.3	2.8-17.8
	Geo mean (GCV%)	9.43 (37.5)	9.28 (36.7)
AUC_{inf} (µg × h/mL)	n	49	53
	Mean (SD)	2259.5 (776.6)	2353.4 (851.5)
	Median	2169.9	2310.0
	Min–Max	468-4170	594-4266
	Geo mean (GCV%)	2109.1 (41.8)	2180.5 (43.8)
Period 2			
C_{max} (µg/mL)	n	53	49
	Mean (SD)	12.14 (3.41)	11.51 (2.90)
	Median	11.80	11.40
	Min–Max	3.6-19.7	1.4-16.3
	Geo mean (GCV%)	11.61 (32.5)	10.94 (39.6)
AUC_{inf} (µg × h/mL)	n	53	49
	Mean (SD)	2888.8 (857.7)	2672.6 (832.9)
	Median	2915.8	2754.9
	Min–Max	621-4619	88-4068
	Geo mean (GCV%)	2739.1 (36.8)	2418.0 (66.0)

AUC_{inf} = area under the curve from 0 hours to infinity; C_{max} = maximum serum drug concentration; Geo = geometric; GCV = geometric coefficient of variation; N = number of subjects; n = number of subjects per category; PK = pharmacokinetic; SD = standard deviation

Source: Table 14.2.1.2.1.1.

The results of the primary endpoint analysis demonstrate that PK equivalence was established between RGB-19 and RoActemra for C_{max} and AUC_{inf} as the two-sided 90% CI for each parameter GMR were within the pre-defined equivalence criterion of 0.80 and 1.25 (C_{max}: point estimate: 1.0384 [90% CI: 0.9787 ~ 1.1018]; AUC_{inf}: point estimate: 1.0468 [90% CI: 0.9710 ~ 1.1285]).

Table 8: Two-Sided 90% Confidence Interval for the Mean Difference of the Primary Pharmacokinetic Parameters of Serum Drug Concentration - PK Analysis Set (n=102)

	LS mean [a]		Difference in LS means [a,b] (N=102)		Geometric LS mean [c]		GMR [d] (N=102)		Intra-Subject CV(%) [e]
	RGB-19 (N=102)	Tocilizumab (RoActemra) (N=102)	Point estimate	Two-sided 90%CI	RGB-19 (N=102)	Tocilizumab (RoActemra) (N=102)	Point estimate	Two-sided 90%CI	
C_{max} (μg/mL)	2.348	2.310	0.038	-0.022 ~ 0.097	10.46	10.08	1.0384	0.9787 ~ 1.1018	25.9
AUC_{inf} (μg × h/mL)	7.785	7.739	0.046	-0.029 ~ 0.121	2403.6	2296.2	1.0468	0.9710 ~ 1.1285	33.2

ANOVA = analysis of variance; AUC_{inf} = area under the curve from 0 hours to infinity; CI = confidence interval; C_{max} = maximum serum drug concentration; GMR = geometric mean ratio; LS = least square; N = number of subjects, PK = pharmacokinetic

a. Natural log-transformed value
b. Difference in LS means = (LS mean in RGB-19) - (LS mean in Tocilizumab [RoActemra])
c. Geometric LS mean = exp{ LS mean (log-transformed scale) }
d. GMR = exp{ Difference in LS means (log-transformed scale) }
e. Intra-subject CV% = square root {exp (residual variance) -1 } × 100

Notes: Using the ANOVA model with PK parameter (natural log-transformed) as response variable and allocation sequence, subjects, period, and treatment as fixed effect.

Source: Table 14.2.1.1.1.1.

Secondary PK Parameters

Descriptive statistics of the PK parameters of the serum drug concentration are summarised in Table 9. There was a difference in mean (standard deviation [SD]) CL/F between treatments (RGB-19: 73.70 [41.88] mL/h; RoActemra: 92.76 [180.59] mL/h). According to the applicant, this can be explained by very high ADA titers for two subjects.

Table 9: Descriptive Statistics of the Secondary Pharmacokinetic Parameters of Serum Drug Concentration (Overall) - PK Analysis Set (n=102)

		Treatment	
		RGB-19 (N=102)	Tocilizumab (RoActemra) (N=102)
AUC_{last} (µg × h/mL)	n	102	102
	Mean (SD)	2582.8 (873.8)	2502.9 (852.2)
	Median	2611.9	2487.1
	Min–Max	465-4617	87-4262
	Geo mean (GCV%)	2412.1 (41.6)	2287.6 (55.2)
AUC_{0-144} (µg × h/mL)	n	102	102
	Mean (SD)	1167.8 (426.6)	1101.0 (369.1)
	Median	1180.1	1102.6
	Min–Max	222-2097	88-1991
	Geo mean (GCV%)	1080.7 (43.9)	1019.5 (47.4)
AUC_{144-t} (µg × h/mL)	n	102	101
	Mean (SD)	1415.0 (541.0)	1415.9 (556.9)
	Median	1371.9	1365.9
	Min–Max	244-2846	28-2742
	Geo mean (GCV%)	1299.6 (46.7)	1263.4 (63.9)
t_{max} (h)	n	102	102
	Mean (SD)	108.305 (29.579)	111.470 (26.760)
	Median	107.500	107.700
	Min–Max	47.57-172.30	48.00-172.63
	Geo mean (GCV%)	–	–
$t_{1/2}$ (h)	n	102	102
	Mean (SD)	33.70 (20.06)	32.98 (17.01)
	Median	29.54	29.41
	Min–Max	22.0-192.7	7.6-182.7
	Geo mean (GCV%)	31.52 (30.6)	31.08 (31.7)

		Treatment	
		RGB-19 (N=102)	Tocilizumab (RoActemra) (N=102)
V_d/F (L)	n	102	102
	Mean (SD)	4.07 (6.24)	4.37 (8.81)
	Median	2.75	2.78
	Min–Max	1.3-51.0	1.6-87.9
	Geo mean (GCV%)	3.05 (63.0)	3.17 (63.1)
CL/F (mL/h)	n	102	102
	Mean (SD)	73.70 (41.88)	92.76 (180.59)
	Median	61.99	65.09
	Min–Max	35.1-346.3	38.0-1846.6
	Geo mean (GCV%)	67.06 (41.5)	70.70 (55.1)
k_{el} (/h)	n	102	102
	Mean (SD)	0.0227 (0.0048)	0.0233 (0.0083)
	Median	0.0235	0.0236
	Min–Max	0.004-0.031	0.004-0.091
	Geo mean (GCV%)	0.0220 (30.6)	0.0223 (31.7)
MRT (h)	n	102	102
	Mean (SD)	171.65 (21.71)	172.39 (26.41)
	Median	172.54	176.89
	Min–Max	130.8-230.9	69.0-226.5
	Geo mean (GCV%)	170.29 (12.7)	170.09 (17.4)
AUC_{last} / AUC_{inf} (%)	n	102	102
	Mean (SD)	99.84 (0.20)	99.83 (0.23)
	Median	99.89	99.89
	Min–Max	98.4-100.0	98.0-100.0
	Geo mean (GCV%)	99.84 (0.2)	99.83 (0.2)

AUC_{0-144} = area under the curve from 0 hours (immediately before administration) to 144 hours after administration; $AUC_{144\,t}$ = area under the curve from 144 hours after administration to the last quantifiable time; AUC_{inf} = area under the curve from 0 hours (immediately before administration) to infinity; AUC_{last} = area under the curve from 0 hours (immediately before administration) to the last quantifiable time; CL/F = apparent total clearance; Geo = geometric; GCV = geometric coefficient of variation; k_{el} = elimination rate constant; MRT = mean residence time; N = number of subjects; n = number of subjects per category; PK = pharmacokinetic; SD = standard deviation; $t_{1/2}$ = elimination half-life; t_{max} = time to maximum serum concentration; V_d/F = volume of distribution

Source: Table 14.2.1.2.1.1.

5.2.2.3. Dose proportionality, time dependency and immunogenicity

Study RGB192101 - PK similarity in healthy subjects

Immunogenicity Analysis Set

The population in the Immunogenicity Analysis Set included subjects who met all of the following criteria:

- Subjects who were administrated at least one (full or partial dose) investigational product
- Subjects who had the pre-dose immunogenicity result and at least one available post-dose immunogenicity assessment

- Subjects with no protocol deviations that could have an impact on immunogenicity results

Immunogenicity Results

- In Period 1 on Day 43, 26 subjects and 23 subjects were ADA positive for RGB-19 and RoActemra, respectively. Combining the results for the two treatment periods (i.e., at Day 43 following administration of either IP in Period 1 or Period 2), the number of ADA positive subjects in RGB-19-treated subjects was 61 compared to 62 in RoActemra-treated subjects. The incidence of ADA positivity was similar for RGB-19 and RoActemra.
- In Period 1 on Day 43, 18 and 16 subjects were NAb positive following administration of RGB-19 or RoActemra, respectively. Combining the results for the two treatment periods (i.e., at Day 43 following administration of either IP in Period 1 or Period 2), the number of NAb positive subjects in RGB-19-treated subjects was 44 compared to 48 in RoActemra-treated subjects. The incidence of NAb positivity was similar for RGB-19 and RoActemra.
- On Day 43 (Period 1) and on Day 85 (Period 2), the median (range) ADA titers were comparable after RoActemra treatment and after RGB-19 treatment (129.0 [10–4480] versus 58.5 [10–20480] in Period 1 and 256.0 [10–139746] versus 229.0 [10–7964] in Period 2). According to the applicant, the higher maximum ADA titer after RGB-19 treatment can be attributed to very high ADA titers in two subjects.

Table 10: Summary of Immunogenicity by Time Point and Period - Immunogenicity Analysis Set (n=110)

Parameter	Finding	Period 1					
		Day 1 pre-IP		Day 13		Day 43	
		RGB-19 n/N (%) (Sequence A)	Tocilizumab (RoActemra) n/N (%) (Sequence B)	RGB-19 n/N (%) (Sequence A)	Tocilizumab (RoActemra) n/N (%) (Sequence B)	RGB-19 n/N (%) (Sequence A)	Tocilizumab (RoActemra) n/N (%) (Sequence B)
ADA	Positive	2/55 (3.6)	2/55 (3.6)	2/53 (3.8)	7/55 (12.7)	26/52 (50.0)	23/53 (43.4)
	Negative	53/55 (96.4)	53/55 (96.4)	51/53 (96.2)	48/55 (87.3)	26/52 (50.0)	30/53 (56.6)
NAb	Positive	0/2 (0.0)	0/2 (0.0)	1/2 (50.0)	5/7 (71.4)	18/26 (69.2)	16/23 (69.6)
	Negative	2/2 (100.0)	2/2 (100.0)	1/2 (50.0)	2/7 (28.6)	8/26 (30.8)	7/23 (30.4)
		Period 2					
		Day 43 pre-IP		Day 55		Day 85	
		RGB-19 n/N (%) (Sequence B)	Tocilizumab (RoActemra) n/N (%) (Sequence A)	RGB-19 n/N (%) (Sequence B)	Tocilizumab (RoActemra) n/N (%) (Sequence A)	RGB-19 n/N (%) (Sequence B)	Tocilizumab (RoActemra) n/N (%) (Sequence A)
ADA	Positive	23/53 (43.4)	26/52 (50.0)	23/53 (43.4)	28/49 (57.1)	35/53 (66.0)	39/49 (79.6)
	Negative	30/53 (56.6)	26/52 (50.0)	30/53 (56.6)	21/49 (42.9)	18/53 (34.0)	10/49 (20.4)
NAb	Positive	16/23 (69.6)	18/26 (69.2)	21/23 (91.3)	26/28 (92.9)	26/35 (74.3)	32/39 (82.1)
	Negative	7/23 (30.4)	8/26 (30.8)	2/23 (8.7)	2/28 (7.1)	9/35 (25.7)	7/39 (17.9)

ADA = antidrug antibody; IP = investigational product; N = number of subjects; n = number of cases; NAb = neutralizing antibody
Sequence A: RGB-19 on Day 1 followed by tocilizumab (RoActemra) on Day 43; Sequence B: tocilizumab (RoActemra) on Day 1 followed by RGB-19 on Day 43.
Source: Table 14.3.10.1.1.

Impact of ADA on PK

Subgroup analysis for Primary PK Parameters

To consider the impact of ADA occurrences on the primary PK endpoints of each treatment, analyses were performed for subjects from the PK Analysis Set who had a negative ADA test (ADA negative subjects) post investigational product administration (i.e., all available results at Days 13, 43, 55, and 85). If at least one ADA test result was positive at post administration (i.e., at Days 13, 43, 55, or 85), the subject was considered ADA-positive.

Descriptive statistics of the primary PK parameters for ADA positive/negative subjects are summarised in Table 11 (at post administration). The PK parameters C_{max} and AUC_{inf} geometric means (GCV%) were similar between ADA subgroups for both treatments, indicating that ADA status did not impact C_{max} and AUC_{inf} regardless of treatment.

Table 11: Descriptive Statistics of the Primary Pharmacokinetic Parameters of Serum Drug Concentration (Overall) - PK Analysis Set, ADA Positive/Negative at Post Administration (n=102)

		Treatment			
		RGB-19 (N=102)		Tocilizumab (RoActemra) (N=102)	
		Positive	Negative	Positive	Negative
C_{max} (µg/mL)	n	80	22	80	22
	Mean (SD)	10.94 (3.41)	11.72 (3.76)	10.76 (3.07)	10.18 (3.48)
	Median	11.20	11.25	11.00	9.20
	Min–Max	2.6-18.1	6.4-19.7	1.4-17.8	2.8-16.3
	Geo mean (GCV%)	10.33 (37.4)	11.16 (33.1)	10.19 (38.3)	9.52 (41.6)
AUC_{inf} (µg × h/mL)	n	80	22	80	22
	Mean (SD)	2499.1 (850.1)	2904.3 (909.4)	2506.4 (829.3)	2507.8 (957.7)
	Median	2501.1	2904.7	2647.9	2355.6
	Min–Max	468-4619	1213-4534	88-4266	594-3882
	Geo mean (GCV%)	2330.8 (42.3)	2752.6 (36.1)	2289.1 (57.1)	2300.4 (48.4)

ADA = antidrug antibody; AUC_{inf} = area under the curve from 0 hours to infinity; C_{max} = maximum serum drug concentration; Geo = geometric; GCV = geometric coefficient of variation; N = number of subjects; n = number of subjects per category; PK = pharmacokinetic; SD = standard deviation

Notes: If at least one ADA test result was positive at Days 13, 43, 55, or 85, the subject was included in the "positive" group; otherwise, if all available results were negative at Days 13, 43, 55, and 85, the subject was included in the "negative" group.

Source: Table 14.2.1.2.2.2.

Two-sided 90% CIs for the mean difference of the primary PK parameters of serum drug concentration for ADA negative subjects are presented in Table 12.

As per the equivalence criteria of 0.80 to 1.25, 90% CIs of GMRs for C_{max} and AUC_{inf} for ADA negative subjects were also within these limits.

Table 12: Two-Sided 90% Confidence Interval for the Mean Difference of the Primary Pharmacokinetic Parameters of Serum Drug Concentration - PK Analysis Set, ADA Negative at Post Administration (n=22)

	LS mean [a]		Difference in LS means [a b] (N=22)		Geometric LS mean [c]		GMR [d] (N=22)	
	RGB-19 (N=22)	Tocilizumab (RoActemra) (N=22)	Point estimate	Two-sided 90% CI	RGB-19 (N=22)	Tocilizumab (RoActemra) (N=22)	Point estimate	Two-sided 90% CI
C_{max} (μg/mL)	2.420	2.335	0.085	-0.048 ～ 0.219	11.24	10.32	1.0891	0.9531 ～ 1.2445
AUC_{inf} (μg × h/mL)	7.896	7.818	0.079	-0.060 ～ 0.217	2687.8	2484.6	1.0818	0.9420 ～ 1.2424

ADA = antidrug antibodies; ANOVA = analysis of variance; AUC_{inf} = area under the curve from 0 hours to infinity; CI = confidence interval; C_{max} = maximum serum drug concentration; GMR = geometric mean ratio; LS = least square; PK pharmacokinetic

a. Natural log-transformed value

b. Difference in LS means = (LS mean in RGB-19) - (LS mean in Tocilizumab [RoActemra])

c. Geometric LS mean= exp{ LS mean (log-transformed scale) }

d. GMR = exp{ Difference in LS mean (log-transformed scale) }

Notes: Using the ANOVA model with PK parameter (natural log-transformed) as response variable and allocation sequence, subjects, period, and treatment as fixed effect.

If all ADA test results were negative at Days 13, 43, 55, and 85, the subject was included in the "negative" group.

Source: Table 14.2.1.1.4.2.

Study RGB19101 in patients with active rheumatoid arthritis

Immunogenicity Results

Table 13: Number and percentage of patients with ADA / NAb in study from baseline to Week 24 (Study RGB19101)

Statistic	RGB-19 (N = 182)		RoActemra (N = 186)	
	Patient n	(Patient %)	Patient n	Patient %
Pre-treatment (baseline)				
Patients with ADA result	182	(100.0)	186	(100.0)
ADA Positive	12	(6.6)	12	(6.5)
ADA Negative	170	(93.4)	174	(93.5)
Missing	0		0	
NAb Positive	2	(1.1)	2	(1.1)
NAb Negative	10	(5.5)	10	(5.4)
Post-dose Week 2 to Week 24				
Patients with result	182	(100.0)	186	(100.0)
ADA Positive ≥ 1 time-point up to Week 24[a]	4	(2.2)	6	(3.2)
ADA Negative [b]	178	(97.8)	180	(96.8)
Missing	0		0	
NAb Positive ≥ 1 time-point up to Week 24[a]	5	(2.7)	7	(3.8)
NAb Negative	0		1	(0.5)

ADA=anti-drug antibody; NAb=neutralising antibody

N=total number of subjects in analysis set and treatment group

n=number of subjects within the specified category or total number of subjects pre-dose/ post-dose

%=(number of subjects within the specified category / total number of subjects pre-dose/ post-dose)*100

[a] For subjects with positive baseline, positive at a post-baseline timepoint up to Week 24 with a significant titer increase

[b] ADA negative includes all subjects with a ADA negative result post-baseline. Subjects with a positive ADA baseline and post-baseline result but no significant titer increase are not included in the ADA negative count, as these subjects have NAb results available post-baseline.

Source: Table 2.1.1 & Table 2.1.2 in TLFs for ISI SAP

Impact of ADA on PK

Descriptive statistics for serum drug concentrations over time, by ADA status, are summarised in Table 14. The ADA status did not appear to impact the serum drug concentration profile for either investigational product.

Data from baseline to week 52 have been submitted during the evaluation phase, and the results show generally similar profiles regardless of ADA status or treatment group.

Table 14: Descriptive Statistics of Serum Drug Concentration Subgroup by ADA Status - (Positive or Negative Post-administration) - PK Analysis Set

Test items	ADA Positive/Negative at post administration	Assessment time point	Treatment group	N	Mean (SD)	Min, Max	Median
Serum Drug Concentration (µg/mL)	Negative	Baseline	RGB-19	177	0	0	0
			Tocilizumab (RoActemra)	177	0	0	0
		Week 2	RGB-19	177	28.526 (7.829)	5.15, 53.20	28.100
			Tocilizumab (RoActemra)	177	25.368 (7.697)	5.50, 53.60	24.800
		Week 4	RGB-19	172	7.605 (5.263)	0.06, 26.30	7.650
			Tocilizumab (RoActemra)	170	5.594 (3.901)	0.03, 19.20	5.250
		Week 12	RGB-19	168	14.936 (9.128)	0.05, 43.60	14.300
			Tocilizumab (RoActemra)	168	11.894 (7.987)	0.04, 56.60	10.850
		Week 24	RGB-19	164	17.779 (11.091)	0.06, 69.60	16.600
			Tocilizumab (RoActemra)	162	15.518 (10.685)	0.03, 76.30	13.500
		EOT24	RGB-19	175	17.509 (11.034)	0.06, 69.60	16.100
			Tocilizumab (RoActemra)	173	15.099 (10.531)	0.03, 76.30	13.000
Serum Drug Concentration (µg/mL)	Positive	Baseline	RGB-19	5	0	0	0
			Tocilizumab (RoActemra)	9	0	0	0
		Week 2	RGB-19	5	27.440 (6.053)	17.80, 32.90	28.200
			Tocilizumab (RoActemra)	9	23.978 (7.044)	13.40, 33.30	26.600
		Week 4	RGB-19	5	7.798 (4.787)	0.27, 13.10	9.020
			Tocilizumab (RoActemra)	9	3.948 (3.224)	0.20, 9.13	3.970
		Week 12	RGB-19	4	11.665 (9.869)	1.81, 22.20	11.325
			Tocilizumab (RoActemra)	7	10.431 (4.877)	4.13, 19.50	10.000
		Week 24	RGB-19	4	17.353 (7.935)	6.61, 25.40	18.700
			Tocilizumab (RoActemra)	6	12.267 (5.992)	5.56, 20.60	11.130
		EOT24	RGB-19	5	16.502 (7.131)	6.61, 25.40	17.100
			Tocilizumab (RoActemra)	8	10.038 (6.746)	0.20, 20.60	8.470

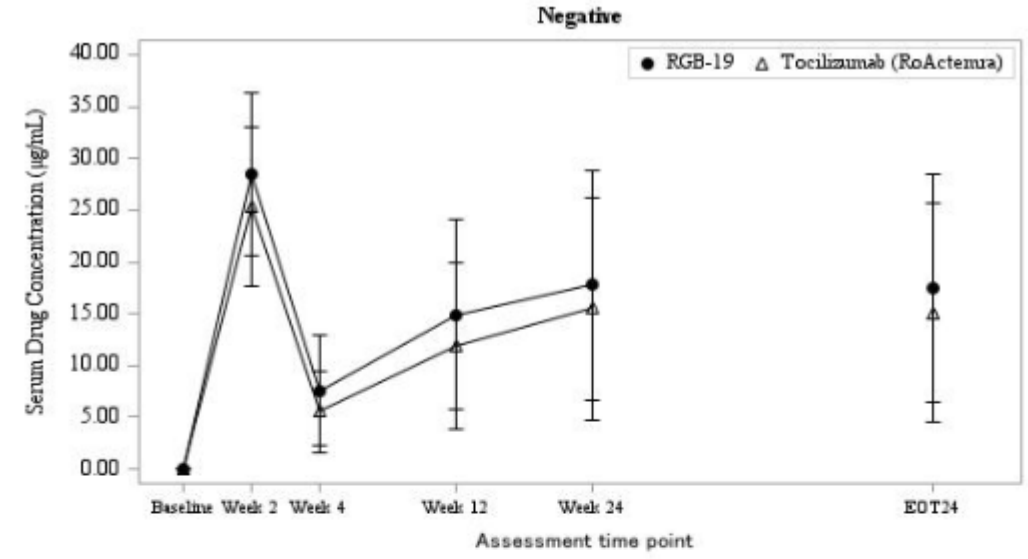
EOT24 = end of treatment at Week 24; IP = investigational product; Max = maximum; Min = minimum; N = number of subjects; OC = observed cases; SD = standard deviation

Imputation method: OC.

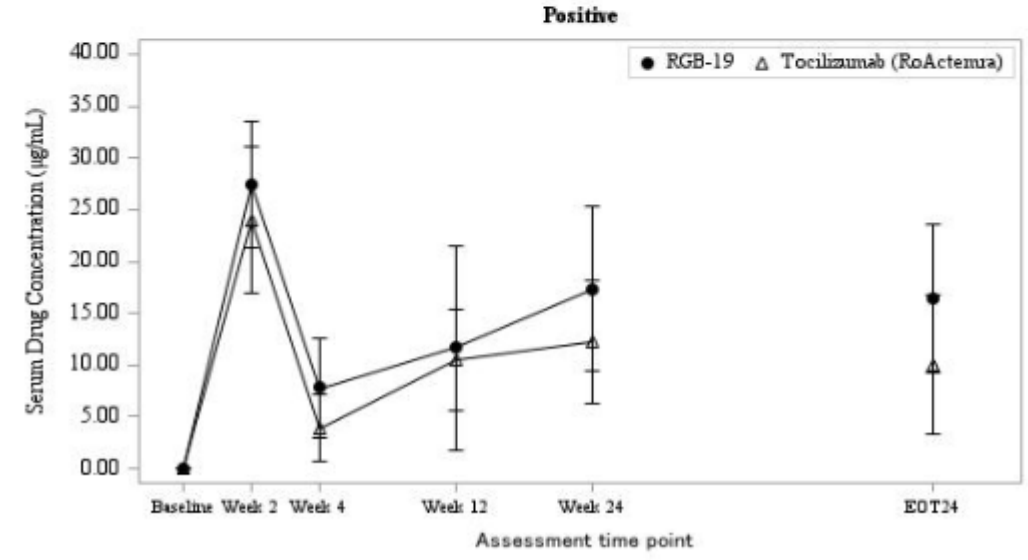
All available test results collected on or before the date when the last subject completed the assessments at Week 24 (14 May 2024) were used for the classification of ADA status. One subject in the Tocilizumab (RoActemra) treatment group was ADA positive for the first time after Week 24.

Source: Table 14.4.1.1.2.

Figure 2: Profiles of Serum Drug Concentration - ADA Positive/Negative at post-administration - PK analysis set



RGB-19	177	177	172	168	164	175
Tocilizumab (RoActemra)	177	177	170	168	162	173



RGB-19	5	5	5	4	4	5
Tocilizumab (RoActemra)	9	9	9	7	6	8

5.2.2.4. Pharmacokinetics in the target population

Study RGB19101 in patients with active rheumatoid arthritis

Study Title: RGB-19 Phase III clinical study A randomized, double-blind, multicenter Phase III study to assess the efficacy and safety of RGB-19 compared to RoActemra in patients with active Rheumatoid Arthritis (RA).

Study Period

Study site: The study was conducted at 81 study sites in Japan.

First Subject First Visit (FSFV): 16-Jan-2023. Last Subject Last Visit (LSLV [Week 24]): 14-May-2024.

Secondary Objectives

Secondary objectives included to investigate the safety profile, including immunogenicity, between RGB-19 and RoActemra and to evaluate serum drug concentrations for RGB-19 and RoActemra.

Methods

In total, it was planned to randomly assign 358 subjects (male and female) with active RA in a 1:1 ratio (179 subjects per group) to either 8 mg/kg intravenous (IV) drip infusion RGB-19 or 8 mg/kg IV drip infusion RoActemra (active control) once every 4 weeks.

Blood samples to measure serum concentrations of IP were collected before IP administration at time points: serum drug concentration at Week 2, 4, 12, 24, 36, and 52 after the first administration of IP.

Duration of treatment was 52 weeks (24 weeks for the CSR submission at time of initial MAA). The 52 week data were submitted during the evaluation phase.

Investigational Products

RGB-19 and Tocilizumab (RoActemra)

Pharmacokinetic Results

Mean values of serum drug concentration were plotted for changes over time (0 hours [baseline; before IP administration] and Weeks 2, 4, 12, and 24, end of treatment [at Week 24 or the time of discontinuation of IP before Week 24 (EOT24) and Week 52 or at the time of discontinuation of IP (EOT52)]) by treatment.

Descriptive statistics for serum drug concentrations over time are summarised for the PK analysis set.

The time course of mean (SD) serum drug concentrations for both investigational products was similar. The maximum mean (SD) serum drug concentration was observed at Week 2, which was the only measured timepoint 2 weeks after investigational product administration through the study. After Week 2, the trough serum drug concentrations increased until reaching the steady state. The mean (SD) serum concentrations were higher at all time points for the RGB-19 group than for the RoActemra group. Up to Week 24, serum drug concentrations for both investigational products followed a similar time course. Data up to week 52 also followed a similar trend.

Table 15: Descriptive Statistics of Serum Drug Concentration - PK Analysis Set

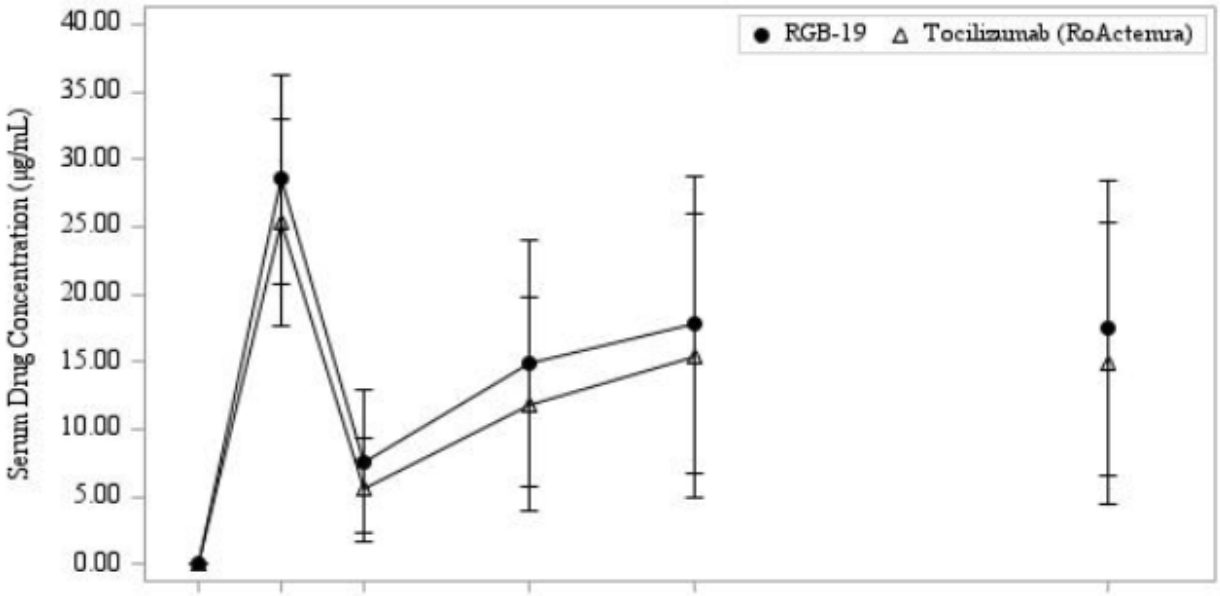
Test items	Assessment time point	Treatment group	N	Mean (SD)	Min, Max	Median
Serum Drug Concentration (µg/mL)	Baseline	RGB-19	182	0	0	0
		Tocilizumab (RoActemra)	186	0	0	0
	Week 2	RGB-19	182	28.496 (7.775)	5.15, 53.20	28.100
		Tocilizumab (RoActemra)	186	25.301 (7.655)	5.50, 53.60	24.900
	Week 4	RGB-19	177	7.610 (5.238)	0.06, 26.30	7.650
		Tocilizumab (RoActemra)	179	5.512 (3.879)	0.03, 19.20	5.240
	Week 12	RGB-19	172	14.859 (9.128)	0.05, 43.60	14.300
		Tocilizumab (RoActemra)	175	11.835 (7.882)	0.04, 56.60	10.800
	Week 24	RGB-19	168	17.769 (11.009)	0.06, 69.60	16.700
		Tocilizumab (RoActemra)	168	15.402 (10.560)	0.03, 76.30	13.500
	EOT24	RGB-19	180	17.481 (10.932)	0.06, 69.60	16.150
		Tocilizumab (RoActemra)	181	14.876 (10.432)	0.03, 76.30	12.800

EOT24 = end of treatment at Week 24; Max = maximum; Min = minimum; N = number of subjects; OC = observed cases; SD = standard deviation

Imputation method: OC.

Source: Table 14.4.1.1.1.

Figure 3: Profiles of Serum Drug Concentration - PK analysis set



RGB-19	182	182	177	172	168	180
Tocilizumab (RoActemra)	186	186	179	175	168	181

5.2.2.5. Special populations

Not relevant for biosimilars.

5.2.2.6. Pharmacokinetic interaction studies

Not relevant for biosimilars.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Tocilizumab is a recombinant humanised monoclonal antibody of the IgG1 subclass. It binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit mIL-6R- as well as sIL-6R-mediated signaling (i.e. the classical and the trans signaling pathway). In the classical pathway, IL-6 binds to its mIL-6R present in the cell surface of mainly immunogenic cells. The complex binds with signaling transducer molecule glycoprotein 130 dimer (gp-130). This complex then transduces the signaling pathway through Janus kinases-signal transducer and activator of transcription pathway (JAK-STAT) or mitogen-activated protein kinase/nuclear factor 'kappa-light-chain-enhancer' of activated B-cells (MAPK/NF-kB)-IL-6 pathway, which activates different kinds of inflammatory effects in the innate immune system (Natural killer [NK] cells, neutrophils and macrophages) as well as acquired immune system (B and T cells). Via the trans signaling pathway, IL-6 can activate a pro-inflammatory effect via its sIL-6R and gp-130 present on virtually all cell surfaces,

specifically different kinds of endothelial cells. The trans signaling pathway can induce a marked pro-inflammatory response in possibly every type of cells. The binding of tocilizumab to the receptor prevents receptor binding to IL-6. The tocilizumab/receptor complex cannot be bioactive since it is unable to effect the dimerization of the gp-130 molecule. In the absence of this dimerization, the IL-6 signal is completely blocked.

IL-6 is produced by a variety of cell types involved in local paracrine function as well as regulation of systemic physiological and pathological processes. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 has been implicated in the pathogenesis of inflammatory diseases. The cytokine is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis.

5.2.3.2. Primary and secondary pharmacology

Comparative assessment based on in vivo pharmacodynamics in healthy volunteers

PD endpoints were the observed values and changes from baseline at each measurement timepoint and area under the effect-time curve (AUEC) for the following PD parameters: Absolute neutrophil count (ANC), high-sensitivity C-Reactive Protein (hsCRP), and sIL-6R.

The measurement values and change from baseline (before IP administration in each period) at each time point were summarized by treatment and the AUEC of each parameter was also summarized.

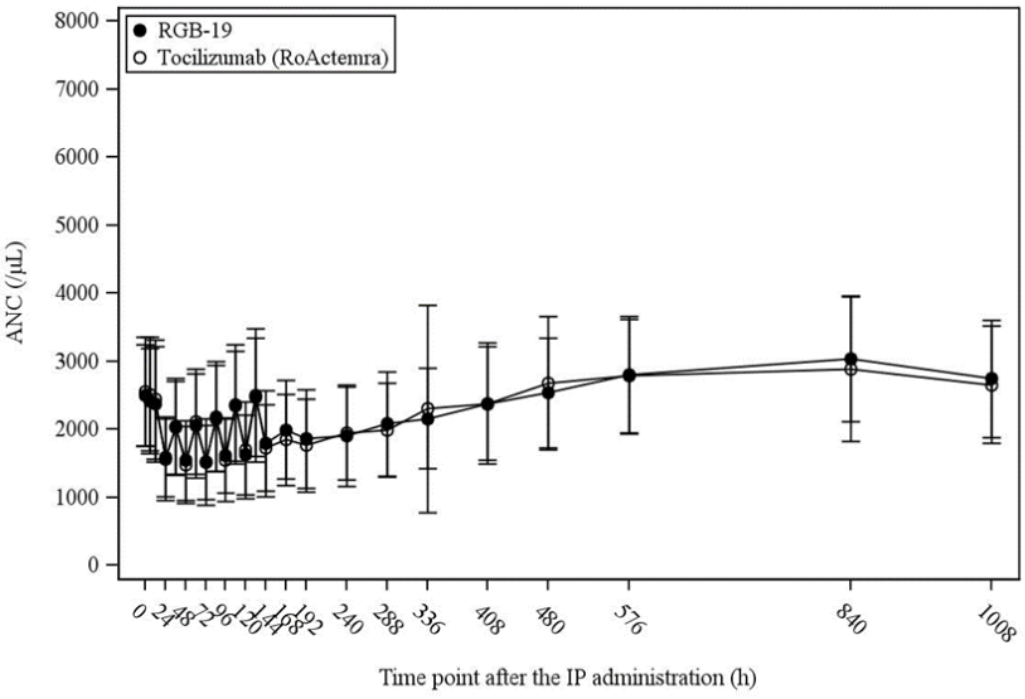
Table 16: Descriptive Statistics of Pharmacodynamic Parameters by Period – Pharmacodynamic Analysis Set (N=102)

Period		Treatment	
		RGB-19 (N=102)	Tocilizumab (RoActemra) (N=102)
Overall			
ANC AUEC (h/µL)	n	102	102
	Mean (SD)	-9688.0 (671552.0)	-96000.3 (781791.5)
	Median	47738.5	-43774.6
	Min–Max	-3580430-1181313	-3293483-1995680
hsCRP AUEC (mg × h/dL)	n	102	102
	Mean (SD)	-51.8 (529.7)	-44.5 (205.4)
	Median	-5.8	-8.0
	Min–Max	-5307-361	-1211-446
sIL-6R AUEC (ng × h/mL)	n	102	102
	Mean (SD)	71410.9 (18750.4)	70303.2 (23085.2)
	Median	69190.8	68852.5
	Min–Max	22897-126130	-3814-144452
Period 1			
ANC AUEC (h/µL)	n	49	53
	Mean (SD)	-43238.2 (770120.4)	-160678.8 (790550.9)
	Median	109501.9	-104598.1
	Min–Max	-3580430-1084621	-3054736-1995680
hsCRP AUEC (mg × h/dL)	n	49	53
	Mean (SD)	-12.5 (53.1)	-68.6 (259.7)
	Median	-5.4	-8.7
	Min–Max	-230-118	-1211-446
sIL-6R AUEC (ng × h/mL)	n	49	53
	Mean (SD)	66937.8 (16150.9)	74023.3 (21426.9)
	Median	64494.8	71825.7
	Min–Max	22897-112644	39888-144452
Period 2			
ANC AUEC (h/µL)	n	53	49
	Mean (SD)	21330.2 (571350.3)	-26041.9 (774206.3)
	Median	39225.1	42206.2
	Min–Max	-1968097-1181313	-3293483-1739094
hsCRP AUEC (mg × h/dL)	n	53	49
	Mean (SD)	-88.1 (734.5)	-18.5 (120.1)
	Median	-6.4	-7.4
	Min–Max	-5307-361	-600-394
sIL-6R AUEC (ng × h/mL)	n	53	49
	Mean (SD)	75546.5 (20144.5)	66279.4 (24334.9)
	Median	76218.9	66793.9
	Min–Max	30266-126130	-3814-120684

AUEC = area under the effect-time curve; ANC = absolute neutrophil count; hsCRP = high-sensitivity C-reactive protein; N = number of subjects; n = number of subjects per category; PD = pharmacodynamics; SD = standard deviation; sIL-6R = soluble interleukin-6 receptor
Source: Table 14.2.2.2.1.1.

Overall, the mean (SD) ANC AUEC with tocilizumab treatment was -96000.3 (781791.5) h/µL versus -9 688 (671552.0) h/µL forRGB-19 treatment. The lower ANC might result in higher susceptibility of infections; however, according to the applicant, despite the apparent differences in mean and SD between treatments, neither the number and severity of AEs in infectious disease category nor the trends in the respective clinical laboratory values showed any clinically meaningful differences.

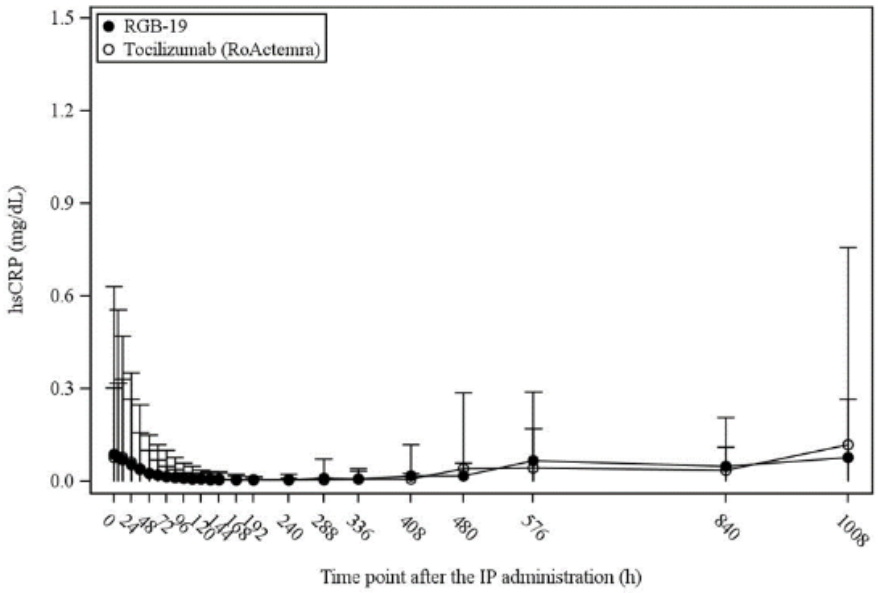
Figure 4: GB-19 and Tocilizumab (RoActemra) Absolute Neutrophil Count [/μL] – mean ± SD PD Analysis set



ANC = absolute neutrophil count

No meaningful difference was observed for hsCRP AUEC. The mean (SD) value was -51.8 [529.7] mg × h/dL with RGB-19 treatment compared with -44.5 [205.4] mg × h/dL with tocilizumab treatment.

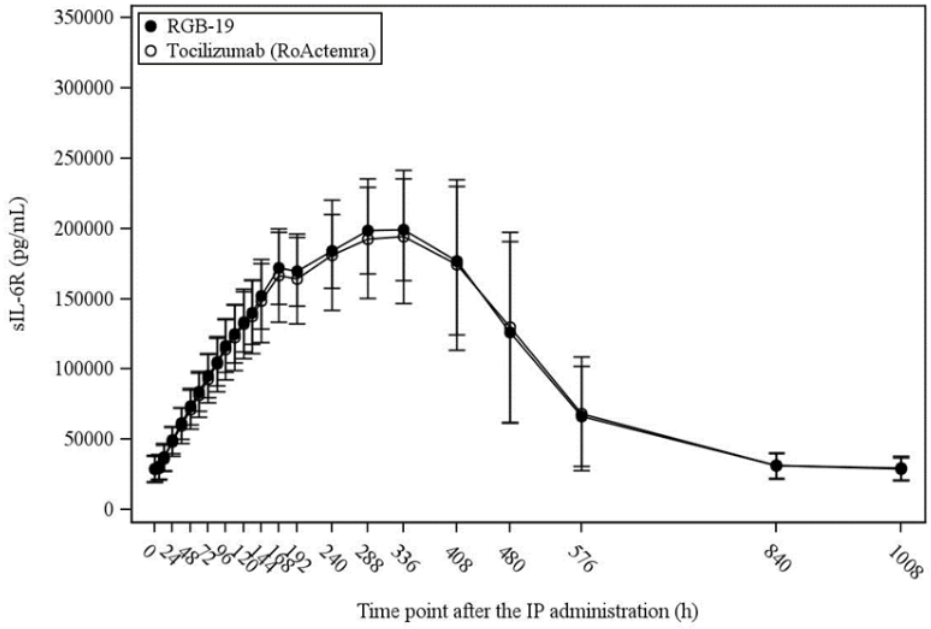
Figure 5: RGB-19 and Tocilizumab (RoActemra) high-sensitivity C-reactive Protein [mg/dL] – mean ± SD PD Analysis Set



hsCRP = high-sensitivity C-reactive protein

The mean (SD) sIL-6R AUEC values were similar between treatments with a value of 71410.9 (18750.0) pg × h/mL for RGB-19 versus 70303.2 (23085.2) pg × h/mL for tocilizumab. The pattern over time for this parameter is given in the Figure 6 below.

Figure 6: Mean (± SD) sIL-6R concentration-time profiles (linear scale; PKS)



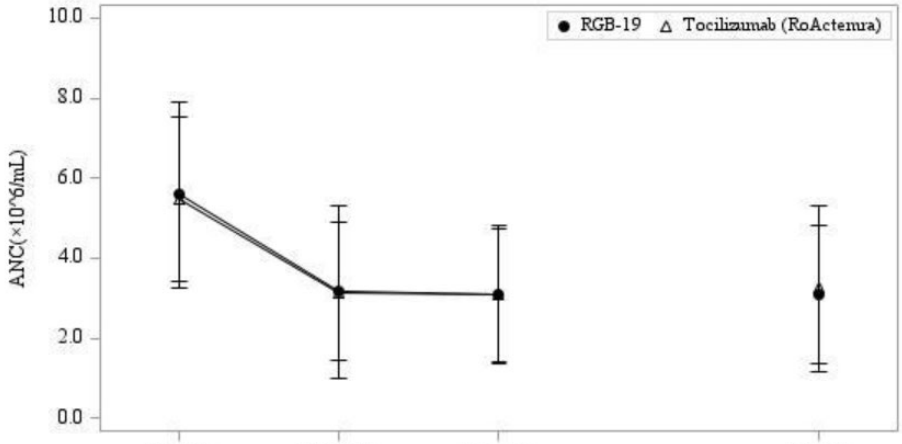
sIL-6R = soluble interleukin-6 receptor

The concentration-time profiles are reported to be very similar. According to the applicant, the increase in sIL-6R levels with tocilizumab exposure is believed to be a consequence of the binding of tocilizumab to the receptor and the accumulation of sIL-6R in serum with increasing tocilizumab exposure probably reflects the slow clearance of the tocilizumab/sIL-6R complex.

Comparative assessment based on in vivo pharmacodynamics in patients with active rheumatoid arthritis

The evaluation of the PD parameters ANC, CRP, and sIL-6R over time is presented in the figures below.

Figure 7: Mean (± SD) of ANC profiles (PD analysis set)



RGB-19	180	175	170	180
Tocilizumab (RoActemra)	185	181	172	185

EOT end of treatment; EOT24 end of treatment Week 24

Figure 8: Mean (± SD) CRP profiles (PD analysis set)

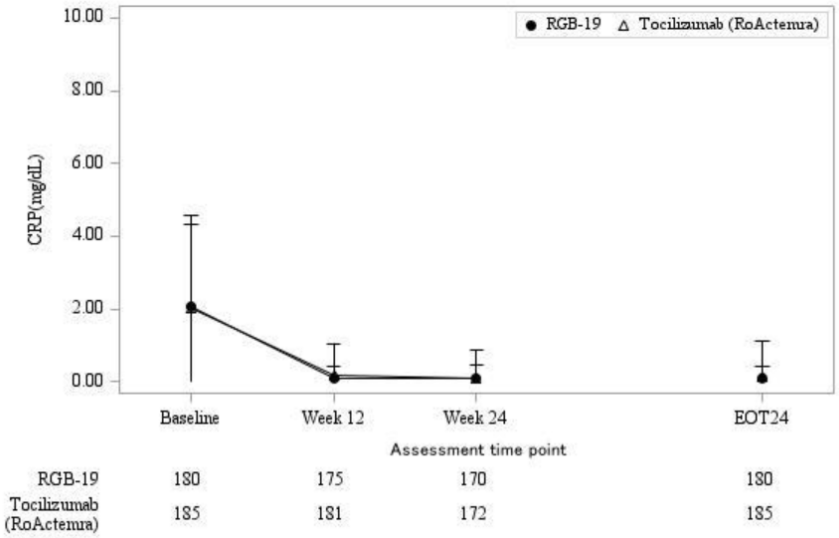
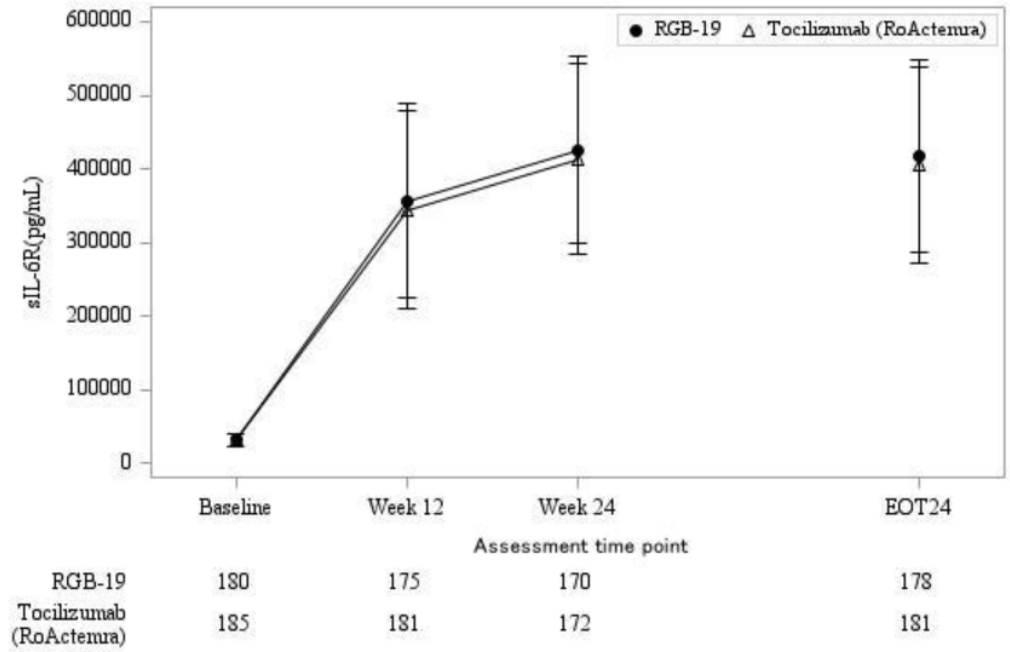


Figure 9: Mean (± SD) sIL-6R concentration-time profiles (PD analysis set)



5.2.3.3. Immunological events

Impact of ADA on PD (sIL6-R) in Study RGB192101

The relationship of the PD parameter, area under the effect vs. time curve (AUEC) for sIL-6R, to ADA negative/positive status for each treatment group in each study period is summarised in the Table 17 and Figure 10 below. Mean values are shown with 95% confidence interval to indicate variability of the data in each category.

Table 17: Area under effect vs. time curve (AUEC) for sIL-6R by ADA category and treatment group in Period 1 and Period 2 of Study RGB192101 – PDS

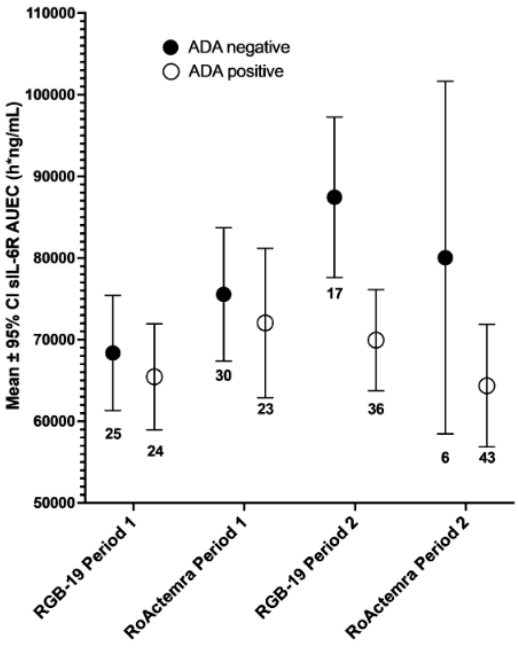
Parameter	Statistic	RGB-19	RoActemra
Period 1: ADA positive subgroup			
sIL-6R AUEC (h*ng/mL)	n Mean 95% CI mean	24 65443 58962 - 71924	23 72055 62897 - 81212
Period 1: ADA negative subgroup			
sIL-6R AUEC (h*ng/mL)	n Mean 95% CI mean	25 68373 61325 - 75421	30 75533 67372 - 83693
Period 2: ADA positive subgroup			
sIL-6R AUEC (h*ng/mL)	n Mean 95% CI mean	36 69932 63744 - 76121	43 64359 56849 - 71870
Period 2: ADA negative subgroup			
sIL-6R AUEC (h*ng/mL)	n Mean 95% CI mean	17 87435 77599 - 97272	6 80039 58446 - 101632

ADA=anti-drug antibody; AUEC=area under effect vs. time curve; CI=confidence interval; sIL-6R=soluble interleukin-6 receptor

n = number of subjects with titre assessment at the respective visit

Source: Phase 1 ISI Tables [Unblinded Results], v02 Final, 22-Jul-2024, Table 1.3.1

Figure 10: Mean ± 95% CI sIL-6R by ADA status, treatment group and period in Study RGB192101 – PDS



ADA=anti-drug antibody; AUEC=area under effect vs. time curve; CI=confidence interval; sIL-6R=soluble interleukin-6 receptor

The value under each error bar indicates the number of subjects in each category

Source: Phase 1 ISI Tables [Unblinded Results], v02 Final, 22-Jul-2024, Table 1.3.1

In Period 1, the mean ± 95% CI sIL-6R for the different ADA categories and treatment groups were substantially overlapping, and in line with the results from the PK parameters. In Period 2, the mean sIL-6R AUEC values for the ADA positive subgroup were lower than those for the ADA negative

subgroups in both treatment groups. According to the applicant, this difference was also observed for the serum concentration at day 55, indicating that a higher ADA/Nab incidence may have reduced the PD response in period 2. However, the magnitude of the difference seems to be of a similar magnitude for RGB-19- and RoActemra-treated subjects. Thus, there was no apparent treatment-related difference in the relationship of the sIL-6R response associated with either ADA negative or ADA positive status in either study period.

Relationship of ADA/NAb response to efficacy

Analysis of the change in DAS28-ESR from baseline at Week 12 and Week 24 did not reveal differences in efficacy related to either ADA or NAb status, or to the treatment group, see tables below.

Table 18: Change in DAS28-ESR from baseline by visit and ADA status in Study RGB19101 – FAS

		RGB-19 (N=182)		RoActemra (N=186)	
Week	**Category**	**ADA Positive (N=4)**	**ADA Negative (N=178)**	**ADA Positive (N=6)**	**ADA Negative (N=180)**
12	n	3	176	6	177
	Mean	-4.35	-3.66	-3.74	-3.39
	95% CI mean	-5.62 - -3.08	-3.85 - -3.48	-5.61 - -1.87	-3.57 - -3.22
	Median	-4.47	-3.63	-3.51	-3.44
	Min/Max	-4.8/-3.8	-7.4/-0.4	-6.6/-1.2	-6.9/2.3
24	n	3	166	4	168
	Mean	-4.57	-4.06	-4.11	-3.84
	95% CI mean	-5.89 - -3.25	-4.24 - -3.87	-7.19 - -1.04	-4.01 - -3.67
	Median	-4.85	-4.12	-3.21	-3.93
	Min/Max	-4.9/-4.0	-7.3/-0.3	-7.0/-3.0	-7.1/-0.4

ADA=anti-drug antibody; CI=Confidence Interval; DAS=disease activity score; ESR=erythrocyte sedimentation rate; Min=minimum; Max=maximum

N=number of subjects within the analysis set and treatment group at the visit of interest

n=number of subjects with non-missing values at the respective visit

Source: Table 2.3.1 in TLFs for ISI SAP

Table 19: Change in DAS28-ESR from baseline by visit and NAb status in Study RGB19101 – FAS

		RGB-19 (N=182)		RoActemra (N=186)	
Week	**Category**	**NAb Positive (N=5)**	**NAb Negative (N=177)**	**NAb Positive (N=7)**	**NAb Negative (N=179)**
12	n	4	175	7	176
	Mean	-4.09	-3.67	-3.11	-3.42
	95% CI mean	-5.15 - -3.03	-3.85 - -3.49	-4.78 - -1.44	-3.59 - -3.24
	Median	-4.13	-3.63	-3.20	-3.45
	Min/Max	-4.8/-3.3	-7.4/-0.4	-6.6/-1.2	-6.9/2.3
24	n	4	165	5	167
	Mean	-4.14	-4.06	-3.86	-3.85
	95% CI mean	-5.67 - -2.61	-4.25 - -3.88	-6.05 - -1.66	-4.02 - -3.68
	Median	-4.40	-4.13	-3.18	-3.93
	Min/Max	-4.9/-2.9	-7.3/-0.3	-7.0/-2.8	-7.1/-0.4

CI=Confidence Interval; DAS=disease activity score; ESR=erythrocyte sedimentation rate; Mi =minimum; Max=maximum; NAb=neutralising antibody

N=number of subjects within the analysis set and treatment group at the visit of interest

n=number of subjects with non-missing values at the respective visit

Source: Table 2.3.2 in TLFs for ISI SAP

5.2.4. Overall discussion and conclusions on clinical pharmacology

5.2.4.1. Discussion

Clinical studies:

The pharmacokinetics of RGB-19 was investigated in two clinical studies: one pivotal PK study in healthy subjects [study RGB192101] and one clinical study in patients with active rheumatoid arthritis [study RGB19101]. In study RGB192101, subjects received a single subcutaneous (upper arm) injection of either RGB-19 162 mg or RoActemra 162 mg. In study RGB19101, patients were administered 8 mg/kg intravenous (IV) drip infusion of RGB-19 or RoActemra (active control) once every 4 weeks. The duration of treatment was 52 weeks.

The clinical studies were performed in accordance with GCP as claimed by the applicant. No issues regarding GCP have been identified.

In the comparative PK study (RGB192101) tocilizumab was administered using the Pre-Filled Syringe with Needle Safety Device (PFS-NSD). In a scientific advice (SA) procedure given by EMA (EMA/SA/0000157362), it was concluded that referring to the provided information on the formulation and manufacturing of both PFS-NSD and AutoInjector (AI) presentations of biosimilar drug product for subcutaneous delivery, it could be expected that PK and related clinical performance after delivery of biosimilar using both presentations would be bioequivalent. Injection angle, injection depth, and injection time might differ between injections using the PFS-NSD or AI (a more consistent injection procedure can be expected for the AI). Published results for the reference product RoActemra show bioequivalence between administration of tocilizumab via PFS-NSD and the same PFS in the ACTPen AI[1]. A justification has been provided supporting the conclusion that any differences between the biosimilar PFS-NSD and PFS-AI presentations are not expected to impact PK. The justification included an assessment of the drug product, the container closure system, and the device design and delivery performance, and the potential PK impact of these elements. Both presentations contain the same drug product formulation, produced using the same manufacturing processes and the same manufacturing line, and are intended to deliver the same nominal dose (strength and volume) to the patient. Both presentations use the same container closure system, including identical needle gauge and length. The same injection site is used for both presentations. Reference is also made to the analytical comparability study. The justification is considered acceptable, and no additional comparative PK study is needed.

Bioanalytical methods:

Bioanalytical assays were developed and validated for the determination of tocilizumab serum concentration (PK), determination of sIL-6R (soluble Interleukin-6 receptor) serum concentration (PD), detection of anti-tocilizumab antibodies (ADA) and neutralising anti-tocilizumab antibodies (NAb) from serum samples. Overall, the performance of the analytical methods is acceptable, and the methods can be considered adequately validated for the intended purpose. Validation reports and bioanalytical reports including ISR were provided. For the PK assay, long-term stability data covering the storage period and conditions in study RGB19101 (232 days at -80°C) have been provided.

Pharmacokinetics:

Study RGB192101 – PK similarity in healthy subjects

This study was a Phase I, randomised, double-blind, 2-treatment, 2-period, 2-sequence crossover study to compare the PK, PD, and safety of a single subcutaneous dose of RGB-19 and RoActemra

[1] (Fettner *et al*., 2019)

162 mg in healthy Japanese male volunteers.

The primary objective was to demonstrate PK equivalence of RGB-19 and RoActemra after a single 162 mg subcutaneous injection in healthy subjects.

A crossover design was selected following the Japanese Ministry of Health, Labour and Welfare Guideline on Follow-On Biologics (MHLW, February 2020). Compared to a parallel design, a crossover design reduces the influence of inter-subject covariates, as subjects themselves act as a control group. Moreover, the number of cases to maintain the same power is lower in a crossover design than in a parallel design.

In previous EMA Scientific Advice (SA), the applicant proposed to conduct a parallel group PK study to compare the PK profile of RoActemra and the proposed biosimilar RGB-19, after a single subcutaneous administration of 162 mg in Japanese healthy subjects. As there is the potential risk of immunogenicity and thereby bearing in mind that this will be the only study to investigate the SC administration route, the applicant's plan to use a parallel group design was endorsed. However, the applicant designed the comparative PK study as a crossover study following the Japanese Ministry of Health, Labour and Welfare Guideline on Follow-On Biologics (MHLW, February, 2020). A crossover study design is considered acceptable. Immunogenicity data is provided also from the phase 3 study.

The duration of the study is considered long enough to allow adequate characterisation of the whole PK profile, including the late elimination phase and subsequently demonstrate PK similarity. Sampling timepoints for ADA/NAb testing are adequate for assessment of ADA/NAb response dynamics.

In the study, tocilizumab was administered at the same dose and via the same route as RoActemra for subcutaneous formulation. The selected dose is acceptable.

Only males were included in the study to ensure the homogeneity of the study population. Healthy subjects are also considered a homogenous and sensitive model to detect PK differences. The safety and PK of tocilizumab in healthy adults have been concluded in prior studies for the reference product.

Overall, the study design is acceptable.

Demographic characteristics were comparable between the two treatment groups. The applicant has justified that the chosen Japanese population is sufficiently sensitive to detect differences in pharmacokinetics. Furthermore, according to RoActemra SmPC, population pharmacokinetic analyses in RA and COVID-19 patients, showed that age, gender and ethnic origin did not affect the pharmacokinetics of tocilizumab.

The population studied is appropriate.

According to the Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010) AUC_{inf} should be the primary parameter for single-dose studies. In case of subcutaneous administration, C_{max} should be a co-primary parameter.

The reference product can be administered intravenously and subcutaneously and both routes are applied for. As the evaluation of subcutaneous administration covers both absorption and elimination, it may be possible to waive the evaluation of intravenous administration if comparability in both absorption and elimination has been demonstrated for the subcutaneous route using using additional PK parameters such as partial AUCs. The secondary PK parameters include pAUC and are considered sufficient.

The mean serum drug concentration-time profiles after administration of RGB-19 and RoActemra were similar. The mean serum drug concentrations of RGB-19 and RoActemra reached t_{max} at 96

hours post-dose and then decreased.

The results of ANOVA analysis of the PK parameters showed significant subject effect ($p<0.001$) for C_{max} and AUC_{inf}. Furthermore, there was a significant period effect ($p<0.001$) for C_{max} and AUC_{inf}. The ANOVA analysis showed no significant sequence effect; the serum drug concentrations prior to the second IP administration were below the lower limit of quantification in all subjects, and the variability of the PK parameters was comparable for the two periods, all suggesting that there was no carryover effect.PK equivalence was demonstrated between RGB-19 and RoActemra for C_{max} and AUC_{inf} as the 90% CIs for the GMRs were contained within the predefined 80.00-125.00% equivalence range. Also, the secondary PK endpoints were comparable between RGB-19 and RoActemra.

The incidence of ADA positivity was similar for RGB-19 and RoActemra. In Period 1 on Day 43, 50% (26/52) and 43% (23/53) were ADA positive following administration of RGB-19 and RoActemra, respectively. Combining the results for the two treatment periods, the ADA incidence was 58% (61/105) for RGB-19 compared to 61% (62/102) for RoActemra. The NAb incidence was also similar for RGB-19 and RoActemra.

Analyses of ADA positive/negative status indicated that ADA status did not impact C_{max} and AUC_{inf} for either RGB-19 or RoActemra treatment.

Study RGB19101 in patients with active rheumatoid arthritis

This was a Phase III, randomised, double-blind, active control, parallel-group, multicenter study to assess the efficacy and safety of 2 investigational products, RGB-19 and RoActemra, in subjects with active RA who had an inadequate response to MTX.

Secondary objectives included to investigate the safety profile, including immunogenicity, between RGB-19 and RoActemra and to evaluate serum drug concentrations for RGB-19 and RoActemra.

Blood samples to measure serum concentrations of IP were collected before investigational product administration at time points at Week 2, 4, 12, 24, 36, and 52 after the first administration of investigational product. PK data from the phase 3 study in patients with rheumatoid arthritis is supportive. The mean serum concentrations were higher at all time points for the RGB-19 group compared to the RoActemra group. However, the time course of the mean serum drug concentration for both RGB-19 and RoActemra was similar. Based on these considerations, the applicant concludes that evaluation of bioequivalence was not affected by the presence of the period effect.

Treatment-emergent ADA incidence up to and including Week 24 was similarly low in the RGB-19 and RoActemra treatment groups. The ADA status did not appear to impact the serum drug concentration profile, and there was no apparent treatment-related difference in the relationship of the sIL-6R response associated with either ADA negative or ADA positive status in either study period. However, it is noted that the number of ADA positive subjects was small.

Data from baseline to week 52 have been submitted during the evaluation, and the results show generally similar profiles regardless of ADA status or treatment group.

Pharmacodynamics: No validated PD marker exist for tocilizumab. The chosen endpoints absolute neutrophil count (ANC), hsCRP, and sIL-6R are however accepted biomarkers in patients with inflammatory diseases and have been used previously in similar studies. No meaningful difference was observed for hsCRP AUEC or sIL-6R AUEC values in neither of the studies, however the ANC AUEC with tocilizumab treatment was lower than for RGB-19 treatment in the healthy control study. This did not have any impact on the susceptibility of infections.

5.2.4.2. Conclusions

The available PK/PD data supports biosimilarity versus the EU reference product RoActemra.

PK similarity has been demonstrated between RGB-19 and EU-RoActemra in the pivotal PK study in healthy subjects. PK data from the phase 3 study in patients with rheumatoid arthritis is supportive.

5.3. Clinical efficacy

The clinical studies are tabulated in section 5.1.2.

5.3.1. Dose response study

Not applicable for biosimilars.

5.3.2. Main study

5.3.2.1. Study RGB19101

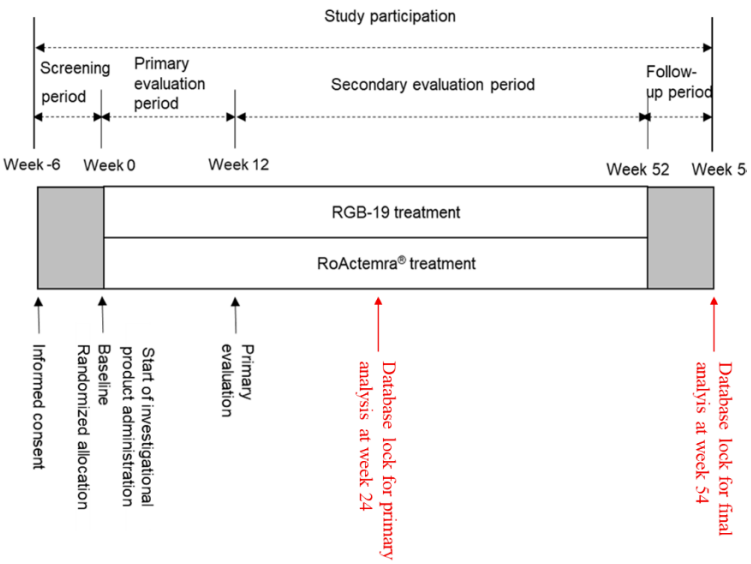
5.3.2.1.1. Study title

RGB-19 Phase III clinical study: A randomised, double-blind, multicenter phase III study to assess the efficacy and safety of RGB-19 compared to RoActemra in patients with active rheumatoid arthritis.

5.3.2.1.2. Study design

The study is a randomised, double blinded, active controlled, multicenter study designed to evaluate similarity in efficacy, PK, safety and immunogenicity of RGB-19 to RoActemra administered as 8 mg/kg intravenous drip infusion once every 4 weeks. The study consists of 4 periods: A screening period (day -42 to Day-1), a double-blind 12-week primary evaluation period, a secondary evaluation period up until 52 weeks (also double blinded) and a follow up period at week 54.

Figure 11: Study schema



Treatment

Subjects were randomized in a 1:1 ratio to receive either 8 mg/kg IV drip infusion RGB-19 or 8 mg/kg IV drip infusion tocilizumab (RoActemra) (active control) once every 4 weeks.

Oral MTX (6–16 mg/week) was an essential concomitant medication, and in principle, changes in dosage during the study period were prohibited. However, a dose reduction for safety reasons at the Investigator's discretion was allowed, and it was acceptable to increase the dose back only to a dose no higher than prior to the reduction. To prevent adverse drug reactions (ADRs) to MTX, the treatment of folic acid was permitted during the study period.

Randomisation

Eligible subjects were randomised at week 0 (day 1). Randomisation was stratified by site. The investigational product allocation table was prepared using the substitution block method with the study site as a block according to the allocation specifications. They were then handed over to the person responsible for allocating the investigational product (IP) on the basis of the table. Randomisation of subjects were performed using an electronic-based IWRS system. The person responsible for the IP allocation table was to ensure that blinded personnel did not have access to the allocation table.

Blinding

This is a double-blind study: the subjects and the personnel involved in the study at each site including e.g. the investigator and dedicated nurses were to be unaware of to which treatment arm a subject had been assigned. Although the test drug and the active comparator had the same outer box to ensure that they were indistinguishable, the appearance of primary packaging differed. To maintain blinding, operational procedures for handling the IPs were established as predefined in the study protocol including e.g., that operations involving the direct handling of vials were to be performed only by predetermined, unblinded personnel and that unblinded personnel were not to disclose the allocation of the IPs or any information that could lead to their disclosure to anyone other than the unblinded personnel.

The primary analysis of the study was performed after the database lock (DBL) at Week 24. To maintain the blinding at the study site (except for the unblinded personnel) and prevent bias in the evaluation after Week 24, a separate Partial Blind Procedure Manual was prepared.

Unblinding was only permitted in case of emergency and after DBL.

Patient population

Inclusion Criteria

Subjects who met all of the following inclusion criteria were selected as subjects in this study:

1. Subjects who voluntarily gave written consent to participate in the study.
2. Male or female subjects who were 20 to 75 years of age (both inclusive) when signing the informed consent.
3. Subjects who, at least 12 weeks before signing the informed consent, were diagnosed with active RA and who, at Screening, had RA according to the revised 2010 American College of

Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA and classified as functional class I, II, or III according to the 1991 revised ACR.

4. Subjects who met all the following 3 criteria for active RA (Guidance on the Use of IL-6 Inhibitors for Rheumatoid Arthritis, Japan College of Rheumatology, 2020):

    a) Swollen joint counts ≥ 6 (out of total 66* assessing joint counts) and tender joint counts ≥ 6 (out of total 68* assessing joint counts) at Screening and Baseline.

    *Not including artificial joints, fixing joints with arthrodesis, or joints that the Investigators considered difficult to appropriately assess because of concomitant diseases or other reasons.

    b) Erythrocyte sedimentation rate (ESR) ≥ 28 mm/h at Screening and Baseline or C-reactive protein (CRP) ≥ 1.0 mg/dL at Screening.

    c) Disease activity score (DAS) 28-ESR ≥ 3.2 at Screening and Baseline

5. Subjects with disease activity defined as in inclusion criterion (4) who had an inadequate response to oral MTX administered for at least 12 weeks at the time of signing the informed consent and on a stable dose of 6 to 16 mg/week for at least 4 weeks before the joint assessment at Baseline.

Main exclusion criteria:

- Subjects who have received treatment with ≥2 biological disease-modifying antirheumatic drugs (DMARDs)/biosimilar products.
- Subjects who have previously received tocilizumab, any other interleukin-6 (IL-6) inhibitors or IL-6 receptor inhibitors, or Janus kinase inhibitors in the past.
- Subjects who are pregnant or possibly pregnant and/or breast-feeding, or planning to become pregnant during the study period.

5.3.2.1.3. Objectives and estimands

Primary objective

Primary objective: To evaluate the equivalence in efficacy between RGB-19 and tocilizumab (RoActemra).

Primary endpoint: Mean change from baseline in DAS28-ESR at Week 12 after the first administration of IP

Estimands for the primary objective

The treatment effect of interest on the efficacy (primary estimand) was the treatment effect as determined by the change from baseline in DAS28-ESR in the hypothetical scenario that all subjects receiving IP had continued treatment up to Week 12 as planned in the protocol (hypothetical strategy).

Assuming that the time course of efficacy data could be obtained from subjects for whom DAS28-ESR was handled as unmeasured or missing because of the discontinuation of IP or violation or conflict with the rules regarding prohibited and permitted concomitant therapies (intercurrent events), which were comparable with the efficacy data obtained from subjects who continued treatment up to Week 12

without the occurrence of intercurrent events, the treatment effect was estimated in all subjects treated with IP.

Additionally, a secondary estimate of the treatment effect, regardless of whether or not the intercurrent events occurred up to 12 weeks after the first IP administration, was performed assuming the situation in clinical practice (treatment policy strategy).

The following two types of intercurrent events handling was defined in this study: the primary estimand based on the hypothetical strategy and the secondary estimand based on the treatment policy strategy:

- Discontinuation of the investigational product administration
    - If the subjects discontinued the IP administration prior to Week 12 after the first administration, DAS28-ESR measured on or after the date of discontinuation was to be handled as missing in case of using the hypothetical strategy and used in the analysis in case of using the treatment policy strategy.
- Violation or conflict with the rules regarding prohibited and permitted concomitant therapies
    - If the subject violated or a conflict was detected with the protocol defined criteria regarding prohibited and permitted concomitant therapies prior to Week 12 after the first administration of the IP, DAS28-ESR measured on or after the date of the violation/conflict was to be handled as missing in case of using the hypothetical strategy and used in the analysis in case of using the treatment policy strategy.

Statistical methods for estimation and sensitivity analysis on primary estimand

The primary efficacy analysis set was the Full Analysis Set (FAS). FAS was to include all randomised subjects who were administered at least one infusion of the investigational product (IP) and who had a DAS28-ESR score at baseline and at least one post-baseline assessment.

The Per Protocol Set (PPS) was to be used for a sensitivity analysis only. The PPS was to include subjects in the FAS who in addition were administered the IP at baseline and at Weeks 4 and 8; had a DAS28-ESR score at Week 12 and who had no major protocol deviations that could affect DAS28-ESR score assessment at Week 12.

For the comparison of RGB-19 and RoActemra, an analysis of covariance was used. The predefined ANCOVA analysis model included the change from baseline in DAS28-ESR at Week 12 as the response variable, the treatment group and the presence/absence of administration history of biological DMARDs as factors, and DAS28-ESR score at baseline as the covariate. The difference between the treatment groups in change from baseline in DAS28-ESR at Week 12 has been presented with a two-sided 95% confidence interval.

If DAS28-ESR was unmeasured or handled as missing due to the occurrence of an intercurrent event, DAS28-ESR was to be imputed using multiple imputation based on an assuming of missing at random (MAR). The imputation procedure was as follows:

1. Only non-monotonic missing data was to be imputed based on multiple imputation using Markov Chain Monte Carlo by treatment group.
2. Data obtained from the imputation in Step 1) including monotone missing data was to be imputed based on multiple imputation using monotone regression method by treatment group.
3. For the 100 pseudo-complete data that was generated in step 2), the primary ANCOVA model

was to be used to estimate the difference between groups independently for each dataset.

4. The analysis results (100) obtained in step 3) were to be pooled according to Rubin's rule.

In a supplementary analysis, the primary endpoint analysis was repeated based on the secondary estimand. The ANCOVA model applied was the same as for the primary analysis. The strategy for how to handle intercurrent events was treatment policy. If DAS28-ESR was missing for any reason, imputation was performed using the same multiple imputation method as described for the primary analysis.

For both the primary and secondary estimand aligned analysis, respectively, a sensitivity analysis based on the PPS and a tipping point analysis assuming missing not at random (MNAR) were planned. In the tipping point analysis, the difference between groups and corresponding two-sided 95% confidence interval was calculated for each value of a sensitivity parameter (Δ) using the same analysis model as that of the primary analysis for the FAS. For handling of missing data in DAS28-ESR, after multiple imputation based on the same procedure as that of the primary analysis, only Δ was to be added to all imputed values in the RGB-19 treatment group. Sensitivity parameters in the direction of worsening ($0 \leq \Delta \leq 1.2$) as well as sensitivity parameters in the direction of improvement ($-1.2 \leq \Delta < 0$) was applied. The analysis results for the 100 pseudo-complete data after addition of Δ were pooled in accordance with the primary analysis.

No multiple testing procedure was implemented.

Secondary objectives

Secondary efficacy objectives:

- To examine the equivalence in efficacy between RGB-19 and tocilizumab (RoActemra) in the following endpoints.
- Mean change from baseline in DAS28-ESR score at Weeks 8, 16, 24, and 52 after the first administration of IP.
- The response rate of ACR20, ACR50, and ACR70 at Weeks 8, 12, 16, 24, and 52 after the first administration of IP.
- Remission rate based on DAS28-ESR (DAS28-ESR < 2.6) at Weeks 8, 12, 16, 24, and 52 after the first administration of IP.
- EULAR response rate at Weeks 8, 12, 16, 24, and 52 after the first administration of IP.
- Mean change from baseline in CDAI score at Weeks 8, 12, 16, 24, and 52 after the first administration of IP.
- Mean change from baseline in CDAI score at Weeks 8, 12, 16, 24, and 52 after the first administration of IP.
- Remission rate based on CDAI (CDAI ≤ 2.8) at Weeks 8, 12, 16, 24, and 52 after the first administration of IP.
- Mean change from baseline in SDAI score at Weeks 8, 12, 16, 24, and 52 after the first administration of IP.
- Remission rate based on SDAI (SDAI ≤ 3.3) at Weeks 8, 12, 16, 24, and 52 after the first administration of IP.

- Other secondary objectives: To investigate the safety profile, including immunogenicity, between RGB-19 and tocilizumab (RoActemra). To evaluate serum drug concentrations for RGB-19 and tocilizumab (RoActemra). To compare pharmacodynamics (PD) between RGB-19 and tocilizumab (RoActemra)

Estimands for the secondary objectives

There were no estimands defined for any of the secondary endpoints.

Statistical methods for estimation and sensitivity analysis on the secondary estimand

Secondary efficacy endpoints were to be analysed descriptively.

For secondary continuous endpoints, descriptive statistics were to be provided by treatment group.

For secondary binary variables, percentages were to be calculated for each treatment group.

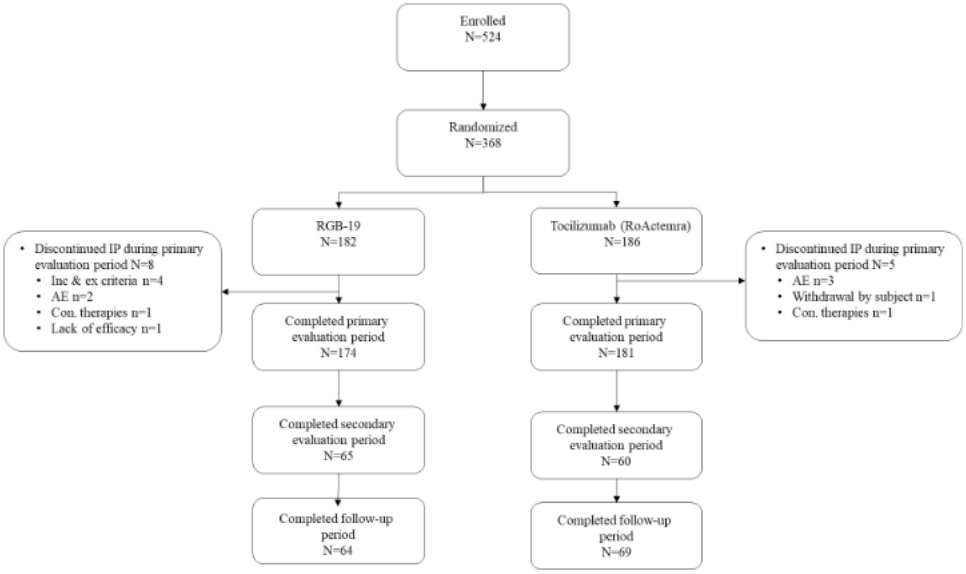
5.3.2.1.4. Results

Participant flow and numbers analysed

First Subject First Visit (FSFV): 16-Jan-2023

Last Subject Last Visit (LSLV [Week 24]): 14-May-2024

Figure 12: Subject Disposition (All Available Data)



AE = adverse event; con=concomitant; ex=exclusion; inc=inclusion; IP=investigational product; N/n = number of subjects; Wk = week
For all available data collected on or before the date when the last subject completed the assessments at Week 24 (14-May-2024), in the RGB-19 group, 3 subjects withdrew from the secondary evaluation period after Week 24 (2 subjects: AEs, 1 subject: lack of efficacy). In the tocilizumab (RoActemra) group, 5 subjects withdrew from the secondary evaluation period after Week 24 (2 subjects: AEs, 1 subject: withdrawal by subject, 2 subjects: concomitant therapies) and 1 subject withdrew from the follow-up period due to withdrawal by subject.
Source: Table 14.1.1.1.1 and Table 14.1.1.1.2.

Deviations from study plan

Table 20: Summary of Important Deviations by Category – Subjects with Informed Consent (N=524)

Category	Randomized Subjects				Subjects Who Withdrew Screening Period		Total	
	RGB-19 (N=182)		Tocilizumab (RoActemra) (N=186)		(N=156)		(N=524)	
	n (%)	e	n (%)	e	n (%)	e	n (%)	e
Data up to Week 24 for each subject								
(1) When the subject is enrolled in the study despite violations of GCP or failure to satisfy inclusion criteria	4 (2.2)	4	1 (0.5)	1	0 (0.0)	0	5 (1.0)	5
(2) When the subject meets the criteria for withdrawal during the study but is not withdrawn	2 (1.1)	2	0 (0.0)	0	0 (0.0)	0	2 (0.4)	2
(3) When the subject violates the rules about dose (administration regulations)	5 (2.7)	7	2 (1.1)	2	0 (0.0)	0	7 (1.3)	9
(4) When the subject uses prohibited concomitant therapies	9 (4.9)	10	12 (6.5)	18	0 (0.0)	0	21 (4.0)	28
(5) When the subject does not receive observations, examinations, and assessment related to the primary endpoints	4 (2.2)	5	3 (1.6)	4	0 (0.0)	0	7 (1.3)	9
(6) When any other important protocol deviation occurs[a]	1 (0.5)	1	2 (1.1)	2	0 (0.0)	0	3 (0.6)	3
Subjects who meet any of the above deviations	**21 (11.5)**	**29**	**17 (9.1)**	**27**	**0 (0.0)**	**0**	**38 (7.3)**	**56**
All available data[b]								
(1) When the subject is enrolled in the study despite violations of GCP or failure to satisfy inclusion criteria	4 (2.2)	4	1 (0.5)	1	0 (0.0)	0	5 (1.0)	5
(2) When the subject meets the criteria for withdrawal during the study but is not withdrawn	2 (1.1)	2	0 (0.0)	0	0 (0.0)	0	2 (0.4)	2
(3) When the subject violates the rules about dose (administration regulations)	5 (2.7)	7	3 (1.6)	3	0 (0.0)	0	8 (1.5)	10
(4) When the subject uses prohibited concomitant therapies	9 (4.9)	10	16 (8.6)	23	0 (0.0)	0	25 (4.8)	33
(5) When the subject does not receive observations, examinations, and assessment related to the primary endpoints	4 (2.2)	5	4 (2.2)	5	0 (0.0)	0	8 (1.5)	10
(6) When any other important protocol deviation occurs[b]	1 (0.5)	1	2 (1.1)	2	0 (0.0)	0	3 (0.6)	3
Subjects who meet any of the above deviations	**21 (11.5)**	**29**	**23 (12.4)**	**34**	**0 (0.0)**	**0**	**44 (8.4)**	**63**

Baseline data

Table 21: Demographic and other baseline characteristics (FAS N=368)

Characteristics	RGB-19 (N=182)	RoActemra (N=186)	Total (N=368)
Sex n (%)			
Male	41 (22.5)	48 (25.8)	89 (24.2)
Female	141 (77.5)	138 (74.2)	279 (75.8)
Age (years)			
Mean (SD)	56.7 (12.4)	55.4 (12.7)	56.0 (12.6)
Median	58.0	56.0	57.0
Min–Max	20-75	20-75	20-75
Race n (%)			
Asian	182 (100.0)	186 (100.0)	368 (100.0)
Body weight (kg) (Baseline)			
Mean (SD)	56.87 (12.29)	58.50 (13.58)	57.69 (12.97)
Median	54.00	56.20	55.30
Min–Max	36.0-94.0	32.1-98.5	32.1-98.5
BMI (kg/m^2)			
Mean (SD)	22.45 (3.91)	23.06 (4.87)	22.76 (4.43)
Median	21.75	22.47	22.01
Min–Max	14.9-33.3	13.8-39.5	13.8-39.5

Table 22: Rheumatoid arthritis baseline characteristics and previous drug treatment (FAS N=368)

Characteristics	RGB-19 (N=182)	RoActemra (N=186)	Total (N=368)
Functional classification of RA* n (%)			
Class I	43 (23.6)	42 (22.6)	85 (23.1)
Class II	117 (64.3)	116 (62.4)	233 (63.3)
Class III	22 (12.1)	28 (15.1)	50 (13.6)
Class IV	0	0	0
Duration from first diagnosis of RA (years)			
Mean (SD)	5.78 (7.01)	5.60 (6.99)	5.69 (6.99)
Median	3.22	2.63	2.95
Min–Max	0.2-46.3	0.2-37.2	0.2-46.3

Characteristics	RGB-19 (N=182)	RoActemra (N=186)	Total (N=368)
Administration history of biological DMARDs			
n (%) No	144 (79.1)	155 (83.3)	299 (81.3)
Yes	38 (20.9)	31 (16.7)	69 (18.8)
Administration history of NSAIDs[a]			
n (%) No	89 (48.9)	93 (50.0)	182 (49.5)
Yes	93 (51.1)	93 (50.0)	186(50.5)
Administration history of analgesic drugs[a]			
n (%) No	170 (93.4)	178 (95.7)	348 (94.6)
Yes	12 (6.6)	8 (4.3)	20 (5.4)
Administration history of corticosteroids[a]			
n (%) No	114 (62.6)	123 (66.1)	237 (64.4)
Yes	68 (37.4)	63 (33.9)	131 (35.6)
Concomitant diseases**			
n (%) No	11 (6.0)	18 (9.7)	29 (7.9)
Yes	171 (94.0)	168 (90.3)	339 (92.1)
***Dose of MTX (mg/week) (Baseline)**			
Mean (SD)	9.6 (2.7)	9.6 (2.6)	9.6 (2.7)
Median	10.0	10.0	10.0
Min–Max	0-16	6-16	0-16
n (%) 6-<8	33 (18.1)	35 (18.8)	68 (18.5)
8-<10	51 (28.0)	50 (26.9)	101 (27.4)
10-<12	37 (20.3)	42 (22.6)	79 (21.5)
12-<14	46 (25.3)	46 (24.7)	92 (25.0)
14-<16	8 (4.4)	6 (3.2)	14 (3.8)
<10	85 (46.7)	85 (45.7)	170 (46.2)
≥10	97 (53.3)	101 (54.3)	198 (53.8)

*Class I = able to perform usual activities of daily living (self-care, vocational, and avocational); class II = able to perform usual self-care and vocational activities, but limited in avocational activities; class III = able to perform usual self-care activities but limited in vocational and avocational activities; class IV = limited in ability to perform usual self-care, vocational, and avocational activities. Usual self-care activities include dressing, feeding, bathing, grooming, and toileting; vocational and avocational activities are both patient-desired and age-, and sex-specific.[43]

Outcomes and estimation

Primary efficacy variable

Table 23: ANCOVA analysis of change from baseline in DAS28-ESR at Week 12 (FAS)

Response variable	Treatment group	N	Adjusted mean[a]	SE	Adjusted mean difference[b]		
					Point estimate	Two-sided 95% CI	
						Lower	Upper
Change from baseline in DAS28-ESR	**RGB-19**	182	-3.62	0.09	-0.21	-0.43	0.02
	RoActemra	185[c]	-3.41	0.09			

ANCOVA = analysis of covariance; CI = confidence interval; DAS28-ESR = disease activity score in 28 joints-erythrocyte sedimentation rate; DMARDs = disease-modifying antirheumatic drugs; FAS = full analysis set; n = number of subjects with DAS28-ESR at Week 12 (observed cases); MI = multiple imputation; N = number of subjects included in the ANCOVA (imputed by MI); SE = standard error

a. ANCOVA model included the treatment group and the administration history of biological DMARDs as factors, and DAS28-ESR score at baseline as the covariate.

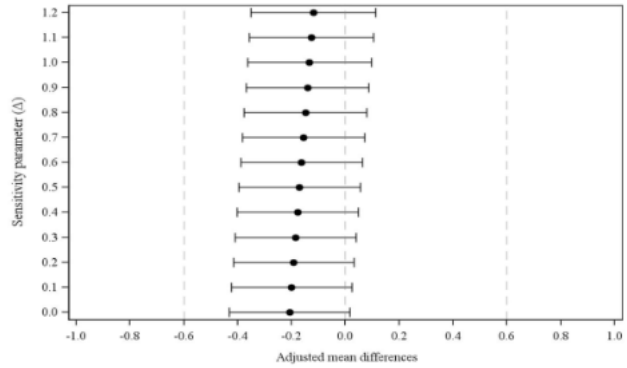
b. RGB-19 treatment group - RoActemra treatment group.

c.One subject in the RoActemra treatment group (Subject 78-03) discontinued the IP administration at the same day as the date of first IP administration due to a severe, IP-related AE of drug hypersensitivity. According to the definition of the primary estimand, all DAS-28 ESR values for this subject, including baseline, were handled as missing and were not imputed in this case (hypothetical strategy).

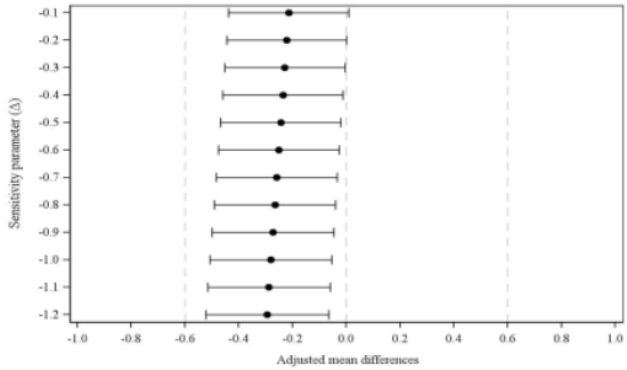
Sensitivity analyses

The difference between groups and the 2-sided 95% CI for each value of sensitivity parameter (Δ), was calculated using the same analysis model as that of the primary analysis. For handling of missing data in DAS28-ESR, after multiple imputation (MI) based on the same procedure as that of the primary analysis, only Δ was added to all imputed values in the RGB- 19 treatment group. The sensitivity parameters in the direction of worsening (0≤Δ≤1.2) were the primary focus of the study. Results are shown in the Figure 13 below:

Figure 13: Forest plot for tipping point analysis of change from baseline in DAS28-ESR at Week 12 (FAS)



Imputation method: Delta adjustment



Secondary estimand

This evaluation is based on the FAS, including measures after onset of ICEs.

Table 24: ANCOVA analysis of change from baseline in DAS28-ESR at Week 12 (FAS after onset of ICEs)

Response variable	Treatment group	N / n	Adjusted mean[a]	SE	Adjusted mean difference[b]		
					Point estimate	Two-sided 95% CI	
						Lower	Upper
Change from baseline in DAS28-ESR	RGB-19	182/ 179	-3.60	0.09	-0.21	-0.44	0.02
	RoActemra	186/ 183	-3.39	0.10			

N = number of subjects included in the ANCOVA (imputed by MI); n = number of subjects with DAS28-ESR at Week 12 (OC); OC = observed cases

a. ANCOVA model included the treatment group and the administration history of biological DMARDs as factors, and DAS28-ESR score at baseline as the covariate.

b. RGB-19 treatment group - RoActemra treatment group.

A tipping point analysis was also conducted for this FAS population. The results of the tipping point analysis were supportive of the primary ANCOVA analysis. Data were consistent across sensitivity parameters in the direction of worsening ($0 \leq \Delta \leq 1.2$) and in the direction of improvement ($-1.2 \leq \Delta < 0$). Results were within the equivalence range of -0.6 to 0.6.

Supportive Analysis based on the Primary Estimand

Table 25: ANCOVA analysis of change from baseline in DAS28-ESR at Week 12 (PPS)

Response variable	Treatment group	N / n	Adjusted mean[a]	SE	Adjusted mean difference[b]		
					Point estimate	Two-sided 95% CI	
						Lower	Upper
Change from baseline in DAS28-ESR	RGB-19	169/ 167	-3.66	0.09	-0.21	-0.43	0.01
	RoActemra	168/168	-3.45	0.09			

N = number of subjects included in the ANCOVA (imputed by MI); n = number of subjects with DAS28-ESR at Week 12 (OC); OC = observed cases; Patients included in the PPS did not experience ICEs.

a. ANCOVA model included the treatment group and the administration history of biological DMARDs as factors, and DAS28-ESR score at baseline as the covariate.

b. RGB-19 treatment group - RoActemra treatment group.

Selected secondary endpoints

Table 26: Change from baseline in DAS28-ESR (FAS) at different timepoints

Assessment time point	ICEs	Treatment group	N	Mean (SD)	Min, Max	Two-sided 95% CI for Mean	
						Lower	Upper
Week 8	Exclude	RGB-19	176	-3.39 (1.05)	-7.8, -1.2	-3.55	-3.24
		RoActemra	181	-3.09 (1.02)	-6.9, -0.5	-3.24	-2.94
	Include	RGB-19	181	-3.34 (1.08)	-7.8 -0.6,	-3.50	-3.18
		RoActemra	183	-3.06 (1.06)	-6.9, 0.6	-3.22	-2.91
Week 12	Exclude	RGB-19	173	-3.72 (1.19)	-7.4, -0.4	-3.90	-3.54
		RoActemra	181	-3.45 (1.12)	-6.9, -0.9	-3.61	-3.29
	Include	RGB-19	179	-3.68 (1.21)	-7.4, -0.4	-3.85	-3.50
		RoActemra	183	-3.41 (1.20)	-6.9, 2.3	-3.58	-3.23
Week 16	–	RGB-19	171	-3.89 (1.11)	-6.7, -1.5	-4.05	-3.72
		RoActemra	176	-3.62 (1.17)	-7.1, 0.0	-3.79	-3.44
Week 24	–	RGB-19	169	-4.07 (1.18)	-7.3, -0.3	-4.24	-3.89
		RoActemra	172	-3.85 (1.13)	-7.1, -0.4	-4.02	-3.68

Imputation method: OC

Descriptive statistics for the secondary endpoint of the response rate of ACR20, ACR50, and ACR70 at Weeks 8, 12, 16, and 24 after the first administration of IP for the FAS are presented in the Table 27 below.

Table 27: Response rate of ACR20, ACR50, and ACR70 (FAS) at different timepoints

Endpoints	Assessment time point	Treatment group	N	n	Achievement rate (%)	Difference of achievement rate[a]		
						Point estimate	Two-sided 95% CI	
							Lower	Upper
ACR20	Week 8	RGB-19	176	150	85.2	7.9	-0.2	15.9
		Tocilizumab (RoActemra)	181	140	77.3			
	Week 12	RGB-19	173	152	87.9	2.2	-5.0	9.3
		Tocilizumab (RoActemra)	181	155	85.6			
	Week 12 (LOCF)	RGB-19	177	155	87.6	1.9	-5.3	9.0
		Tocilizumab (RoActemra)	182	156	85.7			
	Week 16	RGB-19	172	158	91.9	6.6	-0.1	13.4
		Tocilizumab (RoActemra)	176	150	85.2			
	Week 24	RGB-19	170	162	95.3	4.0	-1.4	9.7
		Tocilizumab (RoActemra)	172	157	91.3			
	Week 24 (LOCF)	RGB-19	177	167	94.4	3.7	-1.9	9.4
		Tocilizumab (RoActemra)	182	165	90.7			
ACR50	Week 8	RGB-19	176	90	51.1	5.3	-5.0	15.4
		Tocilizumab (RoActemra)	181	83	45.9			
	Week 12	RGB-19	173	110	63.6	2.3	-7.8	12.2
		Tocilizumab (RoActemra)	181	111	61.3			
	Week 12 (LOCF)	RGB-19	177	113	63.8	2.3	-7.6	12.2
		Tocilizumab (RoActemra)	182	112	61.5			
	Week 16	RGB-19	172	123	71.5	5.0	-4.7	14.6
		Tocilizumab (RoActemra)	176	117	66.5			
	Week 24	RGB-19	170	124	72.9	-0.3	-9.7	9.0
		Tocilizumab (RoActemra)	172	126	73.3			
	Week 24 (LOCF)	RGB-19	177	127	71.8	-0.8	-10.0	8.4

Endpoints	Assessment time point	Treatment group	N	n	Achievement rate (%)	Difference of achievement rate[a]		
						Point estimate	Two-sided 95% CI	
							Lower	Upper
ACR70	Week 8	RGB-19	176	47	26.7	8.5	-0.2	17.0
		Tocilizumab (RoActemra)	181	33	18.2			
	Week 12	RGB-19	173	60	34.7	3.7	-6.0	13.4
		Tocilizumab (RoActemra)	181	56	30.9			
	Week 12 (LOCF)	RGB-19	177	61	34.5	3.1	-6.5	12.8
		Tocilizumab (RoActemra)	182	57	31.3			
	Week 16	RGB-19	172	74	43.0	-2.4	-12.7	7.9
		Tocilizumab (RoActemra)	176	80	45.5			
	Week 24	RGB-19	170	90	52.9	1.2	-9.3	11.6
		Tocilizumab (RoActemra)	172	89	51.7			
	Week 24 (LOCF)	RGB-19	177	91	51.4	0.9	-9.4	11.1
		Tocilizumab (RoActemra)	182	92	50.5			

ACR = American College of Rheumatology; CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; N = number of subjects; n = number of responders; OC = observed cases; % = n / N × 100

a. RGB-19 treatment group - tocilizumab (RoActemra) treatment group.

Imputation method: OC/LOCF (Week 12 and Week 24).

Source: Table 14.2.3.1.1.1.

Pre-defined and post-hoc subgroup analyses

Figure 14: Forest Plot for ANCOVA Analysis of Change from Baseline in DAS28-ESR at Week 12 (Demographic Variables) - FAS

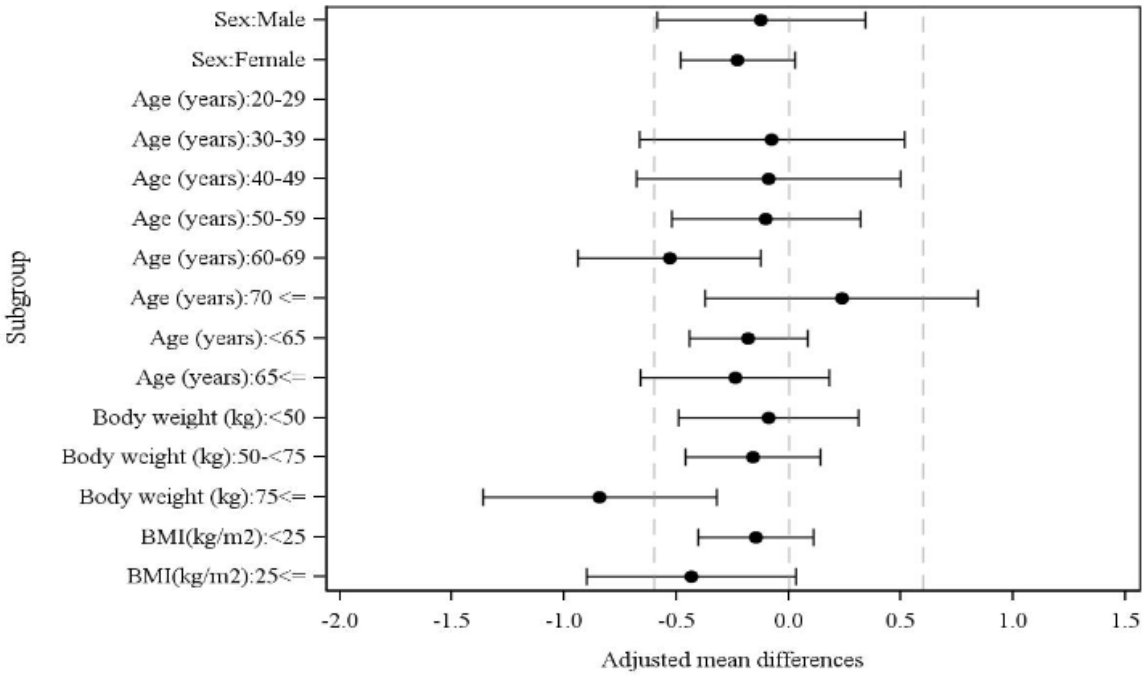
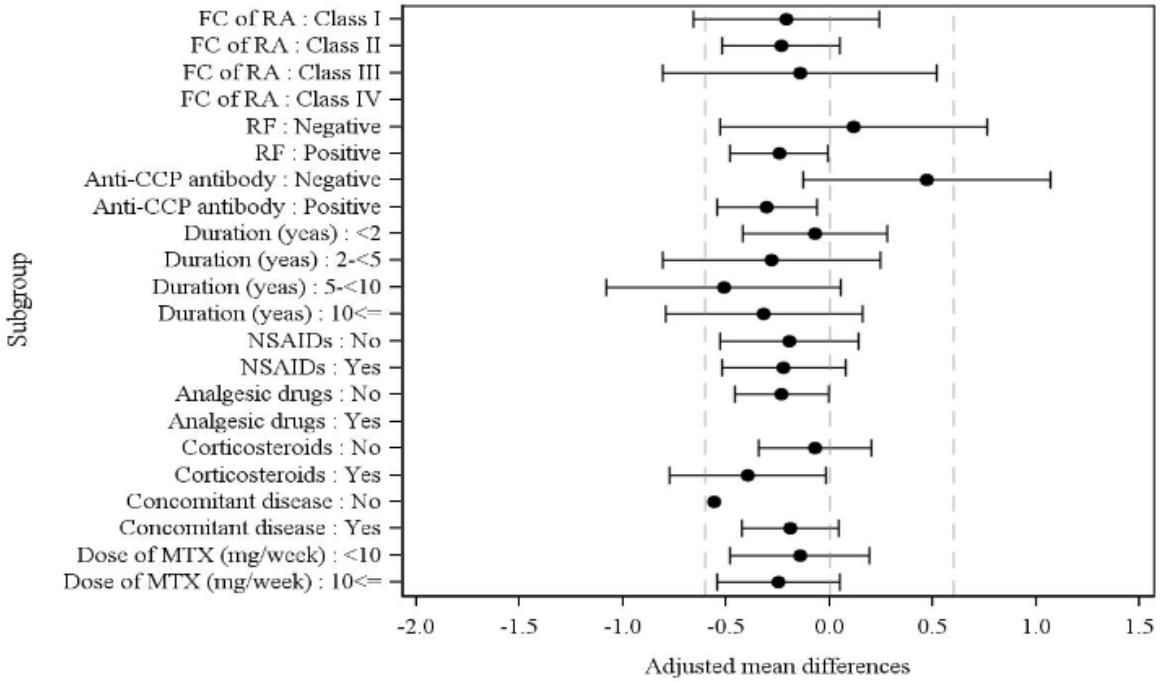


Figure 15: Forest Plot for ANCOVA Analysis of Change from Baseline in DAS28-ESR at Week 12 (Other Factors) - FAS



5.3.3. Clinical studies in special populations

This section is not relevant for biosimilars.

5.3.4. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

5.3.5. Overall discussion and conclusions on clinical efficacy

5.3.5.1. Discussion

Design and conduct of clinical studies

The overall study plan has been revised on several occasions during the development of the drug (from 2 to 1 phase 1 study in healthy subjects, from sc to iv formula in the phase 3 study in RA patients, change of primary endpoint from ACR 20 at week 24 to change from baseline in DAS-28 at week 12). The applicant has however sought CHMP advice on the development program on several occasions, and principally followed the received recommendations for the clinical studies. Thus, the clinical study program now consists of one phase 1 single dose study in healthy males, and one phase 3 study in RA-patients.

The phase 3 study, RGB19101 (RGB-19) is a randomised, double-blind, active control, parallel-group multicentre clinical study conducted in patients with active RA who have experienced an inadequate clinical response to methotrexate (MTX) and currently receiving a stable dose of MTX. The overall aim

is to evaluate efficacy, safety, and immunogenicity similarity of RGB-19 to RoActemra administered as 8 mg/kg intravenous drip infusion once every 4 weeks.

The study consisted of 4 periods: A screening period (day -42 to Day-1), a double-blind 12-week primary evaluation period, a secondary evaluation period up until 52 weeks (also double blinded) and a follow up period at week 54. The primary analysis of the study was performed unblinded after the DBL at week 24. The provided CSR includes data up until week 24 and the study is still ongoing. The final report, with data up until week 52 has been provided at day 120 according to the applicant. This is endorsed.

The choice of the study population (patients with active rheumatoid arthritis not adequately controlled with methotrexate) are in line with the CHMP guidance and were endorsed in CHMP Scientific Advice. It should be noted that all patients needed to be treated with concomitant methotrexate in the study. This could potentially have impact on the extrapolation to indications where tocilizumab is intended for monotherapy, since concomitant methotrexate is expected to decrease the risk for immunogenicity. However, taking in account the overall low immunogenicity of tocilizumab, this issue is not considered to prevent extrapolation to other indications for use.

All participants in the study were from Japan. As requested in the CHMP scientific advice, the applicant has provided a justification that the Japanese population is not less sensitive than the Caucasian population to detect potential differences between biosimilar and RMP. According to the applicant, intrinsic and extrinsic factors are comparable between patients with active RA in Japanese and Caucasian patients. This is agreed.

The treatment effect of interest on the efficacy (primary estimand) was the treatment effect as determined by the change from baseline in DAS28-ESR in the hypothetical scenario that all subjects receiving IP had continued treatment up to Week 12 as planned in the protocol (hypothetical strategy). Two types of intercurrent events were defined: discontinuation of investigational treatment administration and violation or conflict with the rules regarding prohibited and permitted concomitant therapies. A secondary estimand was defined to estimate the treatment effect regardless of whether or not the intercurrent events had occurred up to 12 weeks assuming the situation in clinical practice (treatment policy strategy). It is endorsed that two different estimands had been defined. Both are accepted as being relevant.

The primary endpoint, mean change from baseline of DAS28 (ESR) at Week 12, is a continuous score based on tender/swollen joint counts (out of 28 joints), VAS scores for patient's global assessment of disease activity, and erythrocyte sedimentation rate. The prespecified equivalence margins of the primary efficacy estimand set to [-0.6, 0.6] is also endorsed. Thus, the clinical model is considered sufficiently sensitive to enable the detection of differences between the two products.

The secondary efficacy endpoints included among others mean change from baseline in DAS-28 (ESR) score at week 8,16,24 and 52 and the response rates of ACR20,50 and 70 at week 8, 12, 16, 24 and 52. The endpoints are validated and common measures of disease activity in RA studies.

The time period for enrolment into the study and the included study sites and setting are also acknowledged. There is no concern about the 2 amendments to the study protocol. The steps taken to protect and maintain blinding appears overall adequate. Regarding the randomisation procedure, the allocation table was prepared using the substitution block method with the study site as a block. Upon request, the applicant provided a clarification regarding the substitution block method by stating that this method is synonymous with permutated block randomization.

Statistical methods

The submitted SAP is version 2.0, dated July 30, 2024. The database was locked on 31-Jul-2024 and unblinding occurred on 05-Aug-2024. The SAP version 1.0 as of 20-Jan-2023 was not provided but the changes implemented with version 2.0 have been described. No concern is raised.

The primary analysis of the primary endpoint was sufficiently well defined including the imputation approach to be used irrespective of whether observed data after an intercurrent event (IE) was ignored (primary IE hypothetical strategy), or in case of a less successful treatment policy approach after an IE or missing for other reasons than the occurrence of an IE.

The planned total sample size was 358 subjects, 179 in each treatment arm. The sample size calculation was adequate, and the assumptions made are considered well justified. The equivalence margins (-0.6, 0.6) have been both clinically and statistically justified.

The primary analysis set was the full analysis set (FAS). The definition of the FAS is not fully agreed but has been shown not to present an issue: all the subjects that were randomised were also included in the FAS. Nevertheless, in the analysis of the primary endpoint aligned with the primary estimand, one subject randomised to the control arm was excluded due to having discontinued treatment at the day of first administration due to drug hypersensitivity. All DAS-28 ESR values for this subject, including baseline, were handled as missing and were in this case not imputed. This is accepted. In comparison, data from this subject was included in the analysis aligned with the secondary estimand.

The primary endpoint was analysed using an ANCOVA model including treatment, administration history of biological DMARDs (present/absent), and DAS28-ESR score at baseline. The model did not include the only stratification site. However additional analyses where site adjustment is included is provided and no concern is raised.

For all missing data, truly missing or if handled as missing after an intercurrent event, DAS28-ESR was to be imputed using multiple imputation (MI) under the assumption of missing at random (MAR). The multiple imputation was to occur in four steps with a difference depending on whether data was non-monotone (using Markov Chain Monte Carlo) or monotone missing (monotone regression method). Irrespective of imputation step, imputation was by treatment arm. This is endorsed.

The amount of non-monotone missing data has seemingly not been summarised but appears from the outcome table presenting the primary endpoint outcomes over time not to raise any concern. However, upon request, a dedicated table listing frequency of different intercurrent events and different types of missing data by treatment arm was provided for completeness since the MAR assumption is not agreed and can only be accepted because the number of missing values is low. The provided data did not evoke any further concerns. While the hypothetical strategy is used for all intercurrent events for the primary estimand a secondary estimand for the primary analysis is provided where treatment policy was used for all intercurrent events, this can be agreed. The number of intercurrent events is low.

Judging from the subject disposition few subjects (in total 13) discontinued randomised treatment during the primary assessment period (up to week 12) whereof 6/8 in the RGB19 arm and 2/5 in the tocilizumab arm completed week 12 assessments after IP discontinuation. From the subject disposition it appears as if only 2 subjects, one in each treatment arm, needed concomitant medication.

According to the presentation of the primary estimand, there was a total of 9 subjects (/182) who did not have DAS28-ESR values available at Week 12 in RGB-19 group. In the tocilizumab arm, and after having excluded one subject, the corresponding number was 4 (/185). According to the presentation of the secondary estimand, only three subjects in each arm had missing DAS28-ESR assessments at week 12 in that 179/182 and 183/186 in the RBG19 and tocilizumab arm respectively have been stated to represent subjects "with DAS28-ESR at week 12".

The study lacked a multiple testing procedure. All secondary endpoints were to be descriptively analysed only. Concerning for example, ACR20, ACR50, and ACR70 remission rates, the applicant has concluded that since the 95% CIs covered 0, there were no statistically significant differences between the treatment arms. It had been preferred if instead the outcomes had been discussed based on agreed/relevant equivalence margins, but this is no further pursued.

Results

Participants flow, protocol deviations

Of the 524 subjects screened, a total of 368 subjects were randomised (RGB-19: 182 subjects; RoActemra: 186 subjects). All of these received study drug according to the randomized treatment and were included in the Full Analysis Set.

The proportions of patients discontinuing study drug prior to Week 12 were few, 8 (4%) and 5 (3%) in the RGB-19 and RoActemra groups respectively. According to the provided flowchart, 4 of the patients in the RBG-19 group discontinued treatment because of inclusion/exclusion criteria. Otherwise, 2 patients discontinued due to AEs, 1 due to lack of efficacy and one due to concomitant therapies. In the RoActemra group, 3 patients discontinued due to AEs, 1 due to withdrawal by subject and 1 due to concomitant therapies. The occurrence and type of major protocol deviations up until week 24 does not evoke any concerns and was around 10%, with the most common deviation being "use of prohibited medication".

Baseline characteristics

Demographic characteristics, baseline disease characteristics, medical history and prior medication were overall balanced across treatment groups and are representative for the intended population. Most of the included patients had high disease activity at baseline according to multiple measures of disease activity. The majority of patients were female (75.8%) and mean age was 56 years. Median MTX dose were 10 mg/week and around 19% of the patients had a previous use of biological treatment. However, appropriate 23% in both arms fulfil Class I of the Functional classification of RA, i.e. are able to perform usual activities of daily living (self-care, vocational, and avocational). Baseline criteria suggestive that the study population may not fully represent a moderate to severe RA most sensitive to address biosimilar efficacy include that some participants have i) a relatively short duration of RA; and low ESR at baseline and/or ii) relatively short duration of MTX therapy prior to randomisation. The median (min-max) duration since diagnosis of RA were 3.22 (0.2-46.3) and 2.63 (0.2-37.2) years for participants receiving RGB-19 and RoActemra, respectively. The lower end of CI was 0.2. Therefore, not all participants fulfilled the criteria of at least 12 weeks since diagnosis of RA and such individuals may not be sensitive enough to determine efficacy in a biosimilarity study, where disease duration of 6 months is advised. However, the applicant has provided subgroup analysis, showing minimal difference in response, irrespective of functional RA class or duration of RA and thus no concern was raised.

Efficacy analyses

The primary endpoint, mean change from baseline in DAS28-ESR at week 12 was -3.62 (SE 0.09) for RGB-19 and -3.41 (SE 0.09) for RoActemra. The adjusted mean difference was -0.21 with 95% CI of -0.43, 0.02. The point estimate and two-sided 95% CIs for the between-group differences were within the predefined equivalence range of -0.6 to 0.6, thus the equivalence claim was met. The mean change of DAS28-ESR in both treatment groups is considered high and clinically relevant. The outcome from the secondary estimand primary endpoint aligned analysis was almost identical: -0.21, 95% CI:-0.44, 0.02. In this analysis using a treatment policy strategy, there were only a few patients with missing primary endpoint values at week 12 (3 patients in each group). Neither was there any significant differences in the analysis based on the PPS nor in the supplementary analysis adjusting for

the stratification variable "site" (/medical institution). In addition, a tipping point analysis was planned and supports the robustness of the primary conclusion.

Regarding the secondary endpoints, the applicant states that the mean (SD) changes from baseline in DAS28-ESR score remained similar over time, and that excluding or including measurements after the occurrence of ICEs did not impact the results. It is acknowledged that for secondary endpoints, only descriptive data were provided. Regarding the proportion of patients achieving ACR 20/50/70 at different timepoints, the applicant states that there were no statistically significant differences in remission rates between groups as 0 was included in each 95% CI. However, it should be noted that at almost all timepoints, there was a numerical favour towards RGB-19 treatment. In addition, when looking at some of the timepoints (e.g. ACR20/50/70 at week 8), the upper limit of the 95% CI exceeds 15%. Upon request, the applicant provided ACR 20/50/70 results using NRC instead of OC and LOCF. In general efficacy were similar between the two products at all time points. The numbers were slightly in favour of RGB-19 at week 8 and week 52, however this finding does not preclude biosimilarity.

Regarding subgroup analysis, the point estimate for the between-group differences were within the equivalence tolerance range for the majority of subgroups examined. It is acknowledged that several subgroups included only a few subjects, and the study was not powered to detect differences between subgroups. Four out of 182 (2.2%) patients treated with RGB-19 and 6 out of 186 (3.2%) patients treated with RoActemra developed ADA response up to and including Week 24. The ADA positive subjects were also classified as NAb positive. It is agreed with the applicant that analysis of the change in DAS28-ESR from baseline at Week 12 and Week 24 did not reveal differences in efficacy related to either ADA or NAb status, or to the treatment group. The number of patients that developed ADA was small in both arms and is, as the applicant states, probably related to the use of MTX as background medication. It could however also be related to the fact that the intravenous route is less immunogenic than the subcutaneous route. Since the immunogen response was evaluated with subcutaneous injection in the study in healthy participants, this will not be further pursued.

One subgroup not evaluated that may have been interesting to explore is patients with previous b-DMARD treatment. Administration history of biological DMARDs (present/absent) was included in the primary analysis model but was not a stratification factor at randomisation which may explain the minor imbalance between the arms. A total of 38/182 (20.9%) subjects in the RGB19 group and 31/186 (16.7%) subjects in the tocilizumab arm had received biological DMARDs. A subgroup analysis based on the presence/absence of an administration history of biological DMARDs seems to have been planned although it is uncertain whether performed. However, since the numbers of patients in this subgroup were small, this has not be further pursued.

Regarding extrapolation to all indications the applicant has provided a sound justification. This is agreed.

5.3.5.2. Conclusions on the clinical efficacy

The point estimate and two-sided 95% CIs for the between-group differences in change from baseline in DAS-28 (ESR) were within the predefined equivalence range of -0.6 to 0.6, thus the equivalence claim was met. The mean change of DAS28-ESR in both treatment groups is considered high and clinically relevant.

5.4. Clinical safety

Please refer to the table of studies in section 5.1.2.

5.4.1. Safety data collection

The clinical safety of RGB-19 was investigated in two pivotal clinical studies:

- A Randomized, Double-Blind, 2-Treatment, 2-Period, 2-sequence Crossover Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, and Immunogenicity of a Single 162 mg fixed Subcutaneous Dose of RGB-19 and RoActemra Subcutaneous Formulation in Healthy Male Volunteers (protocol number: RGB192101) in Japan and
- A Randomized, Double-blind, Multicenter Comparative Clinical study to Assess the Efficacy and Safety of RGB-19 Compared to RoActemra in Patients with Active Rheumatoid Arthritis (protocol number: RGB19101) in Japan

The clinical development programme of RGB-19 with respect to safety endpoints are summarized in Table 28 below:

Table 28: Summary of RGB-19 clinical development programme with safety endpoints.

Study Description Protocol	Study Design	Study Drugs	Subjects	Safety Endpoints
Phase I comparative PK/PD study in healthy subjects in Japan (RGB192101)	Randomized, Double-blind, 2-Treatment, 2-Period, 2-Sequence, Single-Dose Crossover Study	Single subcutaneous dose of 162 mg RoActemra and RGB-19 in pre-filled syringe with needle safety device	110 healthy male volunteers (aged 20-40) N=55 per sequence (104 subjects received RoActemra and 108 subjects received RGB-19) Safety analysis set = 110 subjects	• Adverse events (AE), Serious Adverse Event (SAE) • Clinical laboratory safety assessments (hematology, blood biochemistry, blood coagulation test, urinalysis) • ECGs • Vital signs • Physical examination • Body weight • Injection site reaction • Immunogenicity test (ADA positivity, titer, Nab)
Phase III comparative efficacy and safety study in patients with active rheumatoid arthritis in Japan (RGB19101)	Multicenter, randomized, double-blind, active control (RoActemra), parallel-group study	RGB-19 or RoActemra 8 mg/kg intravenous drip infusion (once every 4 weeks) as adjunctive therapy to 6-16 mg/week dose of MTX	368 female or male patients with active rheumatoid arthritis (RGB-19 = 182; RoActemra = 186) Safety analysis set = 368 subjects (up to Week 24)	• AE, SAE • Clinical laboratory safety assessments (hematology, blood biochemistry, blood coagulation test, urinalysis) • ECGs • Vital signs, • Physical examination • Body weight • Autoantibody tests (RF, anti-CCP antibody), • TBC, hepatitis virus test • Immunogenicity test (ADA positivity, titer, Nab)

Key: ADA = Anti-drug antibody, AE = Adverse Event, CCP = Cyclic Citrullinated Peptide, ECG = Electrocardiogram, MTX = Methotrexate, Nab = Neutralizing antibody, PD = Pharmacodynamic, PK = Pharmakinetic, RF = Rheumatoid Factor, SAE = Serious Adverse Event, TBC = Tuberculosis.

PK/PD study RGB192101 (healthy adult males)

From Screening to the end of the study (Day 85), and at the time points specified in the schedule of assessments (and), the Investigator(s) examined, documented, and recorded AEs and SAEs in the case report form. Any recurring AE (including the same AE) following the subject's recovery for which

the causal relationship to the investigational product was determined to be different, was entered as a distinct AE in the case report form.

The study participants were hospitalized the day before IP administration and remained hospitalized day 2-7 after IP administration. The study participants were instructed to visit the study site on each scheduled outpatient visit day.

The physical examination included a visual inspection, percussion, palpation, and auscultation.

Vital signs included measures of subjects' body temperature (axillary), systolic and diastolic blood pressures (supine), pulse rate (supine), and respiratory rate after at least 5 minutes of rest in a sitting position.

Laboratory tests were performed and included haematology test, blood biochemistry test, blood coagulation test, and urinalysis. All laboratory tests were performed at the study site's laboratory.

Injection site reactions were examined at 1, 2, 6, 12 and 24 hours after administration of the investigational product.

Comparative efficacy and safety study RGB19101 (patients with active rheumatoid arthritis)

The physical examination was performed at days 1, 15, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, and 365, and included a visual inspection, percussion, palpation, and auscultation. Vital signs were measured at the same occasions, including measures of subjects' body temperature (axillary), systolic and diastolic blood pressures, and pulse rate after 5 minutes of rest in a sitting position.

Subjects' blood and urine samples were collected at days 1, 15, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, and 365 for the laboratory tests listed in Table 29. The samples were sent to the central laboratory for analysis.

Table 29: Laboratory investigations.

Hematological tests	• RBC count • Platelets • WBC count • WBC differential count (% and absolute values): neutrophils, eosinophils, basophils, monocytes, lymphocytes. • Hematocrit • Hemoglobin	
Blood biochemistry tests	• Total cholesterol • LDL cholesterol • HDL cholesterol • Triglyceride • AST • ALT • ALP • γ-GTP (GGT) • LDH • Total protein • Uric acid • TSH	• Albumin • Total bilirubin • Direct bilirubin • BUN • Creatinine • eGFR • Glucose • Na • K • CRP • ESR* • β-D-glucan
Blood coagulation test	• Fibrinogen	
Urine tests	• Protein (qualitative) • Glucose (qualitative) • WBC count (qualitative) • Occult blood • Urobilinogen	

β-D-glucan = blood beta D-glucan; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; ESR = erythrocyte sedimentation rate γ-GTP = gamma-glutamyl transferase HDL = high-density lipoprotein; K = potassium; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; Na = sodium; RBC = red blood cell; TSH = thyroid stimulating hormone; WBC = white blood cell
*Efficacy parameter

5.4.2. Patient exposure

Phase I PK/PD study RGB192101 (healthy adult males)

A total of 55 subjects were enrolled in each of Sequences A and B to receive IP according to the following:

- A single SC injection of RGB-19 162 mg on Day 1 in Period 1 (Sequence A) or Day 1 in Period 2 (Day 43) (Sequence B).
- A single SC injection of tocilizumab (RoActemra) 162 mg on Day 1 (Sequence B) in Period 1 or Day 1 in Period 2 (Day 43) (Sequence A).

All 110 subjects received IP in Period 1. A total of 49 subjects received IP in both Periods 1 and 2 of Sequence A and 53 subjects received IP in both Periods 1 and 2 of Sequence B. Overall, 108 subjects received one dose of RGB-19 and 104 subjects received one dose of tocilizumab (RoActemra).

Phase III Comparative efficacy and safety study RGB19101 (patients with active rheumatoid arthritis)

Table 30: Extent of exposure (study RGB19101, data cutoff date 14 May 2024).

Characteristics	RGB-19 (N=182)	Tocilizumab (RoActemra) (N=186)	Total (N=368)
Number of administrations of IP (times)			
n	182	186	368
Mean (SD)	6.7 (1.2)	6.6 (1.1)	6.6 (1.1)
Median	7.0	7.0	7.0
Min–Max	1-7	1-7	1-7
25th percentile	7.0	7.0	7.0
75th percentile	7.0	7.0	7.0
Number of administrations of IP at the dose based on the protocol (times)			
n	182	186	368
Mean (SD)	6.6 (1.2)	6.6 (1.2)	6.6 (1.2)
Median	7.0	7.0	7.0
Min–Max	1-7	1-7	1-7
25th percentile	7.0	7.0	7.0
75th percentile	7.0	7.0	7.0
Duration of administration of IP (days)[a]			
n	182	186	368
Mean (SD)	161.7 (32.3)	160.9 (31.3)	161.3 (31.7)
Median	169.0	169.0	169.0
Min–Max	1-185	1-187	1-187
25th percentile	169.0	167.0	168.0
75th percentile	169.0	169.0	169.0
Compliance rate of IP (%)[b]			
n	182	185	367
Mean (SD)	98.31 (6.52)	97.51 (7.67)	97.91 (7.12)
Median	100.00	100.00	100.00
Min–Max	50.0-100.0	50.0-100.0	50.0-100.0
25th percentile	100.00	100.00	100.00
75th percentile	100.00	100.00	100.00
n (%) <75	6 (3.3)	7 (3.8)	13 (3.5)
≥75	176 (96.7)	178 (95.7)	354 (96.2)

FAS = full analysis set; IP = investigational product; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects per category; SD = standard deviation

a. Date of the last IP administration - Date of the first IP administration + 1.

b. The number of times IP at the dose based on the protocol (times) / Planned number of administrations (times) × 100

Demographics

Phase I PK/PD study RGB192101 (healthy adult males)

Table 31: Demographic variables study RGB192101.

Characteristics	Allocation sequence		
	Sequence A: RGB-19 - Tocilizumab (N=55)	Sequence B: Tocilizumab – RGB-19 (N=55)	Total (N=110)
Age (years)			
n	55	55	110
Mean (SD)	28.4 (6.0)	30.6 (6.2)	29.5 (6.2)
Median	27.0	30.0	28.5
Min–Max	20-40	20-40	20-40
Race n (%)			
n	55	55	110
American Indian or Alaska Native Asian	0 (0.0)	0 (0.0)	0 (0.0)
Asian	55 (100.0)	55 (100.0)	110 (100.0)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
White	0 (0.0)	0 (0.0)	0 (0.0)
Height (cm)			
n	55	55	110
Mean (SD)	171.44 (5.24)	170.05 (5.27)	170.75 (5.28)
Median	171.90	169.00	170.30
Min–Max	159.6-183.8	156.2-183.2	156.2-183.8
Body weight (kg) (Day -1)			
n	55	55	110
Mean (SD)	62.75 (5.49)	61.07 (6.87)	61.91 (6.25)
Median	61.90	59.30	61.15
Min–Max	50.8-76.3	51.9-78.6	50.8-78.6
BMI (kg/m^2)			
n	55	55	110
Mean (SD)	21.37 (1.87)	21.08 (1.72)	21.22 (1.79)
Median	21.22	20.56	20.89
Min–Max	18.6-24.7	18.5-24.8	18.5-24.8

BMI = body mass index; Max= maximum; Min = minimum; N = number of subjects; n = number of subjects for category; SD = standard deviation

Phase III Comparative efficacy and safety study RGB19101 (patients with active rheumatoid arthritis)

Table 32: Demographic variables study RGB19101.

Characteristics	RGB-19 (N=182)	Tocilizumab (RoActemra) (N=186)	Total (N=368)
Sex n (%)			
Male	41 (22.5)	48 (25.8)	89 (24.2)
Female	141 (77.5)	138 (74.2)	279 (75.8)
Age (years)			
Mean (SD)	56.7 (12.4)	55.4 (12.7)	56.0 (12.6)
Median	58.0	56.0	57.0
Min–Max	20-75	20-75	20-75
n (%) 20-29	6 (3.3)	6 (3.2)	12 (3.3)
30-39	12 (6.6)	15 (8.1)	27 (7.3)
40-49	32 (17.6)	35 (18.8)	67 (18.2)
50-59	45 (24.7)	55 (29.6)	100 (27.2)
60-69	56 (30.8)	50 (26.9)	106 (28.8)
≥70	31 (17.0)	25 (13.4)	56 (15.2)
<65	120 (65.9)	131 (70.4)	251 (68.2)
≥65	62 (34.1)	55 (29.6)	117 (31.8)
Race n (%)			
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Asian	182 (100.0)	186 (100.0)	368 (100.0)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
White	0 (0.0)	0 (0.0)	0 (0.0)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)
Body weight (kg) (Baseline)			
n	182	186	368
Mean (SD)	56.87 (12.29)	58.50 (13.58)	57.69 (12.97)
Median	54.00	56.20	55.30
Min–Max	36.0-94.0	32.1-98.5	32.1-98.5
BMI (kg/m^2) (Baseline)			
n	182	186	368
Mean (SD)	22.45 (3.91)	23.06 (4.87)	22.76 (4.43)
Median	21.75	22.47	22.01
Min–Max	14.9-33.3	13.8-39.5	13.8-39.5

BMI = body mass index; FAS = full analysis set; Max= maximum; Min = minimum; N = number of subjects; n = number of subjects for category; SD = standard deviation; % = n / N ×100

.

Table 33: Demographic and other baseline characteristics study RGB19101.

Characteristics	RGB-19 (N=182)	Tocilizumab (RoActemra) (N=186)	Total (N=368)
DAS28-ESR (Baseline)			
n	182	186	368
Mean (SD)	6.19 (0.87)	6.09 (0.89)	6.14 (0.88)
Median	6.10	5.96	6.05
Min–Max	4.2-8.6	3.9-8.5	3.9-8.6
CDAI (Baseline)			
n	182	186	368
Mean (SD)	34.61 (11.57)	33.57 (11.37)	34.09 (11.46)
Median	32.07	31.57	32.00
Min–Max	11.9-73.2	14.2-72.3	11.9-73.2
SDAI (Baseline)			
n	182	186	368
Mean (SD)	36.65 (12.49)	35.60 (12.19)	36.12 (12.34)
Median	34.70	33.66	34.02
Min–Max	12.1-83.7	15.2-74.9	12.1-83.7
TJC68 (Baseline)			
n	182	186	368

Characteristics	RGB-19 (N=182)	Tocilizumab (RoActemra) (N=186)	Total (N=368)
Mean (SD)	16.1 (9.7)	16.4 (10.0)	16.3 (9.8)
Median	13.0	14.0	13.0
Min–Max	6-61	6-60	6-61
TJC28 (Baseline)			
n	182	186	368
Mean (SD)	11.3 (6.0)	11.2 (5.8)	11.2 (5.9)
Median	10.0	10.0	10.0
Min–Max	2-28	3-28	2-28
SJC66 (Baseline)			
n	182	186	368
Mean (SD)	14.2 (7.5)	13.8 (7.3)	14.0 (7.4)
Median	12.0	12.0	12.0
Min–Max	6-43	6-47	6-47
SJC28 (Baseline)			
n	182	186	368
Mean (SD)	10.5 (5.0)	10.2 (5.0)	10.3 (5.0)
Median	9.0	9.0	9.0
Min–Max	1-28	1-28	1-28
ESR (mm/hr) (Baseline)			
n	182	186	368
Mean (SD)	45.88 (21.31)	45.22 (24.37)	45.55 (22.88)
Median	42.50	40.00	41.00
Min–Max	5.0-130.0	7.0-138.0	5.0-138.0
PtAP (mm) (Baseline)			
n	182	186	368
Mean (SD)	65.22 (21.16)	61.94 (22.61)	63.56 (21.94)
Median	67.00	67.50	67.50
Min–Max	7.0-100.0	3.0-100.0	3.0-100.0
PGA (mm) (Baseline)			
n	182	186	368
Mean (SD)	63.89 (20.97)	59.98 (22.36)	61.91 (21.74)
Median	67.50	63.50	65.00
Min–Max	5.5-100.0	5.0-100.0	5.0-100.0
EGA (mm) (Baseline)			
n	182	186	368
Mean (SD)	64.66 (20.29)	61.73 (19.31)	63.18 (19.83)
Median	67.15	64.00	66.00
Min–Max	16.0-100.0	15.0-95.0	15.0-100.0
HAQ-DI (Baseline)			
n	182	186	368
Mean (SD)	1.1188 (0.6867)	1.0665 (0.6247)	1.0924 (0.6557)

Characteristics	RGB-19 (N=182)	Tocilizumab (RoActemra) (N=186)	Total (N=368)
Median	1.0000	1.0000	1.0000
Min–Max	0.000-2.750	0.000-2.500	0.000-2.750
CRP (mg/dL) (Baseline)			
n	182	186	368
Mean (SD)	2.0411 (2.2633)	2.0297 (2.5597)	2.0353 (2.4144)
Median	1.2900	1.1650	1.2400
Min–Max	0.010-17.020	0.030-19.470	0.010-19.470

CDAI = clinical disease activity index; CRP = C-reactive protein; DAS28-ESR = disease activity score in 28 joints-erythrocyte sedimentation rate; EGA = evaluator's global assessment; FAS = full analysis set; ESR = erythrocyte sedimentation rate; HAQ-DI = health assessment questionnaire-disability index; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects for category; PGA = physician global assessment; PtAP = patient's assessment of pain; SD = standard deviation; SDAI = simplified disease activity index; SJC28 = swollen joint count 28 joints; SJC66 = swollen joint count 66 joints; TJC28 = tender joint count 28 joints; TJC68 = tender joint count 68 joints

5.4.3. Adverse events

Summary of adverse events

Phase I PK/PD study RGB192101 (healthy adult males)

Table 34: Summary of adverse events study RGB192101.

	Treatment						Total		
	RGB-19			Tocilizumab (RoActemra)					
	N	n (%)	e	N	n (%)	e	N	n (%)	e
All AEs	–	–	–	–	–	–	110	70 (63.6)	154
PTAEs	–	–	–	–	–	–	110	0 (0)	0
TEAEs	108	51 (47.2)	76	104	53 (51.0)	78	110	70 (63.6)	154

AE = adverse event; e = number of events; IP = investigational product; N for all AEs and PTAEs = number of subjects who received IP; N for TEAEs = number of subjects in SAF; n = number of subjects reporting at least one event in the specific category; PTAE = pre-treatment adverse event; TEAE = treatment-emergent adverse event; % = n / N × 100

Notes: TEAEs starting after IP administration in Period 1 were assigned to the treatment in Period 1; TEAEs starting after IP administration in Period 2 were assigned to the treatment in Period 2.

Table 35: Summary of treatment-emergent adverse events – safety analysis set

	Treatment				Total	
	RGB-19		Tocilizumab (RoActemra)			
	(N=108)		(N=104)		(N=110)	
	n (%)	e	n (%)	e	n (%)	e
TEAEs	51 (47.2)	76	53 (51.0)	78	70 (63.6)	154
ADRs	36 (33.3)	45	45 (43.3)	59	55 (50.0)	104
Severe AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
Severe ADRs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
AEs resulting in death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
ADRs resulting in death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
SAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
Serious ADRs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
AEs resulting in study withdrawal	3 (2.8)	4	0 (0.0)	0	3 (2.7)	4
ADRs resulting in study withdrawal	2 (1.9)	2	0 (0.0)	0	2 (1.8)	2

AE = adverse event; ADR = adverse drug reaction; e = number of events; IP = investigational product; N = number of subjects in SAF who received IP at either period; n = number of subjects reporting at least one event in the specific category; SAE = serious adverse event; TEAE = treatment-emergent adverse event; % = n / N × 100

Notes: TEAEs starting after IP administration in Period 1 were assigned to the treatment in Period 1; TEAEs starting after IP administration in Period 2 were assigned to the treatment in Period 2. All TEAEs for which a causal relationship with the IP cannot be ruled out were considered ADRs.

<u>Phase III Comparative efficacy and safety study RGB19101 (patients with active rheumatoid arthritis)</u>

Table 36: Summary of adverse events – subjects with informed consent (N=524) – up to week 24 for each subject.

	RGB-19 (N=182)			Tocilizumab (RoActemra) (N=186)			Total (N=524)		
	N	n (%)	e	N	n (%)	e	N	n (%)	e
All AEs	–	–	–	–	–	–	524	307 (58.6)	887
PTAEs	–	–	–	–	–	–	518[a]	40 (7.7)	45
TEAEs	182	143 (78.6)	389	186	150 (80.6)	453	368	293 (79.6)	842

AE = adverse event; e = number of events; N for all AEs = number of subjects with informed consent; N for PTAEs = number of subjects adopted as SAF in screening period; N for TEAEs = number of subjects in SAF; n = number of subjects reporting at least 1 event in the specific category; PTAE = pre-treatment adverse event; SAF = safety analysis set in the primary evaluation and secondary evaluation periods; TEAE = treatment-emergent adverse event; % = n / N × 100

a. Six subjects signed the informed consent form but did not receive at least one essential concomitant medication or have any safety assessments during screening period, so are not in included in the denominator for PTAEs (SAF during the screening period [Section 9.7.3]).

Table 37: Summary of treatment emergent adverse events (treatment period and follow-up period) – SAF (N=368) – up to week 24 for each subject.

	RGB-19 (N=182)		Tocilizumab (RoActemra) (N=186)		Total (N=368)	
	n (%)	e	n (%)	e	n (%)	e
TEAEs	143 (78.6)	389	150 (80.6)	453	293 (79.6)	842
ADRs	82 (45.1)	151	91 (48.9)	168	173 (47.0)	319
Severe AEs	3 (1.6)	3	13 (7.0)	13	16 (4.3)	16
Severe ADRs	1 (0.5)	1	6 (3.2)	6	7 (1.9)	7
AEs resulting in death	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
ADRs resulting in death	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
SAEs	4 (2.2)	4	14 (7.5)	15	18 (4.9)	19
Serious ADRs	2 (1.1)	2	6 (3.2)	7	8 (2.2)	9
AEs resulting in discontinuation of IP administration	3 (1.6)	3	12 (6.5)	12	15 (4.1)	15
ADRs resulting in discontinuation of IP administration	3 (1.6)	3	7 (3.8)	7	10 (2.7)	10

ADR = adverse drug reaction; AE = adverse event; e = number of events; IP = investigational product; N = number of subjects in SAF; n = number of subjects reporting at least 1 event in the specific category; SAE = serious adverse event; SAF = safety analysis set in the primary evaluation and secondary evaluation periods; TEAE = treatment-emergent adverse event; % = n / N × 100

All TEAEs for which a causal relationship with the IP cannot be ruled out were considered ADRs.

Adverse events by system organ class and preferred term

Phase I PK/PD study RGB192101 (healthy adult males)

Table 38: Summary of treatment-emergent adverse events by system organ class and preferred term (overall) – safety analysis set.

SOC PT	TEAEs					
	Treatment				Total	
	RGB-19 (N=108)		Tocilizumab (RoActemra) (N=104)		(N=110)	
	n (%)	e	n (%)	e	n (%)	e
All TEAEs	**51 (47.2)**	**76**	**53 (51.0)**	**78**	**70 (63.6)**	**154**
Infections and infestations	**9 (8.3)**	**10**	**7 (6.7)**	**7**	**15 (13.6)**	**17**
Upper respiratory tract infection	5 (4.6)	5	5 (4.8)	5	9 (8.2)	10
Influenza	3 (2.8)	3	0 (0.0)	0	3 (2.7)	3
Oral herpes	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Bacterial urethritis	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Nasopharyngitis	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1
Tonsillitis	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1
Immune system disorders	**1 (0.9)**	**1**	**0 (0.0)**	**0**	**1 (0.9)**	**1**
Food allergy	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Psychiatric disorders	**0 (0.0)**	**0**	**1 (1.0)**	**1**	1 (0.9)	1
Insomnia	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1
Nervous system disorders	**3 (2.8)**	**3**	**4 (3.8)**	**4**	**6 (5.5)**	**7**
Presyncope	0 (0.0)	0	3 (2.9)	3	3 (2.7)	3
Headache	2 (1.9)	2	1 (1.0)	1	2 (1.8)	3
Dizziness postural	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Ear and labyrinth disorders	**2 (1.9)**	**3**	**0 (0.0)**	**0**	**2 (1.8)**	**3**
Eustachian tube obstruction	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Motion sickness	1 (0.9)	2	0 (0.0)	0	1 (0.9)	2
Respiratory, thoracic and mediastinal disorders	**3 (2.8)**	**3**	**4 (3.8)**	**4**	**6 (5.5)**	**7**
Oropharyngeal pain	1 (0.9)	1	2 (1.9)	2	3 (2.7)	3
Epistaxis	1 (0.9)	1	1 (1.0)	1	1 (0.9)	2
Rhinorrhoea	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Haemoptysis	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1
Gastrointestinal disorders	**7 (6.5)**	**7**	**4 (3.8)**	**5**	**10 (9.1)**	**12**
Diarrhoea	2 (1.9)	2	1 (1.0)	1	3 (2.7)	3
Nausea	1 (0.9)	1	1 (1.0)	1	2 (1.8)	2
Faeces soft	1 (0.9)	1	1 (1.0)	1	2 (1.8)	2
Aphthous ulcer	0 (0.0)	0	2 (1.9)	2	2 (1.8)	2
Abdominal discomfort	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Stomatitis	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Toothache	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Skin and subcutaneous tissue disorders	**4 (3.7)**	**4**	**4 (3.8)**	**4**	**8 (7.3)**	**8**
Drug eruption	2 (1.9)	2	2 (1.9)	2	4 (3.6)	4

SOC PT	TEAEs					
	Treatment				Total	
	RGB-19 (N=108)		Tocilizumab (RoActemra) (N=104)		(N=110)	
	n (%)	e	n (%)	e	n (%)	e
Rash	2 (1.9)	2	1 (1.0)	1	3 (2.7)	3
Miliaria	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1
Musculoskeletal and connective tissue disorders	**2 (1.9)**	**2**	**1 (1.0)**	**1**	**3 (2.7)**	**3**
Arthralgia	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Back pain	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Myalgia	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1
Renal and urinary disorders	**2 (1.9)**	**2**	**1 (1.0)**	**2**	**3 (2.7)**	**4**
Haematuria	1 (0.9)	1	1 (1.0)	2	2 (1.8)	3
Urinary retention	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
General disorders and administration site conditions	**4 (3.7)**	**5**	**1 (1.0)**	**1**	**5 (4.5)**	**6**
Injection site pain	2 (1.9)	2	0 (0.0)	0	2 (1.8)	2
Feeling abnormal	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Vessel puncture site pain	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Vessel puncture site swelling	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Injection site erythema	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1
Investigations	**33 (30.6)**	**36**	**44 (42.3)**	**49**	**53 (48.2)**	**85**
Neutrophil count decreased	27 (25.0)	28	36 (34.6)	36	43 (39.1)	64
White blood cells urine positive	4 (3.7)	4	2 (1.9)	2	5 (4.5)	6
Alanine aminotransferase increased	2 (1.9)	2	3 (2.9)	3	3 (2.7)	5
Aspartate aminotransferase increased	1 (0.9)	1	1 (1.0)	1	2 (1.8)	2
Neutrophil count increased	0 (0.0)	0	2 (1.9)	2	2 (1.8)	2
Blood bilirubin increased	1 (0.9)	1	1 (1.0)	1	1 (0.9)	2
Blood glucose increased	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1
Blood triglycerides increased	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1
Glucose urine present	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1
Urinary occult blood	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1

e = number of events; IP = investigational product; MedDRA/J = Japanese translation of the Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects reporting at least one TEAE within SOC/PT; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event; % = n / N × 100

Notes: TEAEs starting after IP administration in Period 1 were assigned to the treatment in Period 1; TEAEs starting after IP administration in Period 2 were assigned to the treatment in Period 2.

MedDRA/J v27.0

Phase III Comparative efficacy and safety study RGB19101 (patients with active rheumatoid arthritis)

Table 39: Summary of TEAEs by SOC and PT until visit week 24 (treatment period and follow-up period).

System Organ Class Preferred Term	TEAEs								
	RGB-19 (N=182)			Tocilizumab (RoActemra) (N=186)			Total (N=368)		
	n	(%)	e	n	(%)	e	n	(%)	e
Any TEAEs	143	(78.6)	389	150	(80.6)	453	293	(79.6)	842
Infections and infestations	61	(33.5)	88	62	(33.3)	92	123	(33.4)	180
Nasopharyngitis	14	(7.7)	19	26	(14.0)	33	40	(10.9)	52
COVID-19	11	(6.0)	11	10	(5.4)	10	21	(5.7)	21
Upper respiratory tract infection	9	(4.9)	11	6	(3.2)	6	15	(4.1)	17
Pharyngitis	4	(2.2)	5	6	(3.2)	6	10	(2.7)	11
Sinusitis	6	(3.3)	6	2	(1.1)	3	8	(2.2)	9
Paronychia	2	(1.1)	2	6	(3.2)	6	8	(2.2)	8
Bronchitis	4	(2.2)	4	3	(1.6)	4	7	(1.9)	8
Herpes zoster	3	(1.6)	3	2	(1.1)	2	5	(1.4)	5
Gastroenteritis	3	(1.6)	4	1	(0.5)	1	4	(1.1)	5
Gingivitis	2	(1.1)	2	2	(1.1)	2	4	(1.1)	4
Cystitis	1	(0.5)	1	3	(1.6)	3	4	(1.1)	4
Oral herpes	2	(1.1)	2	1	(0.5)	1	3	(0.8)	3
Localised infection	2	(1.1)	2	0	(0.0)	0	2	(0.5)	2
Tonsillitis	2	(1.1)	2	0	(0.0)	0	2	(0.5)	2
Cellulitis	1	(0.5)	2	1	(0.5)	1	2	(0.5)	3
Influenza	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Pneumocystis jirovecii pneumonia	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Appendicitis	0	(0.0)	0	2	(1.1)	2	2	(0.5)	2
Acute sinusitis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Folliculitis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Otitis media	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Pneumonia	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Subcutaneous abscess	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Tinea pedis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Vulvovaginal candidiasis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Pharyngotonsillitis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Enteritis infectious	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Post-acute COVID-19 syndrome	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Conjunctivitis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Hordeolum	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Otitis externa	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Periodontitis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Pulpitis dental	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Pyelonephritis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Rhinitis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Skin infection	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Urinary tract infection	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Biliary tract infection	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1

System Organ Class Preferred Term	TEAEs								
	RGB-19			Tocilizumab (RoActemra)			Total		
	(N=182)			(N=186)			(N=368)		
	n	(%)	e	n	(%)	e	n	(%)	e
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Colon cancer	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Blood and lymphatic system disorders	5	(2.7)	6	3	(1.6)	4	8	(2.2)	10
Leukopenia	2	(1.1)	2	0	(0.0)	0	2	(0.5)	2
Iron deficiency anaemia	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Neutropenia	1	(0.5)	1	1	(0.5)	2	2	(0.5)	3
Anaemia	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Myelosuppression	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Hypochromic anaemia	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Immune system disorders	1	(0.5)	1	3	(1.6)	4	4	(1.1)	5
Seasonal allergy	1	(0.5)	1	2	(1.1)	2	3	(0.8)	3
Drug hypersensitivity	0	(0.0)	0	1	(0.5)	2	1	(0.3)	2
Metabolism and nutrition disorders	14	(7.7)	15	16	(8.6)	17	30	(8.2)	32
Dyslipidaemia	6	(3.3)	6	7	(3.8)	7	13	(3.5)	13
Hyperlipidaemia	3	(1.6)	3	5	(2.7)	5	8	(2.2)	8
Hypercholesterolaemia	1	(0.5)	2	1	(0.5)	1	2	(0.5)	3
Hypertriglyceridaemia	0	(0.0)	0	2	(1.1)	2	2	(0.5)	2
Gout	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Hypoproteinaemia	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Lipid metabolism disorder	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Hypercreatininaemia	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Hypokalaemia	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Decreased appetite	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Psychiatric disorders	3	(1.6)	3	1	(0.5)	1	4	(1.1)	4
Insomnia	2	(1.1)	2	0	(0.0)	0	2	(0.5)	2
Delusion	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Anxiety disorder	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Nervous system disorders	8	(4.4)	10	12	(6.5)	12	20	(5.4)	22
Headache	3	(1.6)	3	2	(1.1)	2	5	(1.4)	5
Dizziness	2	(1.1)	2	1	(0.5)	1	3	(0.8)	3
Hypoaesthesia	1	(0.5)	3	2	(1.1)	2	3	(0.8)	5
Dizziness postural	2	(1.1)	2	0	(0.0)	0	2	(0.5)	2
Amnesia	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Epilepsy	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Nervous system disorder	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Presyncope	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Intercostal neuralgia	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Carotid arteriosclerosis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Taste disorder	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1

System Organ Class Preferred Term	TEAEs								
	RGB-19 (N=182)			Tocilizumab (RoActemra) (N=186)			Total (N=368)		
	n	(%)	e	n	(%)	e	n	(%)	e
Eye disorders	6	(3.3)	6	3	(1.6)	4	9	(2.4)	10
Conjunctivitis allergic	2	(1.1)	2	2	(1.1)	2	4	(1.1)	4
Dry eye	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Eye discharge	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Eyelid oedema	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Keratitis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Asthenopia	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Blepharitis allergic	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Ear and labyrinth disorders	4	(2.2)	4	0	(0.0)	0	4	(1.1)	4
Vertigo	2	(1.1)	2	0	(0.0)	0	2	(0.5)	2
Otorrhoea	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Vertigo positional	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Cardiac disorders	3	(1.6)	3	4	(2.2)	4	7	(1.9)	7
Tachycardia	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Atrial fibrillation	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Palpitations	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Atrioventricular block complete	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Sinus arrhythmia	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Acute coronary syndrome	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Vascular disorders	2	(1.1)	2	5	(2.7)	5	7	(1.9)	7
Hypertension	1	(0.5)	1	3	(1.6)	3	4	(1.1)	4
Thrombosis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Hypotension	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Shock haemorrhagic	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Respiratory, thoracic and mediastinal disorders	9	(4.9)	18	18	(9.7)	23	27	(7.3)	41
Cough	5	(2.7)	6	5	(2.7)	5	10	(2.7)	11
Oropharyngeal pain	5	(2.7)	6	4	(2.2)	6	9	(2.4)	12
Asthma	1	(0.5)	1	2	(1.1)	3	3	(0.8)	4
Rhinorrhoea	2	(1.1)	2	0	(0.0)	0	2	(0.5)	2
Rhinitis allergic	0	(0.0)	0	2	(1.1)	2	2	(0.5)	2
Productive cough	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Upper respiratory tract inflammation	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Lung opacity	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Dry throat	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Epistaxis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Interstitial lung disease	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Pulmonary toxicity	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Diffuse panbronchiolitis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Oropharyngeal discomfort	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Hypersensitivity pneumonitis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1

System Organ Class Preferred Term	TEAEs								
	RGB-19 (N=182)			Tocilizumab (RoActemra) (N=186)			Total (N=368)		
	n	(%)	e	n	(%)	e	n	(%)	e
Gastrointestinal disorders	54	(29.7)	68	45	(24.2)	67	99	(26.9)	135
Stomatitis	27	(14.8)	30	23	(12.4)	28	50	(13.6)	58
Dental caries	4	(2.2)	4	5	(2.7)	5	9	(2.4)	9
Constipation	6	(3.3)	6	1	(0.5)	1	7	(1.9)	7
Nausea	3	(1.6)	3	3	(1.6)	3	6	(1.6)	6
Diarrhoea	2	(1.1)	2	4	(2.2)	4	6	(1.6)	6
Abdominal pain upper	2	(1.1)	2	2	(1.1)	3	4	(1.1)	5
Abdominal discomfort	1	(0.5)	1	3	(1.6)	3	4	(1.1)	4
Toothache	3	(1.6)	3	0	(0.0)	0	3	(0.8)	3
Abdominal pain	1	(0.5)	1	2	(1.1)	2	3	(0.8)	3
Gastritis	1	(0.5)	1	2	(1.1)	2	3	(0.8)	3
Faeces soft	1	(0.5)	1	2	(1.1)	3	3	(0.8)	4
Vomiting	0	(0.0)	0	3	(1.6)	3	3	(0.8)	3
Enterocolitis	2	(1.1)	2	0	(0.0)	0	2	(0.5)	2
Dyspepsia	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Periodontal disease	0	(0.0)	0	2	(1.1)	2	2	(0.5)	2
Abdominal distension	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Abdominal pain lower	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Anal fissure	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Cheilitis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Gastric polyps	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Gastrooesophageal reflux disease	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Glossitis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Large intestine perforation	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Mouth ulceration	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Peptic ulcer	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Large intestine polyp	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Aphthous ulcer	0	(0.0)	0	1	(0.5)	2	1	(0.3)	2
Chronic gastritis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Colitis ischaemic	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Gastric ulcer haemorrhage	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Gastrointestinal disorder	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Anal fissure haemorrhage	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Hepatobiliary disorders	11	(6.0)	11	13	(7.0)	13	24	(6.5)	24
Hepatic function abnormal	8	(4.4)	8	12	(6.5)	12	20	(5.4)	20
Cholecystitis acute	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Cholelithiasis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Liver disorder	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Hepatic steatosis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1

System Organ Class Preferred Term	TEAEs								
	RGB-19 (N=182)			Tocilizumab (RoActemra) (N=186)			Total (N=368)		
	n	(%)	e	n	(%)	e	n	(%)	e
Skin and subcutaneous tissue disorders	23	(12.6)	27	35	(18.8)	40	58	(15.8)	67
Rash	6	(3.3)	6	6	(3.2)	8	12	(3.3)	14
Dermatitis contact	4	(2.2)	4	3	(1.6)	3	7	(1.9)	7
Eczema	2	(1.1)	2	5	(2.7)	5	7	(1.9)	7
Urticaria	2	(1.1)	2	4	(2.2)	4	6	(1.6)	6
Ingrowing nail	2	(1.1)	2	2	(1.1)	2	4	(1.1)	4
Miliaria	1	(0.5)	1	2	(1.1)	2	3	(0.8)	3
Alopecia	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Dermatitis	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Hand dermatitis	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Drug eruption	0	(0.0)	0	2	(1.1)	2	2	(0.5)	2
Skin ulcer	0	(0.0)	0	2	(1.1)	2	2	(0.5)	2
Blister	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Dry skin	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Dyshidrotic eczema	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Erythema multiforme	1	(0.5)	2	0	(0.0)	0	1	(0.3)	2
Haemorrhage subcutaneous	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Nail bed bleeding	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Acne	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Dermal cyst	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Dermatitis allergic	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Eczema asteatotic	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Hyperkeratosis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Onycholysis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Prurigo	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Pruritus	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Rash erythematous	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1

System Organ Class Preferred Term	TEAEs								
	RGB-19			Tocilizumab (RoActemra)			Total		
	(N=182)			(N=186)			(N=368)		
	n	(%)	e	n	(%)	e	n	(%)	e
Musculoskeletal and connective tissue disorders	8	(4.4)	9	20	(10.8)	23	28	(7.6)	32
Rheumatoid arthritis	1	(0.5)	1	3	(1.6)	3	4	(1.1)	4
Back pain	1	(0.5)	1	2	(1.1)	2	3	(0.8)	3
Osteoporosis	1	(0.5)	1	2	(1.1)	2	3	(0.8)	3
Tenosynovitis	0	(0.0)	0	3	(1.6)	3	3	(0.8)	3
Intervertebral disc protrusion	0	(0.0)	0	3	(1.6)	3	3	(0.8)	3
Arthralgia	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Pain in extremity	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Periarthritis	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Neck pain	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Osteoarthritis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Synovial cyst	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Bursitis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Joint effusion	0	(0.0)	0	1	(0.5)	2	1	(0.3)	2
Muscle spasms	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Musculoskeletal stiffness	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Haematoma muscle	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Temporomandibular pain and dysfunction syndrome	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Renal and urinary disorders	2	(1.1)	2	1	(0.5)	1	3	(0.8)	3
Nephrolithiasis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Ureterolithiasis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Renal impairment	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Reproductive system and breast disorders	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Menopausal symptoms	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Benign prostatic hyperplasia	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
General disorders and administration site conditions	4	(2.2)	4	6	(3.2)	9	10	(2.7)	13
Pyrexia	2	(1.1)	2	1	(0.5)	1	3	(0.8)	3
Malaise	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Chest pain	0	(0.0)	0	2	(1.1)	2	2	(0.5)	2
Chills	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Feeling abnormal	0	(0.0)	0	1	(0.5)	2	1	(0.3)	2
Injection site reaction	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Oedema	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Infusion site swelling	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1

System Organ Class Preferred Term	TEAEs								
	RGB-19 (N=182)			Tocilizumab (RoActemra) (N=186)			Total (N=368)		
	n	(%)	e	n	(%)	e	n	(%)	e
Investigations	65	(35.7)	91	70	(37.6)	116	135	(36.7)	207
White blood cell count decreased	12	(6.6)	14	21	(11.3)	25	33	(9.0)	39
Liver function test increased	13	(7.1)	13	11	(5.9)	11	24	(6.5)	24
Hepatic enzyme increased	10	(5.5)	11	12	(6.5)	12	22	(6.0)	23
Liver function test abnormal	10	(5.5)	12	11	(5.9)	12	21	(5.7)	24
Neutrophil count decreased	3	(1.6)	3	10	(5.4)	13	13	(3.5)	16
Alanine aminotransferase increased	3	(1.6)	3	6	(3.2)	7	9	(2.4)	10
Blood triglycerides increased	5	(2.7)	8	3	(1.6)	3	8	(2.2)	11
Aspartate aminotransferase increased	3	(1.6)	3	5	(2.7)	5	8	(2.2)	8
Blood cholesterol increased	1	(0.5)	1	6	(3.2)	6	7	(1.9)	7
Platelet count decreased	4	(2.2)	4	2	(1.1)	3	6	(1.6)	7
Blood bilirubin increased	3	(1.6)	3	2	(1.1)	2	5	(1.4)	5
Eosinophil count increased	3	(1.6)	3	1	(0.5)	1	4	(1.1)	4
Blood lactate dehydrogenase increased	2	(1.1)	2	2	(1.1)	2	4	(1.1)	4
Weight increased	2	(1.1)	2	1	(0.5)	1	3	(0.8)	3
Gamma-glutamyltransferase increased	1	(0.5)	1	2	(1.1)	2	3	(0.8)	3
Lipids increased	0	(0.0)	0	3	(1.6)	3	3	(0.8)	3
Blood pressure increased	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Lipids abnormal	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Lymphocyte count decreased	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Blood urea increased	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Monocyte count increased	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Protein urine	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
White blood cells urine positive	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Interleukin-2 receptor increased	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Haematocrit decreased	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Haemoglobin decreased	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Intraocular pressure increased	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Red blood cell count decreased	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Weight decreased	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1

System Organ Class Preferred Term	TEAEs								
	RGB-19 (N=182)			Tocilizumab (RoActemra) (N=186)			Total (N=368)		
	n	(%)	e	n	(%)	e	n	(%)	e
Injury, poisoning and procedural complications	15	(8.2)	20	14	(7.5)	15	29	(7.9)	35
Arthropod sting	3	(1.6)	3	4	(2.2)	4	7	(1.9)	7
Wound	3	(1.6)	3	3	(1.6)	3	6	(1.6)	6
Contusion	2	(1.1)	2	1	(0.5)	1	3	(0.8)	3
Tendon rupture	2	(1.1)	2	0	(0.0)	0	2	(0.5)	2
Ligament sprain	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Skin abrasion	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Immunisation reaction	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Mallet finger	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Spinal compression fracture	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Thermal burns of eye	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Infusion related reaction	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Heat illness	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Meniscus injury	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Limb fracture	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Chillblains	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Thoracic vertebral fracture	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Tooth fracture	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Nail injury	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Eye contusion	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Social circumstances	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Overwork	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1

e = number of events; N = number of subjects; n = number of subjects reporting at least one TEAE within SOC/PT;

PT = preferred term; SAF = safety analysis set in the primary evaluation and secondary evaluation periods;

SOC = system organ class; TEAE = treatment-emergent adverse event; % = n / N × 100

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5.4.4. Adverse drug reactions

Phase I PK/PD study RGB192101 (healthy adult males)

Table 40: Summary of adverse drug reactions by system organ class and preferred term (overall) – safety analysis set (N=110).

SOC PT	ADRs					
	Treatment				Total	
	RGB-19 (N=108)		Tocilizumab (RoActemra) (N=104)		(N=110)	
	n (%)	e	n (%)	e	n (%)	e
All ADRs	**36 (33.3)**	**45**	**45 (43.3)**	**59**	**55 (50.0)**	**104**
Infections and infestations	**6 (5.6)**	**6**	**6 (5.8)**	**6**	**11 (10.0)**	**12**
Upper respiratory tract infection	5 (4.6)	5	5 (4.8)	5	9 (8.2)	10
Influenza	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Tonsillitis	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1
Nervous system disorders	**0 (0.0)**	**0**	**2 (1.9)**	**2**	**2 (1.8)**	**2**
Presyncope	0 (0.0)	0	2 (1.9)	2	2 (1.8)	2
Respiratory, thoracic and mediastinal disorders	**1 (0.9)**	**1**	**2 (1.9)**	**2**	**3 (2.7)**	**3**
Oropharyngeal pain	1 (0.9)	1	1 (1.0)	1	2 (1.8)	2
Haemoptysis	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1
Gastrointestinal disorders	**2 (1.9)**	**2**	**3 (2.9)**	**4**	**4 (3.6)**	**6**
Aphthous ulcer	0 (0.0)	0	2 (1.9)	2	2 (1.8)	2
Stomatitis	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Faeces soft	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Diarrhoea	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1
Nausea	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1
Skin and subcutaneous tissue disorders	**3 (2.8)**	**3**	**2 (1.9)**	**2**	**5 (4.5)**	**5**
Drug eruption	2 (1.9)	2	2 (1.9)	2	4 (3.6)	4
Rash	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**0**	**1 (1.0)**	**1**	**1 (0.9)**	**1**
Myalgia	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1
General disorders and administration site conditions	**2 (1.9)**	**2**	**1 (1.0)**	**1**	**3 (2.7)**	**3**
Injection site pain	2 (1.9)	2	0 (0.0)	0	2 (1.8)	2
Injection site erythema	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1
Investigations	**30 (27.8)**	**31**	**38 (36.5)**	**41**	**45 (40.9)**	**72**
Neutrophil count decreased	27 (25.0)	27	36 (34.6)	36	43 (39.1)	63
Alanine aminotransferase increased	2 (1.9)	2	2 (1.9)	2	2 (1.8)	4
Blood bilirubin increased	1 (0.9)	1	1 (1.0)	1	1 (0.9)	2
White blood cells urine positive	1 (0.9)	1	1 (1.0)	1	1 (0.9)	2
Urinary occult blood	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1

ADR = adverse drug reaction; e = number of events; IP = investigational product; MedDRA/J = Japanese translation of the Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects reporting at least one ADR within SOC/PT; PT = preferred term; SOC = system organ class; % = n / N × 100

Notes: ADRs starting after IP administration in Period 1 were assigned to the treatment in Period 1; ADRs starting after IP administration in Period 2 were assigned to the treatment in Period 2.

All TEAEs for which a causal relationship with the IP cannot be ruled out were considered ADRs.

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Phase III Comparative efficacy and safety study RGB19101 (patients with active rheumatoid arthritis)

Table 41: Summary of ADRs by SOC and PT until Visit Week 24 (Treatment period and follow-up period).

System Organ Class Preferred Term	ADRs								
	RGB-19 (N=182)			Tocilizumab (RoActemra) (N=186)			Total (N=368)		
	n	(%)	e	n	(%)	e	n	(%)	e
Any ADRs	82	(45.1)	151	91	(48.9)	168	173	(47.0)	319
Infections and infestations	23	(12.6)	30	19	(10.2)	24	42	(11.4)	54
Nasopharyngitis	5	(2.7)	6	4	(2.2)	4	9	(2.4)	10
Upper respiratory tract infection	3	(1.6)	3	3	(1.6)	3	6	(1.6)	6
COVID-19	2	(1.1)	2	3	(1.6)	3	5	(1.4)	5
Herpes zoster	3	(1.6)	3	1	(0.5)	1	4	(1.1)	4
Pharyngitis	2	(1.1)	3	1	(0.5)	1	3	(0.8)	4
Cystitis	0	(0.0)	0	3	(1.6)	3	3	(0.8)	3
Sinusitis	2	(1.1)	2	0	(0.0)	0	2	(0.5)	2
Oral herpes	2	(1.1)	2	0	(0.0)	0	2	(0.5)	2
Cellulitis	1	(0.5)	2	1	(0.5)	1	2	(0.5)	3
Pneumocystis jirovecii pneumonia	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Acute sinusitis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Gastroenteritis	1	(0.5)	2	0	(0.0)	0	1	(0.3)	2
Pneumonia	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Subcutaneous abscess	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Vulvovaginal candidiasis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Appendicitis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Bronchitis	0	(0.0)	0	1	(0.5)	2	1	(0.3)	2
Conjunctivitis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Gingivitis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Pyelonephritis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Biliary tract infection	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Blood and lymphatic system disorders	4	(2.2)	4	1	(0.5)	2	5	(1.4)	6
Leukopenia	2	(1.1)	2	0	(0.0)	0	2	(0.5)	2
Neutropenia	1	(0.5)	1	1	(0.5)	2	2	(0.5)	3
Anaemia	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Immune system disorders	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Drug hypersensitivity	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Metabolism and nutrition disorders	10	(5.5)	11	10	(5.4)	10	20	(5.4)	21
Dyslipidaemia	4	(2.2)	4	4	(2.2)	4	8	(2.2)	8
Hyperlipidaemia	3	(1.6)	3	3	(1.6)	3	6	(1.6)	6
Hypercholesterolaemia	1	(0.5)	2	1	(0.5)	1	2	(0.5)	3
Hypertriglyceridaemia	0	(0.0)	0	2	(1.1)	2	2	(0.5)	2
Hypoproteinaemia	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Lipid metabolism disorder	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Nervous system disorders	0	(0.0)	0	4	(2.2)	4	4	(1.1)	4
Epilepsy	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Hypoaesthesia	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Nervous system disorder	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Taste disorder	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1

System Organ Class Preferred Term	ADRs								
	RGB-19 (N=182)			Tocilizumab (RoActemra) (N=186)			Total (N=368)		
	n	(%)	e	n	(%)	e	n	(%)	e
Respiratory, thoracic and mediastinal disorders	7	(3.8)	14	4	(2.2)	5	11	(3.0)	19
Cough	4	(2.2)	5	1	(0.5)	1	5	(1.4)	6
Rhinorrhoea	2	(1.1)	2	0	(0.0)	0	2	(0.5)	2
Oropharyngeal pain	2	(1.1)	3	0	(0.0)	0	2	(0.5)	3
Asthma	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Productive cough	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Upper respiratory tract inflammation	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Lung opacity	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Interstitial lung disease	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Pulmonary toxicity	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Diffuse panbronchiolitis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Oropharyngeal discomfort	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Gastrointestinal disorders	8	(4.4)	10	8	(4.3)	9	16	(4.3)	19
Stomatitis	5	(2.7)	6	5	(2.7)	5	10	(2.7)	11
Faeces soft	0	(0.0)	0	2	(1.1)	3	2	(0.5)	3
Abdominal distension	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Abdominal pain	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Enterocolitis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Large intestine perforation	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Abdominal pain upper	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Hepatobiliary disorders	7	(3.8)	7	11	(5.9)	11	18	(4.9)	18
Hepatic function abnormal	7	(3.8)	7	10	(5.4)	10	17	(4.6)	17
Hepatic steatosis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Skin and subcutaneous tissue disorders	4	(2.2)	4	5	(2.7)	5	9	(2.4)	9
Rash	3	(1.6)	3	3	(1.6)	3	6	(1.6)	6
Eczema	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Drug eruption	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Hyperkeratosis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
General disorders and administration site conditions	1	(0.5)	1	2	(1.1)	2	3	(0.8)	3
Malaise	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Infusion site swelling	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1

System Organ Class Preferred Term	ADRs								
	RGB-19			Tocilizumab (RoActemra)			Total		
	(N=182)			(N=186)			(N=368)		
	n	(%)	e	n	(%)	e	n	(%)	e
Investigations	50	(27.5)	69	55	(29.6)	95	105	(28.5)	164
White blood cell count decreased	12	(6.6)	14	21	(11.3)	25	33	(9.0)	39
Hepatic enzyme increased	8	(4.4)	9	9	(4.8)	9	17	(4.6)	18
Liver function test increased	8	(4.4)	8	8	(4.3)	8	16	(4.3)	16
Neutrophil count decreased	3	(1.6)	3	10	(5.4)	13	13	(3.5)	16
Liver function test abnormal	5	(2.7)	5	6	(3.2)	6	11	(3.0)	11
Aspartate aminotransferase increased	3	(1.6)	3	5	(2.7)	5	8	(2.2)	8
Alanine aminotransferase increased	3	(1.6)	3	4	(2.2)	5	7	(1.9)	8
Blood cholesterol increased	1	(0.5)	1	6	(3.2)	6	7	(1.9)	7
Platelet count decreased	4	(2.2)	4	2	(1.1)	3	6	(1.6)	7
Blood triglycerides increased	3	(1.6)	6	2	(1.1)	2	5	(1.4)	8
Blood bilirubin increased	3	(1.6)	3	1	(0.5)	1	4	(1.1)	4
Blood lactate dehydrogenase increased	2	(1.1)	2	2	(1.1)	2	4	(1.1)	4
Gamma-glutamyltransferase increased	1	(0.5)	1	2	(1.1)	2	3	(0.8)	3
Lipids increased	0	(0.0)	0	3	(1.6)	3	3	(0.8)	3
Eosinophil count increased	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Lymphocyte count decreased	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Blood pressure increased	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Lipids abnormal	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Monocyte count increased	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Weight increased	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Interleukin-2 receptor increased	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Haematocrit decreased	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Haemoglobin decreased	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Red blood cell count decreased	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Injury, poisoning and procedural complications	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Infusion related reaction	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1

ADR = adverse drug reaction; e = number of events; N = number of subjects; n = number of subjects reporting at least one ADR within SOC/PT; PT = preferred term; SAF = safety analysis set in the primary evaluation and secondary evaluation periods; SOC = system organ class; TEAE = treatment-emergent adverse event; % = n / N × 100
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All TEAEs for which a causal relationship with the IP cannot be ruled out were considered ADRs.

5.4.5. Adverse events of special interest, serious adverse events and deaths, other significant events

AEs of special interest

Phase I PK/PD study RGB192101 (healthy adult males)

The following TEAEs were identified as AESIs

- Infections
- Tuberculosis
- Hypersensitivity
- HBV reactivation
- Pleurisy

- Abnormal lipid levels in tests
- Heart failures
- Interstitial pneumonia
- Diverticulitis/intestinal perforation
- Cytopenia/thrombocytopenia
- Hepatic function disorder
- Malignant tumours and unspecified tumours
- Cerebrovascular disorder
- Demyelinating disorders
- Administration site reactions

.

Table 42: Summary of adverse events of special interest by system organ class and preferred term (overall) – safety analysis set (N=110).

	AESIs					
Category of AESI	**Treatment**				**Total**	
SOC	**RGB-19**		**Tocilizumab (RoActemra)**			
PT	**(N=108)**		**(N=104)**		**(N=110)**	
	n (%)	**e**	**n (%)**	**e**	**n (%)**	**e**
All AESIs	**37 (34.3)**	**48**	**45 (43.3)**	**53**	**59 (53.6)**	**101**
Infections	**9 (8.3)**	**10**	**7 (6.7)**	**7**	**15 (13.6)**	**17**
Infections and infestations	**9 (8.3)**	**10**	**7 (6.7)**	**7**	**15 (13.6)**	**17**
Upper respiratory tract infection	5 (4.6)	5	5 (4.8)	5	9 (8.2)	10
Influenza	3 (2.8)	3	0 (0.0)	0	3 (2.7)	3
Oral herpes	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Bacterial urethritis	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Nasopharyngitis	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1
Tonsillitis	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1
Hypersensitivity	**4 (3.7)**	**4**	**3 (2.9)**	**3**	**7 (6.4)**	**7**
Skin and subcutaneous tissue disorders	**4 (3.7)**	**4**	**3 (2.9)**	**3**	**7 (6.4)**	**7**
Drug eruption	2 (1.9)	2	2 (1.9)	2	4 (3.6)	4
Rash	2 (1.9)	2	1 (1.0)	1	3 (2.7)	3
Abnormal Lipid Levels in Tests	**0 (0.0)**	**0**	**1 (1.0)**	**1**	**1 (0.9)**	**1**
Investigations	**0 (0.0)**	**0**	**1 (1.0)**	**1**	**1 (0.9)**	**1**
Blood triglycerides increased	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1
Cytopenia/Thrombocytopenia	**27 (25.0)**	**28**	**36 (34.6)**	**36**	**43 (39.1)**	**64**
Investigations	**27 (25.0)**	**28**	**36 (34.6)**	**36**	**43 (39.1)**	**64**
Neutrophil count decreased	27 (25.0)	28	36 (34.6)	36	43 (39.1)	64
Hepatic Function Disorder	**4 (3.7)**	**4**	**5 (4.8)**	**5**	**6 (5.5)**	**9**
Investigations	**4 (3.7)**	**4**	**5 (4.8)**	**5**	**6 (5.5)**	**9**
Alanine aminotransferase increased	2 (1.9)	2	3 (2.9)	3	3 (2.7)	5
Aspartate aminotransferase increased	1 (0.9)	1	1 (1.0)	1	2 (1.8)	2
Blood bilirubin increased	1 (0.9)	1	1 (1.0)	1	1 (0.9)	2
Administration Site Reactions	**2 (1.9)**	**2**	**1 (1.0)**	**1**	**3 (2.7)**	**3**
General disorders and administration site conditions	**2 (1.9)**	**2**	**1 (1.0)**	**1**	**3 (2.7)**	**3**
Injections site pain	2 (1.9)	2	0 (0.0)	0	2 (1.8)	2
Injection site erythema	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1

AESI = adverse event of special interest; e = number of events; IP = investigational product; MedDRA/J = Japanese translation of the Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects reporting at least one AESI within SOC/PT; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event; % = n / N × 100

Notes: TEAEs starting after IP administration in Period 1 were assigned to the treatment in Period 1; TEAEs starting after IP administration in Period 2 were assigned to the treatment in Period 2.

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<u>Phase III Comparative efficacy and safety study RGB19101 (patients with active rheumatoid arthritis)</u>

The following TEAEs were identified as AESIs

- Infections
- Tuberculosis
- Hypersensitivity
- HBV reactivation
- Pleurisy

- Abnormal lipid levels in tests
- Heart failures
- Interstitial pneumonia
- Diverticulitis/intestinal perforation
- Cytopenia/thrombocytopenia
- Hepatic function disorder
- Malignant tumours and unspecified tumours
- Cerebrovascular disorder
- Demyelinating disorders
- Administration site reactions

.

Table 43: Summary of AESIs by SOC and PT until visit week 24 (treatment period and follow-up period).

Category of AESI System Organ Class Preferred Term	AESIs								
	RGB-19 (N=182)			Tocilizumab (RoActemra) (N=186)			Total (N=368)		
	n	(%)	e	n	(%)	e	n	(%)	e
Any AESIs	125	(68.7)	214	131	(70.4)	269	256	(69.6)	483
Infections	61	(33.5)	88	63	(33.9)	93	124	(33.7)	181
Infections and infestations	61	(33.5)	88	62	(33.3)	92	123	(33.4)	180
Nasopharyngitis	14	(7.7)	19	26	(14.0)	33	40	(10.9)	52
COVID-19	11	(6.0)	11	10	(5.4)	10	21	(5.7)	21
Upper respiratory tract infection	9	(4.9)	11	6	(3.2)	6	15	(4.1)	17
Pharyngitis	4	(2.2)	5	6	(3.2)	6	10	(2.7)	11
Sinusitis	6	(3.3)	6	2	(1.1)	3	8	(2.2)	9
Paronychia	2	(1.1)	2	6	(3.2)	6	8	(2.2)	8
Bronchitis	4	(2.2)	4	3	(1.6)	4	7	(1.9)	8
Herpes zoster	3	(1.6)	3	2	(1.1)	2	5	(1.4)	5
Gastroenteritis	3	(1.6)	4	1	(0.5)	1	4	(1.1)	5
Gingivitis	2	(1.1)	2	2	(1.1)	2	4	(1.1)	4
Cystitis	1	(0.5)	1	3	(1.6)	3	4	(1.1)	4
Oral herpes	2	(1.1)	2	1	(0.5)	1	3	(0.8)	3
Localised infection	2	(1.1)	2	0	(0.0)	0	2	(0.5)	2
Tonsillitis	2	(1.1)	2	0	(0.0)	0	2	(0.5)	2
Cellulitis	1	(0.5)	2	1	(0.5)	1	2	(0.5)	3
Influenza	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Pneumocystis jirovecii pneumonia	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Appendicitis	0	(0.0)	0	2	(1.1)	2	2	(0.5)	2
Acute sinusitis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Folliculitis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Otitis media	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Pneumonia	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Subcutaneous abscess	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Tinea pedis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Vulvovaginal candidiasis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Pharyngotonsillitis	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Enteritis infectious	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Post-acute COVID-19 syndrome	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Conjunctivitis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Hordeolum	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Otitis externa	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Periodontitis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Pulpitis dental	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Pyelonephritis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Rhinitis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Skin infection	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Urinary tract infection	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Biliary tract infection	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Gastrointestinal disorders	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Chronic gastritis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1

Category of AESI System Organ Class Preferred Term	AESIs								
	RGB-19			Tocilizumab (RoActemra)			Total		
	(N=182)			(N=186)			(N=368)		
	n	(%)	e	n	(%)	e	n	(%)	e
Hypersensitivity	21	(11.5)	22	29	(15.6)	34	50	(13.6)	56
Immune system disorders	0	(0.0)	0	1	(0.5)	2	1	(0.3)	2
Drug hypersensitivity	0	(0.0)	0	1	(0.5)	2	1	(0.3)	2
Eye disorders	3	(1.6)	3	2	(1.1)	3	5	(1.4)	6
Conjunctivitis allergic	2	(1.1)	2	2	(1.1)	2	4	(1.1)	4
Eyelid oedema	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Blepharitis allergic	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Respiratory, thoracic and mediastinal disorders	0	(0.0)	0	3	(1.6)	3	3	(0.8)	3
Rhinitis allergic	0	(0.0)	0	2	(1.1)	2	2	(0.5)	2
Hypersensitivity pneumonitis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Skin and subcutaneous tissue disorders	17	(9.3)	18	23	(12.4)	26	40	(10.9)	44
Rash	6	(3.3)	6	6	(3.2)	8	12	(3.3)	14
Dermatitis contact	4	(2.2)	4	3	(1.6)	3	7	(1.9)	7
Eczema	2	(1.1)	2	5	(2.7)	5	7	(1.9)	7
Urticaria	2	(1.1)	2	4	(2.2)	4	6	(1.6)	6
Dermatitis	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Hand dermatitis	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Drug eruption	0	(0.0)	0	2	(1.1)	2	2	(0.5)	2
Erythema multiforme	1	(0.5)	2	0	(0.0)	0	1	(0.3)	2
Dermatitis allergic	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Rash erythematous	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Injury, poisoning and procedural complications	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Infusion related reaction	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Abnormal Lipid Levels in Tests	18	(9.9)	22	26	(14.0)	28	44	(12.0)	50
Metabolism and nutrition disorders	11	(6.0)	12	15	(8.1)	15	26	(7.1)	27
Dyslipidaemia	6	(3.3)	6	7	(3.8)	7	13	(3.5)	13
Hyperlipidaemia	3	(1.6)	3	5	(2.7)	5	8	(2.2)	8
Hypercholesterolaemia	1	(0.5)	2	1	(0.5)	1	2	(0.5)	3
Hypertriglyceridaemia	0	(0.0)	0	2	(1.1)	2	2	(0.5)	2
Lipid metabolism disorder	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Investigations	7	(3.8)	10	11	(5.9)	13	18	(4.9)	23
Blood triglycerides increased	5	(2.7)	8	3	(1.6)	3	8	(2.2)	11
Blood cholesterol increased	1	(0.5)	1	6	(3.2)	6	7	(1.9)	7
Lipids increased	0	(0.0)	0	3	(1.6)	3	3	(0.8)	3
Lipids abnormal	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Heart Failures	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
General disorders and administration site conditions	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Oedema	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1

Category of AESI System Organ Class Preferred Term	AESIs								
	RGB-19 (N=182)			Tocilizumab (RoActemra) (N=186)			Total (N=368)		
	n	(%)	e	n	(%)	e	n	(%)	e
Interstitial Pneumonia	1	(0.5)	1	3	(1.6)	3	4	(1.1)	4
Respiratory, thoracic and mediastinal disorders	1	(0.5)	1	3	(1.6)	3	4	(1.1)	4
Lung opacity	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Interstitial lung disease	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Pulmonary toxicity	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Hypersensitivity pneumonitis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Diverticulitis/Intestinal Perforation	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Gastrointestinal disorders	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Large intestine perforation	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Cytopenia/Thrombocytopenia	23	(12.6)	25	29	(15.6)	44	52	(14.1)	69
Blood and lymphatic system disorders	3	(1.6)	3	1	(0.5)	2	4	(1.1)	5
Leukopenia	2	(1.1)	2	0	(0.0)	0	2	(0.5)	2
Neutropenia	1	(0.5)	1	1	(0.5)	2	2	(0.5)	3
Investigations	20	(11.0)	22	28	(15.1)	42	48	(13.0)	64
White blood cell count decreased	12	(6.6)	14	21	(11.3)	25	33	(9.0)	39
Neutrophil count decreased	3	(1.6)	3	10	(5.4)	13	13	(3.5)	16
Platelet count decreased	4	(2.2)	4	2	(1.1)	3	6	(1.6)	7
Lymphocyte count decreased	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Hepatic Function Disorder	47	(25.8)	55	54	(29.0)	64	101	(27.4)	119
Hepatobiliary disorders	9	(4.9)	9	13	(7.0)	13	22	(6.0)	22
Hepatic function abnormal	8	(4.4)	8	12	(6.5)	12	20	(5.4)	20
Liver disorder	1	(0.5)	1	0	(0.0)	0	1	(0.3)	1
Hepatic steatosis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Investigations	38	(20.9)	46	42	(22.6)	51	80	(21.7)	97
Liver function test increased	13	(7.1)	13	11	(5.9)	11	24	(6.5)	24
Hepatic enzyme increased	10	(5.5)	11	12	(6.5)	12	22	(6.0)	23
Liver function test abnormal	10	(5.5)	12	11	(5.9)	12	21	(5.7)	24
Alanine aminotransferase increased	3	(1.6)	3	6	(3.2)	7	9	(2.4)	10
Aspartate aminotransferase increased	3	(1.6)	3	5	(2.7)	5	8	(2.2)	8
Blood bilirubin increased	3	(1.6)	3	2	(1.1)	2	5	(1.4)	5
Gamma-glutamyltransferase increased	1	(0.5)	1	2	(1.1)	2	3	(0.8)	3
Malignant Tumors and Unspecified Tumors	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Colon cancer	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Cerebrovascular Disorder	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Nervous system disorders	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Carotid arteriosclerosis	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1

Category of AESI System Organ Class Preferred Term	AESIs								
	RGB-19			Tocilizumab (RoActemra)			Total		
	(N=182)			(N=186)			(N=368)		
	n	(%)	e	n	(%)	e	n	(%)	e
Administration Site Reactions	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
General disorders and administration site conditions	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1
Infusion site swelling	0	(0.0)	0	1	(0.5)	1	1	(0.3)	1

AESI = adverse events of special interest; e = number of events; N = number of subjects; n = number of subjects reporting at least one AESI within SOC/PT; PT = preferred term; SAF = safety analysis set in the primary evaluation and secondary evaluation periods; SOC = system organ class; % = n / N × 100
MedDRA Ver.27.0

Serious adverse events and deaths

Phase I PK/PD study RGB192101 (healthy adult males)

There were no SAEs or deaths reported during the study.

Phase III Comparative efficacy and safety study RGB19101 (patients with active rheumatoid arthritis)

Serious adverse events

Table 44: Summary of serious adverse events by system organ class and preferred term (treatment period and follow-up period).

	Serious Adverse Events					
	RGB-19 (N=182)		Tocilizumab (RoActemra) (N=186)		Total (N=368)	
SOC PT	n (%)	e	n (%)	e	n (%)	e
Any SAEs	**4 (2.2)**	**4**	**14 (7.5)**	**15**	**18 (4.9)**	**19**
Infections and infestations	**1 (0.5)**	**1**	**3 (1.6)**	**4**	**4 (1.1)**	**5**
Pneumocystis jirovecii pneumonia	1 (0.5)	1	1 (0.5)	1	2 (0.5)	2
Appendicitis	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Pyelonephritis	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Biliary tract infection	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps	**0 (0.0)**	**0**	**1 (0.5)**	**1**	**1 (0.3)**	**1**
Colon cancer	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Nervous system disorders	**0 (0.0)**	**0**	**2 (1.1)**	**2**	**2 (0.5)**	**2**
Epilepsy	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Nervous system disorder	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Cardiac disorders	**0 (0.0)**	**0**	**1 (0.5)**	**1**	**1 (0.3)**	**1**
Acute coronary syndrome	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Vascular disorders	**0 (0.0)**	**0**	**2 (1.1)**	**2**	**2 (0.5)**	**2**
Hypotension	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Shock haemorrhagic	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Respiratory, thoracic and mediastinal disorders	**0 (0.0)**	**0**	**3 (1.6)**	**3**	**3 (0.8)**	**3**
Interstitial lung disease	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Pulmonary toxicity	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Hypersensitivity pneumonitis	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Gastrointestinal disorders	**1 (0.5)**	**1**	**0 (0.0)**	**0**	**1 (0.3)**	**1**
Large intestine perforation	1 (0.5)	1	0 (0.0)	0	1 (0.3)	1
Hepatobiliary disorders	**1 (0.5)**	**1**	**0 (0.0)**	**0**	**1 (0.3)**	**1**
Cholecystitis acute	1 (0.5)	1	0 (0.0)	0	1 (0.3)	1
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**0**	**2 (1.1)**	**2**	**2 (0.5)**	**2**
Intervertebral disc protrusion	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Haematoma muscle	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Injury, poisoning and procedural complications	**1 (0.5)**	**1**	**0 (0.0)**	**0**	**1 (0.3)**	**1**
Spinal compression fracture	1 (0.5)	1	0 (0.0)	0	1 (0.3)	1

e = number of events; IP = investigational product; MedDRA/J = Japanese translation of the Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects reporting at least 1 SAE within SOC/PT; PT = preferred term; SAE = serious adverse event; SAF = safety analysis set in the primary evaluation and secondary evaluation periods; SAE = serious adverse event; SOC = system organ class; TEAE = treatment-emergent adverse event; % = n / N × 100
MedDRA/J v27.0
Pre-treatment AEs were not included in this table.

Deaths

There was 1 death during the study due to a TEAE of severe shock haemorrhagic which started 161 days after the first administration of IP. The 56-year-old male subject received tocilizumab (RoActemra) during the study. This was an accidental fatal event due to a road traffic accident. Considering all information available, the Sponsor and Investigator assessed that the event was accidental, and the IP did not contribute to the onset of the event (no other AEs were reported at the time of death and there were no changes in the dosage and administration of the IP). Therefore, the event was considered to be unrelated to IP.

Other significant events

Phase I PK/PD study RGB192101 (healthy adult males)

No other significant events were reported during the study.

Phase III Comparative efficacy and safety study RGB19101 (patients with active rheumatoid arthritis)

No other significant events were reported during the study.

5.4.6. ADRs of special interest, serious ADRs and deaths causally related to the medicinal product.

Phase I PK/PD study RGB192101 (healthy adult males)

Table 45: Summary of drug-related adverse events of special interest by system organ class and preferred term (overall) – safety analysis set (N=110).

Category of AESI SOC PT	Drug-related AESIs					
	Treatment				Total	
	RGB-19 (N=108)		Tocilizumab (RoActemra) (N=104)		(N=110)	
	n (%)	e	n (%)	e	n (%)	e
All Drug-related AESIs	**33 (30.6)**	**41**	**41 (39.4)**	**48**	**52 (47.3)**	**89**
Infections	**6 (5.6)**	**6**	**6 (5.8)**	**6**	**11 (10.0)**	**12**
Infections and infestations	**6 (5.6)**	**6**	**6 (5.8)**	**6**	**11 (10.0)**	**12**
Upper respiratory tract infection	5 (4.6)	5	5 (4.8)	5	9 (8.2)	10
Influenza	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Tonsillitis	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1
Hypersensitivity	**3 (2.8)**	**3**	**2 (1.9)**	**2**	**5 (4.5)**	**5**
Skin and subcutaneous tissue disorders	**3 (2.8)**	**3**	**2 (1.9)**	**2**	**5 (4.5)**	**5**
Drug eruption	2 (1.9)	2	2 (1.9)	2	4 (3.6)	4
Rash	1 (0.9)	1	0 (0.0)	0	1 (0.9)	1
Cytopenia/Thrombocytopenia	**27 (25.0)**	**27**	**36 (34.6)**	**36**	**43 (39.1)**	**63**
Investigations	**27 (25.0)**	**27**	**36 (34.6)**	**36**	**43 (39.1)**	**63**
Neutrophil count decreased	27 (25.0)	27	36 (34.6)	36	43 (39.1)	63
Hepatic Function Disorder	**3 (2.8)**	**3**	**3 (2.9)**	**3**	**3 (2.7)**	**6**
Investigations	**3 (2.8)**	**3**	**3 (2.9)**	**3**	**3 (2.7)**	**6**
Alanine aminotransferase increased	2 (1.9)	2	2 (1.9)	2	2 (1.8)	4
Blood bilirubin increased	1 (0.9)	1	1 (1.0)	1	1 (0.9)	2
Administration Site Reactions	**2 (1.9)**	**2**	**1 (1.0)**	**1**	**3 (2.7)**	**3**
General disorders and administration site conditions	**2 (1.9)**	**2**	**1 (1.0)**	**1**	**3 (2.7)**	**3**
Injections site pain	2 (1.9)	2	0 (0.0)	0	2 (1.8)	2
Injection site erythema	0 (0.0)	0	1 (1.0)	1	1 (0.9)	1

AESI = adverse event of special interest; e = number of events; IP = investigational product; MedDRA/J = Japanese translation of the Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects reporting at least one drug-related AESI within SOC/PT; PT = preferred term; SOC = system organ class; % = n / N × 100

Notes: Drug-related AESIs starting after IP administration in Period 1 were assigned to the treatment in Period 1; drug-related AESIs starting after IP administration in Period 2 were assigned to the treatment in Period 2.
MedDRA/J v27.0

There were no reported serious ADRs or deaths causally related to the medicinal product.

Phase III Comparative efficacy and safety study RGB19101 (patients with active rheumatoid arthritis)

Table 46: Summary of drug-related adverse events of special interest by system organ class and preferred term in ≥2% of subjects in any treatment group – SAF (N=368) - up to week 24 for each subject.

	AESIs					
Category of AESI SOC PT	**RGB-19 (N=182)**		**Tocilizumab (RoActemra) (N=186)**		**Total (N=368)**	
	n (%)	**e**	**n (%)**	**e**	**n (%)**	**e**
Any Drug-related AESIs	**75 (41.2)**	**119**	**84 (45.2)**	**144**	**159 (43.2)**	**263**
INFECTIONS	**23 (12.6)**	30	**19 (10.2)**	24	**42 (11.4)**	54
Infections and infestations	**23 (12.6)**	30	**19 (10.2)**	24	**42 (11.4)**	54
Nasopharyngitis	5 (2.7)	6	4 (2.2)	4	9 (2.4)	10
HYPERSENSITIVITY	**5 (2.7)**	**5**	**5 (2.7)**	**5**	**10 (2.7)**	**10**
Skin and subcutaneous tissue disorders	**4 (2.2)**	**4**	**4 (2.2)**	**4**	**8 (2.2)**	**8**
ABNORMAL LIPID LEVELS IN TESTS	**14 (7.7)**	**18**	**19 (10.2)**	**21**	**33 (9.0)**	**39**
Metabolism and nutrition disorders	**9 (4.9)**	**10**	**10 (5.4)**	**10**	**19 (5.2)**	**20**
Dyslipidaemia	4 (2.2)	4	4 (2.2)	4	8 (2.2)	8
Investigations	**5 (2.7)**	**8**	**9 (4.8)**	**11**	**14 (3.8)**	**19**
Blood cholesterol increased	1 (0.5)	1	6 (3.2)	6	7 (1.9)	7
CYTOPENIA/ THROMBOCYTOPENIA	**23 (12.6)**	**25**	**29 (15.6)**	**44**	**52 (14.1)**	**69**
Investigations	**20 (11.0)**	**22**	**28 (15.1)**	**42**	**48 (13.0)**	**64**
White blood cell count decreased	12 (6.6)	14	21 (11.3)	25	33 (9.0)	39
Neutrophil count decreased	3 (1.6)	3	10 (5.4)	13	13 (3.5)	16
Platelet count decreased	4 (2.2)	4	2 (1.1)	3	6 (1.6)	7
HEPATIC FUNCTION DISORDER	**33 (18.1)**	**39**	**39 (21.0)**	**47**	**72 (19.6)**	**86**
Hepatobiliary disorders	**7 (3.8)**	**7**	**11 (5.9)**	**11**	**18 (4.9)**	**18**
Hepatic function abnormal	7 (3.8)	7	10 (5.4)	10	17 (4.6)	17
Investigations	**26 (14.3)**	**32**	**29 (15.6)**	**36**	**55 (14.9)**	**68**
Hepatic enzyme increased	8 (4.4)	9	9 (4.8)	9	17 (4.6)	18
Liver function test increased	8 (4.4)	8	8 (4.3)	8	16 (4.3)	16
Liver function test abnormal	5 (2.7)	5	6 (3.2)	6	11 (3.0)	11
Aspartate aminotransferase increased	3 (1.6)	3	5 (2.7)	5	8 (2.2)	8
Alanine aminotransferase increased	3 (1.6)	3	4 (2.2)	5	7 (1.9)	8

AESI = adverse event of special interest; e = number of events; MedDRA/J = Japanese translation of the Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects reporting at least 1 drug-related AESI within SOC/PT; PT = preferred term; SAF = safety analysis set in the primary evaluation and secondary evaluation periods; SOC = system organ class; % = n / N × 100
MedDRA/J v27.0

Table 47: Summary of serious adverse drug reactions by system organ class and preferred term (treatment period and follow-up period) – SAF (N=368) - up to week 24 for each subject.

	Serious Adverse Drug Reactions					
	RGB-19 (N=182)		Tocilizumab (RoActemra) (N=186)		Total (N=368)	
SOC PT	n (%)	e	n (%)	e	n (%)	e
Any serious ADRs	**2 (1.1)**	**2**	**6 (3.2)**	**7**	**8 (2.2)**	**9**
Infections and infestations	**1 (0.5)**	**1**	**2 (1.1)**	**3**	**3 (0.8)**	**4**
Pneumocystis jirovecii pneumonia	1 (0.5)	1	1 (0.5)	1	2 (0.5)	2
Pyelonephritis	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Biliary tract infection	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Nervous system disorders	**0 (0.0)**	**0**	**2 (1.1)**	**2**	**2 (0.5)**	**2**
Epilepsy	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Nervous system disorder	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Respiratory, thoracic and Mediastinal disorders	**0 (0.0)**	**0**	**2 (1.1)**	**2**	**2 (0.5)**	**2**
Interstitial lung disease	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Pulmonary toxicity	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Gastrointestinal disorders	**1 (0.5)**	**1**	**0 (0.0)**	**0**	1 (0.3)	1
Large intestine perforation	1 (0.5)	1	0 (0.0)	0	1 (0.3)	1

AE = adverse event; ADR = adverse drug reaction; e = number of events; IP = investigational product; MedDRA/J = Japanese translation of the Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects reporting at least 1 serious ADR within SOC/PT; PT = preferred term; SAF = safety analysis set in the primary evaluation and secondary evaluation periods; SOC = system organ class; TEAE = treatment-emergent adverse event; % = n / N × 100
MedDRA/J v27.0
All TEAEs for which a causal relationship with the IP could not be ruled out were considered to be ADRs.
Pre-treatment AEs were not included in this table.

5.4.7. Discontinuation due to adverse events

Phase I PK/PD study RGB192101 (healthy adult males)

Table 48: Summary of adverse events resulting in study withdrawal by system organ class and preferred term (overall) – safety analysis set (N=110).

SOC PT	AEs Resulting in Study Withdrawal					
	Treatment				Total	
	RGB-19 (N=108)		Tocilizumab (RoActemra) (N=104)		(N=110)	
	n (%)	e	n (%)	e	n (%)	e
All AEs resulting in study withdrawal	**3 (2.8)**	**4**	**0 (0.0)**	**0**	**3 (2.7%)**	**4**
Ear and labyrinth disorders	**1 (0.9)**	**2**	**0 (0.0)**	**0**	**1 (0.9)**	**2**
Motion sickness	1 (0.9)	2	0 (0.0)	0	1 (0.9)	2
Skin and subcutaneous tissue disorders	**2 (1.9)**	**2**	**0 (0.0)**	**0**	**2 (1.8)**	**2**
Drug eruption	2 (1.9)	2	0 (0.0)	0	2 (1.8)	2

AE = adverse event; e = number of events; IP = investigational product; MedDRA/J = Japanese translation of the Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects reporting at least one AE within SOC/PT; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event; % = n / N × 100

Notes: TEAEs starting after IP administration in Period 1 were assigned to the treatment in Period 1; TEAEs starting after IP administration in Period 2 were assigned to the treatment in Period 2.

MedDRA/J v27.0

During Phase I PK/PD study RGB192101, three subjects experienced 2 AEs, which were judged to be possibly related to the study drug and led to early withdrawal: 1 Ear and Labyrinth disorders (motion sickness), and 2 Skin and subcutaneous Tissue disorders (2 Drug eruption).

Phase III Comparative efficacy and safety study RGB19101 (patients with active rheumatoid arthritis)

Table 49: Summary of adverse events resulting in discontinuation of investigational product administration by system organ class and preferred term (treatment period) – SAF (N=368) - up to week 24 for each subject.

SOC PT	Adverse Events Resulting in Discontinuation of IP Administration					
	RGB-19 (N=182)		Tocilizumab (RoActemra) (N=186)		Total (N=368)	
	n (%)	e	n (%)	e	n (%)	e
Any AEs resulting in discontinuation of IP administration	**3 (1.6)**	**3**	**10 (5.4)**	**10**	**13 (3.5)**	**13**
Infections and infestations	**0 (0.0)**	**0**	**1 (0.5)**	**1**	**1 (0.3)**	**1**
Appendicitis	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0 (0.0)**	**0**	**1 (0.5)**	**1**	**1 (0.3)**	**1**
Colon cancer	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Immune system disorders	**0 (0.0)**	**0**	**1 (0.5)**	**1**	**1 (0.3)**	**1**
Drug hypersensitivity	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Nervous system disorders	**0 (0.0)**	**0**	**1 (0.5)**	**1**	**1 (0.3)**	**1**
Nervous system disorder	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Respiratory, thoracic and mediastinal disorders	**0 (0.0)**	**0**	**4 (2.2)**	**4**	**4 (1.1)**	**4**
Cough	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Interstitial lung disease	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Pulmonary toxicity	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Diffuse panbronchiolitis	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Gastrointestinal disorders	**1 (0.5)**	**1**	**0 (0.0)**	**0**	**1 (0.3)**	**1**
Large intestine perforation	1 (0.5)	1	0 (0.0)	0	1 (0.3)	1
Hepatobiliary disorders	**1 (0.5)**	**1**	**0 (0.0)**	**0**	**1 (0.3)**	**1**
Hepatic function abnormal	1 (0.5)	1	0 (0.0)	0	1 (0.3)	1
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**0**	**1 (0.5)**	**1**	**1 (0.3)**	**1**
Invertebral disc protrusion	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Investigations	**1 (0.5)**	**1**	**1 (0.5)**	**1**	**2 (0.5)**	**2**
Hepatic enzyme increased	1 (0.5)	1	0 (0.0)	0	1 (0.3)	1
Liver function test increased	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1

AE = adverse event; e = number of events; IP = investigational product; MedDRA/J = Japanese translation of the Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects reporting at least 1 AE resulting in discontinuation of IP administration within SOC/PT; PT = preferred term; SAF = safety analysis set in the primary evaluation and secondary evaluation periods; SOC = system organ class; % = n / N × 100

MedDRA/J v27.0

Pre-treatment AEs were not included in this table.

Table 50: Summary of drug-related adverse events resulting in discontinuation of investigational product administration by system organ class and preferred term (treatment period) – SAF (N=368) - up to week 24 for each subject.

SOC PT	Adverse Events Resulting in Discontinuation of IP Administration					
	RGB-19 (N=182)		Tocilizumab (RoActemra) (N=186)		Total (N=368)	
	n (%)	e	n (%)	e	n (%)	e
Any ADRs Resulting in Discontinuation of IP Administration	**3 (1.6)**	**3**	**7 (3.8)**	**7**	**10 (2.7)**	**10**
Immune system disorders	**0 (0.0)**	**0**	**1 (0.5)**	**1**	**1 (0.3)**	**1**
Drug hypersensitivity	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Nervous system disorders	**0 (0.0)**	**0**	**1 (0.5)**	**1**	**1 (0.3)**	**1**
Nervous system disorder	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Respiratory, thoracic and mediastinal disorders	**0 (0.0)**	**0**	**4 (2.2)**	**4**	**4 (1.1)**	**4**
Cough	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Interstitial lung disease	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Pulmonary toxicity	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Diffuse panbronchiolitis	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1
Gastrointestinal disorders	**1 (0.5)**	**1**	**0 (0.0)**	**0**	**1 (0.3)**	**1**
Large intestine perforation	1 (0.5)	1	0 (0.0)	0	1 (0.3)	1
Hepatobiliary disorders	**1 (0.5)**	**1**	**0 (0.0)**	**0**	**1 (0.3)**	**1**
Hepatic function abnormal	1 (0.5)	1	0 (0.0)	0	1 (0.3)	1
Investigations	**1 (0.5)**	**1**	**1 (0.5)**	**1**	**2 (0.5)**	**2**
Hepatic enzyme increased	1 (0.5)	1	0 (0.0)	0	1 (0.3)	1
Liver function test increased	0 (0.0)	0	1 (0.5)	1	1 (0.3)	1

ADR = adverse drug reaction; e = number of events; IP = investigational product; MedDRA/J = Japanese translation of the Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects reporting at least 1 ADR resulting in discontinuation of IP administration within SOC/PT; PT = preferred term; SAF = safety analysis set in the primary evaluation and secondary evaluation periods; SOC = system organ class; TEAE = treatment-emergent adverse event; % = n / N × 100
MedDRA/J v27.0
All TEAEs for which a causal relationship with the IP could not be ruled out were considered to be ADRs.

5.4.8. Safety in special populations

Not applicable.

5.4.9. Immunological events

Please see related sections (PK, efficacy and safety).

5.4.10. Safety related to drug-drug interactions and other interactions

Not applicable.

5.4.11. Vital signs and laboratory findings

Laboratory findings

Phase I PK/PD study RGB192101 (healthy adult males)

Table 51: Summary of abnormal changes in laboratory measurements (overall) – safety analysis set (N=110).

Test items	Treatment				Total	
	RGB-19		Tocilizumab (RoActemra)			
	Abnormal Changes		Abnormal Changes		Abnormal Changes	
	n/N (%)	e	n/N (%)	e		
Hematology						
Red blood cell count	0/108 (0.0)	0	0/104 (0.0)	0	0/110 (0.0)	0
Platelet count	1/108 (0.9)	1	0/104 (0.0)	0	1/110 (0.9)	1
White blood cell count	86/108 (79.6)	241	86/104 (82.7)	246	96/110 (87.3)	487
Neutrophils	19/108 (17.6)	26	18/104 (17.3)	28	27/ 110 (24.5)	54
Eosinophils	4/108 (3.7)	4	2/104 (1.9)	4	5/110 (4.5)	8
Basophils	0/108 (0.0)	0	0/104 (0.0)	0	0/110 (0.0)	0
Monocytes	4/108 (3.7)	7	2/104 (1.9)	2	5/110 (4.5)	9
Lymphocytes	15/108 (13.9)	16	16/104 (15.4)	21	25/110 (22.7)	37
Hematocrit	0/108 (0.0)	0	0/104 (0.0)	0	0/110 (0.0)	0
Hb	0/108 (0.0)	0	0/104 (0.0)	0	0/110 (0.0)	0
Blood biochemistry						
Total cholesterol	0/108 (0.0)	0	1/104 (1.0)	1	1/110 (0.9)	1
HDL-C	0/108 (0.0)	0	0/104 (0.0)	0	0/110 (0.0)	0
LDL-C	1/108 (0.9)	1	2/104 (1.9)	2	3/110 (2.7)	3
Triglycerides	10/108 (9.3)	13	13/104 (12.5)	16	21/110 (19.1)	29
AST (GOT)	1/108 (0.9)	1	1/104 (1.0)	2	2/110 (1.8)	3
ALT (GPT)	3/108 (2.8)	4	3/104 (2.9)	4	4/110 (3.6)	8
ALP	0/108 (0.0)	0	0/104 (0.0)	0	0/110 (0.0)	0
γ-GTP (GGT)	0/108 (0.0)	0	0/104 (0.0)	0	0/110 (0.0)	0
LDH	0/108 (0.0)	0	0/104 (0.0)	0	0/110 (0.0)	0
Total bilirubin	17/108 (15.7)	31	22/104 (21.2)	33	27/110 (24.5)	64
Direct bilirubin	21/108 (19.4)	45	18/104 (17.3)	30	27/110 (24.5)	75
Total protein	0/108 (0.0)	0	0/104 (0.0)	0	0/110 (0.0)	0
Albumin	0/108 (0.0)	0	0/104 (0.0)	0	0/110 (0.0)	0
BUN	3/108 (2.8)	3	2/104 (1.9)	2	5/110 (4.5)	5
Creatinine	0/108 (0.0)	0	0/104 (0.0)	0	0/110 (0.0)	0
eGFR	9/108 (8.3)	13	10/104 (9.6)	11	17/110 (15.5)	24
Na	0/108 (0.0)	0	0/104 (0.0)	0	0/110 (0.0)	0
K	1/108 (0.9)	1	1/104 (1.0)	1	2/110 (1.8)	2
Cl	0/108 (0.0)	0	0/104 (0.0)	0	0/110 (0.0)	0
Glucose	3/108 (2.8)	3	3/104 (2.9)	3	5/110 (4.5)	6
Blood coagulation test						
Fibrinogen	60/108 (55.6)	91	58/104 (55.8)	89	74/100 (67.3)	180
Urinalysis						
Protein (qualitative)	3/108 (2.8)	4	5/104 (4.8)	6	8/110 (7.3)	10
Glucose (qualitative)	0/108 (0.0)	0	1/104 (1.0)	1	1/110 (0.9)	1
White blood cell (urine sediment)	13/108 (12.0)	15	12/104 (11.5)	13	23/110 (20.9)	28
Occult blood (qualitative)	0/108 (0.0)	0	2/104 (1.9)	3	2/110 (1.8)	3
Urobilinogen (qualitative)	2/108 (1.9)	3	1/104 (1.0)	1	3/110 (2.7)	4

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Cl = chloride; e = number of events; eGFR = estimated glomerular filtration rate; γ-GTP = gamma-glutamyl transferase; Hb = hemoglobin; HDL-C = high-density lipoprotein cholesterol; K = potassium; LDH = lactate dehydrogenase; LDL-C = low-density lipoprotein cholesterol; N = number of subjects (subjects with no measurements at the relevant period are excluded); n = number of subjects reporting at least one abnormal change; Na = sodium; % = n / N × 100

Phase III Comparative efficacy and safety study RGB19101 (patients with active rheumatoid arthritis)

Clinically significant results from clinical laboratory evaluations were to be reported as AEs.

Haematology

Red blood cell count

- RGB-19 group: 22 subjects had shifts from <LLN to within the reference range; 17 subjects had shifts from within the reference range to <LLN.
- RoActemra group: 4 subjects had shifts from >ULN to within the reference range; 19 subjects had shifts from within reference range to <LLN; 16 subjects had shifts from <LLN to within the reference range.

Platelet count

- RGB-19 group: 62 subjects had shifts from >ULN to within the reference range; 9 subjects had shifts from within reference range to <LLN.
- RoActemra group: 68 subjects had shifts from >ULN to within the reference range; 5 subjects had shifts from within the reference range to <LLN.

White blood cell count

- RGB-19 group: 33 subjects had shifts from >ULN to within the reference range; 3 subjects had shifts from within the reference range to >ULN; 23 subjects had shifts from within the reference range <LLN.
- RoActemra group: 29 subjects had shifts from >ULN to within reference range; 2 subjects had shifts from within reference range to >ULN, 15 subjects had shifts from within the reference range to <LLN.

Neutrophil count

- RGB-19 group: 55 subjects had shifts from >ULN to within the reference range, 3 subjects had shifts from within the reference range to >ULN, 5 subjects had shifts from within the reference range to <LLN.
- RoActemra group: 48 subjects had shifts from >ULN to within reference range; 5 subjects had shifts from within the reference range to >ULN; 13 subjects had shifts from within the reference range to <LLN.

Clinical Chemistry

Total cholesterol

- RGB-19 group: 51 subjects had shifts within the reference range to >ULN.
- RoActemra group: 39 subjects had shifts from within the reference range to >ULN.

Low-density lipoprotein-cholesterol

- RGB-19 group: 30 subjects had shifts within the reference range to >ULN.
- RoActemra group: 25 subjects had shifts from within the reference range to >ULN.

High-density lipoprotein-cholesterol

- RGB-19 group: 14 subjects had shifts within the reference range to >ULN.

- RoActemra group: 14 subjects had shifts from within the reference range to >ULN.

Triglycerides

- RGB-19 group: 25 subjects had shifts within the reference range to >ULN.
- RoActemra group: 21 subjects had shifts from within the reference range to >ULN.

AST

- RGB-19 group: 25 subjects had shifts within the reference range to >ULN.
- RoActemra group: 23 subjects had shifts from within the reference range to >ULN.

ALT

- RGB-19 group: 25 subjects had shifts within the reference range to >ULN.
- RoActemra group: 26 subjects had shifts from within the reference range to >ULN.

Gamma-glutamyl transferase

- RGB-19 group: 17 subjects had shifts within the reference range to >ULN.
- RoActemra group: 24 subjects had shifts from within the reference range to >ULN.

Lactate dehydrogenase

- RGB-19 group: 34 subjects had shifts within the reference range to >ULN.
- RoActemra group: 32 subjects had shifts from within the reference range to >ULN.

Total protein

- RGB-19 group: 47 subjects had shifts within the reference range to <LLN.
- RoActemra group: 37 subjects had shifts from within the reference range to <LLN.

Total bilirubin

- RGB-19 group: 21 subjects had shifts within the reference range to >ULN.
- RoActemra group: 20 subjects had shifts from within the reference range to >ULN.

Glucose

- RGB-19 group: 19 subjects had shifts within the reference range to >ULN.
- RoActemra group: 9 subjects had shifts from within the reference range to >ULN.

Urinalysis

Protein (qualitative)

- RGB-19 group: 7 subjects had shifts within the reference range to >ULN.
- RoActemra group: 6 subjects had shifts from within the reference range to >ULN.

White blood cells (qualitative)

- RGB-19 group: 20 subjects had shifts within the reference range to >ULN.
- RoActemra group: 12 subjects had shifts from within the reference range to >ULN.

Vital signs and physical findings

Phase I PK/PD study RGB192101 (healthy adult males)

Vital signs

According to the applicant, there were no clinically meaningful trends in changes in vital signs between the two treatment arms.

Physical findings

Overall, 24 (22.2%) and 20 (18.9%) subjects had clinically significant abnormal physical examination findings after receiving RGB-19 or tocilizumab (RoActemra), respectively which were reported as AEs.

Body weight

There were no clinically meaningful trends in changes in body weight between the two sequences.

Electrocardiogram

There were no clinically significant abnormal 12-lead ECG findings after receiving either RGB-19 or RoActemra.

Injection site reactions

No subject experienced injection site tenderness or induration/swelling. A total of 2/108 (1.9%) and 1/108 (0.9%) subjects experienced injection pain 1 and 2 hours after RGB-19 administration, respectively. Twelve hours after RoActemra administration, 1/104 (1.0%) subject experienced injection site erythema/redness. All injection site reactions were of mild severity and were reported as TEAEs, which all resolved and were considered to be related to the study drug by the applicant.

Phase III Comparative efficacy and safety study RGB19101 (patients with active rheumatoid arthritis)

Clinically significant values for vital signs, physical examinations, and other observations related to safety were to be reported as AEs.

Vital signs

Results can be summarized as follows:

- Systolic blood pressure mean (SD) change from baseline to Week 24: -0.1 (14.0) mmHg in the RGB-19 group and 1.1 (14.0) mmHg in the RoActemra group.
- Diastolic blood pressure mean (SD) change from baseline to Week 24: 0.9 (8.9) mmHg in the RGB-19 group and -0.4 (9.6) mmHg in the RoActemra group.
- Pulse rate mean (SD) change from baseline to Week 24: -4.9 (11.1) bpm in the RGB-19 group and -5.4 (10.5) bpm in the RoActemra group.
- Body temperature mean (SD) change from baseline to Week 24: -0.10 (0.43)°C in the RGB-19 group and -0.16 (0.43)°C in the RoActemra group.
- Body weight mean (SD) change from baseline to Week 24: 1.44 (2.05) kg in the RGB-19 group and 1.22 (2.49) kg in the RoActemra group.

Physical examination

The proportions of subjects with abnormal clinically significant physical examination findings, at least 1 time point after IP administration, were: RGB-19: 37 (20.3%) subjects and tocilizumab (RoActemra): 36 (19.5%) subjects. The point estimate (95% CI) for the difference of incidence rate was 0.9 (-7.3, 9.1).

Body weight

There were no clinically meaningful trends in changes in body weight between the two treatment groups.

Electrocardiograms

The proportions of subjects with abnormal 12-lead ECG findings, at least 1 time point after IP administration, were: RGB-19: 29 (16.1%) subjects and tocilizumab (RoActemra): 31 (16.8%) subjects. The point estimate (95% CI) for the difference of incidence rate was -0.6 (-8.3, 7.0).

Other Observations Related to Safety

Phase I PK/PD study RGB192101 (healthy adult males)

Immunogenicity

Table 52: **Summary of immunogenicity by time point and period– immunogenicity analysis set (N=110).**

Parameter	Finding	Period 1					
		Day 1 pre-IP		Day 13		Day 43	
		RGB-19 n/N (%) (Sequence A)	Tocilizumab (RoActemra) n/N (%) (Sequence B)	RGB-19 n/N (%) (Sequence A)	Tocilizumab (RoActemra) n/N (%) (Sequence B)	RGB-19 n/N (%) (Sequence A)	Tocilizumab (RoActemra) n/N (%) (Sequence B)
ADA	Positive	2/55 (3.6)	2/55 (3.6)	2/53 (3.8)	7/55 (12.7)	26/52 (50.0)	23/53 (43.4)
	Negative	53/55 (96.4)	53/55 (96.4)	51/53 (96.2)	48/55 (87.3)	26/52 (50.0)	30/53 (56.6)
NAb	Positive	0/2 (0.0)	0/2 (0.0)	1/2 (50.0)	5/7 (71.4)	18/26 (69.2)	16/23 (69.6)
	Negative	2/2 (100.0)	2/2 (100.0)	1/2 (50.0)	2/7 (28.6)	8/26 (30.8)	7/23 (30.4)
		Period 2					
		Day 43 pre-IP		Day 55		Day 85	
		RGB-19 n/N (%) (Sequence B)	Tocilizumab (RoActemra) n/N (%) (Sequence A)	RGB-19 n/N (%) (Sequence B)	Tocilizumab (RoActemra) n/N (%) (Sequence A)	RGB-19 n/N (%) (Sequence B)	Tocilizumab (RoActemra) n/N (%) (Sequence A)
ADA	Positive	23/53 (43.4)	26/52 (50.0)	23/53 (43.4)	28/49 (57.1)	35/53 (66.0)	39/49 (79.6)
	Negative	30/53 (56.6)	26/52 (50.0)	30/53 (56.6)	21/49 (42.9)	18/53 (34.0)	10/49 (20.4)
NAb	Positive	16/23 (69.6)	18/26 (69.2)	21/23 (91.3)	26/28 (92.9)	26/35 (74.3)	32/39 (82.1)
	Negative	7/23 (30.4)	8/26 (30.8)	2/23 (8.7)	2/28 (7.1)	9/35 (25.7)	7/39 (17.9)

ADA = antidrug antibody; IP = investigational product; N = number of subjects; n = number of cases; NAb = neutralizing antibody
Sequence A: RGB-19 on Day 1 followed by tocilizumab (RoActemra) on Day 43; Sequence B: tocilizumab (RoActemra) on Day 1 followed by RGB-19 on Day 43.

Phase III Comparative efficacy and safety study RGB19101 (patients with active rheumatoid arthritis)

Tuberculosis

The majority of subjects in both treatment groups did not have clinically significant chest X-ray abnormalities and there were no reports of tuberculosis.

Autoantibodies

One (0.6%) subject in the RGB-19 group and no subject in the tocilizumab (RoActemra) group were positive for RF autoantibodies (>15 IU/mL) at least 1 time point after the first IP administration. One (0.5%) subject in the tocilizumab (RoActemra) group and no subject in the RGB-19 group was anti-CCP antibody positive after the first IP administration.

Hepatitis Virus

Of subjects who were positive for HBs and/or HBc antibody test at screening, 1 (4.8%) of 21 subjects in the tocilizumab (RoActemra) group and no subject in the RGB-19 group was positive for HBV-DNA assessed by quantitative tests during the study. The point estimate (95% CI) for the difference of rate was -4.8 (-22.7, 8.3).

Immunogenicity

Table 53: Summary of ADA until visit week 24.

Test items	Classification	Treatment group	N	n	(%)	Difference of rate[a]
ADA	ADA Positive at post administration[b]	RGB-19	182	5	(2.7)	-1.6
		Tocilizumab (RoActemra)	186	8	(4.3)	
	ADA Negative at post administration[c]	RGB-19	182	177	(97.3)	1.6
		Tocilizumab (RoActemra)	186	178	(95.7)	
	Negative[d]	RGB-19	182	166	(91.2)	0.3
		Tocilizumab (RoActemra)	186	169	(90.9)	
	Negative (pre-dose positive)[e]	RGB-19	182	12	(6.6)	0.7
		Tocilizumab (RoActemra)	186	11	(5.9)	
	Treatment-induced positive[f]	RGB-19	182	4	(2.2)	-0.5
		Tocilizumab (RoActemra)	186	5	(2.7)	
	Treatment-boosted positive[g]	RGB-19	182	0	(0.0)	-0.5
		Tocilizumab (RoActemra)	186	1	(0.5)	

ADA = antidrug antibodies; IAS = immunogenicity analysis set; IP = investigational product;
N = number of subjects in the IAS; n = number of subjects for each classification; % = n / N × 100
a: RGB-19 Treatment group - Tocilizumab (RoActemra) Treatment group
b: Subjects who were ADA positive at least one time point after first IP administration
c: Subjects who were ADA negative at all available time points after first IP administration
d: Subjects who were ADA negative at all available time points
e: Subjects who were ADA positive at baseline and met any of the following conditions:
1) Subjects who were ADA negative at all available time points after the first IP administration
2) Subjects who were ADA positive at least at one time point after the first IP administration but without significant titer increase from baseline
f: Subjects who were ADA negative at baseline and ADA positive at least one time point after the first IP administration
g: Subjects who were ADA positive at baseline and ADA positive with significant titer increase from baseline at least one time point after the first IP administration

Table 54: Summary of NAb until visit week 24.

Test items	Classification	Treatment group	N	n	(%)	Difference of rate[a]
NAb[b]	NAb Positive at post administration[c]	RGB-19	182	5	(2.7)	-1.0
		Tocilizumab (RoActemra)	186	7	(3.8)	
	NAb Negative at post administration[d]	RGB-19	182	177	(97.3)	1.0
		Tocilizumab (RoActemra)	186	179	(96.2)	

ADA = antidrug antibodies; IAS = immunogenicity analysis set; IP = investigational product;
N = number of subjects in the IAS; n = number of subjects for each classification; NAb = neutralizing antibody;
% = n / N × 100
a: RGB-19 Treatment group - Tocilizumab (RoActemra) Treatment group
b: If ADA is positive, NAb will be measured at the time point
c: Subjects who were NAb positive at least one time point after the first IP administration
d: Subjects who were NAb negative or ADA negative at all available time point after the first IP administration

5.4.12. Post-marketing experience

Not applicable.

5.4.13. In vitro biomarker test for patient selection for safety

Not applicable.

5.4.14. Overall discussion and conclusions on clinical safety

5.4.14.1. Discussion

RGB-19 is proposed as a biosimilar to tocilizumab (RoActemra) in both approved formulations (IV and SC). The most common adverse reactions noted in clinical studies with RoActemra are upper respiratory tract infections, nasopharyngitis, headache, hypertension, and abnormal liver function tests. The most serious adverse events are serious infections, complications of diverticulitis, and hypersensitivity reactions. Regarding immunogenicity, the reported incidence of antidrug antibodies (ADAs) in historical adult studies is <2% for the different approved indications.

The main data supporting biosimilarity originates from two pivotal clinical studies performed in Japan, study RGB192101 (phase I) and study RGB19101 (phase III). Both pivotal studies were performed in Japanese populations. However, the safety results of the clinical studies are considered to be generalizable to a European population.

The schedule for safety data collection is considered suitable both for study RGB192101 and study RGB19101 and the intervals for physical and laboratory assessments are agreed. The size of the safety database is considered sufficient. The length of the planned follow-up (24 weeks) is also acceptable for the purpose of the studies to show biosimilarity between products even though rare events and events which usually take longer time to develop (for example malignancies) might not have been adequately captured. There were no significant differences in patient demographics and other baseline characteristics between treatment arms in the two studies.

Exposure

Overall, 108 subjects received one dose of RGB-19 in study RGB192101. In study RGB19101, a total of 185 participants received at least one dose RGB-19, and the mean exposure during the 24-week treatment period was 161.7 (±32.3) days.

Overview of adverse events

The proportion of participants in the phase I study RGB192101 with at least one AE was slightly lower in the RGB-19 group (n=51, 47.2%) compared with the RoActemra group (n=53, 51.0%). In addition, ADRs were less common in the RGB-19 treatment arm (n=36, 33.3% vs n=45, 43.3%). Three participants in the RGB-19 group experienced AEs leading to study withdrawal, and two experienced ADRs leading to study withdrawal. There were no SAEs, serious ADRs or deaths in the study.

In the main treatment phase of phase III study RGB19101, the proportion of participants experiencing at least one TEAE was similar between RGB-19 (n=143, 78.6%) and RoActemra (n=150, 80.6%). Fewer severe AEs and severe ADRs were reported in the RGB-19 group (n=3, 1.6% vs n=13, 7.0% and n=1, 0.5% vs n=6, 3.2%, respectively). There were no deaths in the RGB-19 treatment arm, but one death in the RoActemra treatment arm (unrelated to the treatment). In addition, SAEs and serious ADRs were less common in the RGB-19 group (n=4, 2.2% vs n=14, 7.5% and n=2, 1.1% vs n=6, 3.2%, respectively). Hence, a lower proportion of study participants in the RGB-19 group experienced severe AEs, severe ADRs, SAEs, and serious ADRs compared with the RoActemra group. This difference is noted, but not considered clinically relevant and therefore not further pursued.

Adverse events by system organ class and preferred term

In phase I study RGB192101, the most reported adverse event in the RGB-19 group was neutrophil count decreased followed by upper respiratory tract infection and white blood cells urine positive.

Differences between groups were noted for the following AEs:

- Neutrophil count decreased: RGB-19 n=27, 25.0%, RoActemra n=36, 34.6%
- Influenza: RGB-19 n=3, 2.8%, RoActemra n=0
- Presyncope: RGB-19 n=0, RoActemra n=3, 2,9%
- Gastrointestinal disorders: RGB-19 n=7, 6.5%, RoActemra n=4, 3.8% (the events were however distributed across several PTs, with no difference in individual PT >2%)
- General disorders and administration site conditions: RGB-19 n=4, 3.7%, RoActemra n=1, 1.0% (the events were however distributed across several PTs, with no difference in individual PT >2%)

Of note, the neutrophil count decreased was less often reported in the RGB-19 group (n=27, 25.0% vs n=36, 34.6%). This difference is noted, but not considered clinically relevant and therefore not further pursued. Since the number of the remaining AEs were few, the differences between treatment arms are not considered clinically relevant.

In phase III study RGB19101, the most reported adverse event in the RGB-19 treatment arm was stomatitis, followed by nasopharyngitis, and liver function test increased.

The following differences between treatment arms were noted:

- Nasopharyngitis: RGB-19 n=14, 7.7%, RoActemra n=26, 14.0%
- White blood cell count decreased: RGB-19 n=12, 6.6%, RoActemra n=21, 11.3%
- Neutrophil count decreased: RGB-19 n=3, 1.6%, RoActemra n=10, 5.4%

- Blood cholesterol increased: RGB-19 n=1, 0.5%, RoActemra n=6, 3.2%
- Stomatitis: RGB-19 n=27, 14.8%, RoActemra n=23, 12.4%
- Sinusitis: RGB-19 n=6, 3.3%, RoActemra n=2, 1.1%
- Hepatic function abnormal: RGB-19 n=8, 4.4%, RoActemra n=12, 6.5%
- Paronychia: RGB-19 n=2, 1.1%, RoActemra n=6, 3.2%
- Musculoskeletal and connective tissue disorders: RGB-19 n=8, 4.4%, RoActemra n=20, 10.8% (the events were however distributed across several PTs, with no difference in individual PT >2%)

In general, the adverse events noted in the studies are in line with the known safety profile of RoActemra.

Adverse drug reactions

In phase I study RGB192101, ADRs were reported in n=36, 33.3% of participants in the RGB-19 group and in n=45, 43.3% in the RoActemra group. The most reported ADR in both treatments arms was neutrophil count decreased and the second most reported ADR in both arms was upper respiratory tract infection. The remaining ADRs were few in both treatment arms.

At week 24 in phase III study RGB19101, the proportion of participants experiencing ADRs were somewhat similar between treatment arms, n=82, 45.1% in the RGB-19 arm and n=91, 48.9% in the RoActemra arm. The most reported ADR in the RGB-19 arm was white blood cell count decreased, followed by hepatic enzyme increased, and liver function test increased.

The following differences between treatment arms were noted:

- White blood cell count decreased: RGB-19 n=12, 6.6%, RoActemra n=21, 11.3%
- Neutrophil count decreased: RBG-19 n=3, 1.6%, RoActemra n=10, 5.4%
- Blood cholesterol increased: RGB-19 n=1, 0.5%, RoActemra n=6, 3.2%

Of note is the difference in neutrophile count decreased between treatment arms. This difference is noted, but not considered clinically relevant.

AEs of special interest

In both studies, the following TEAEs were identified as AESIs: infections, tuberculosis, hypersensitivity, HBV reactivation, pleurisy, abnormal lipid levels in tests, heart failures, interstitial pneumonia, diverticulitis/intestinal perforation, cytopenia/thrombocytopenia, hepatic function disorder, malignant tumours and unspecified tumours, cerebrovascular disorder, demyelinating disorders, and administration site reactions. It is agreed with the applicant that these are adverse events of special interest.

In phase I study RGB192101, a lower proportion of participants experienced neutrophil count decreased in the RGB-19 arm compared with the RoActemra arm (n=27, 25.0% vs n=36, 34.6%). This difference is noted, but not considered clinically relevant. Infections, hypersensitivity, abnormal lipid levels in tests, cytopenia/thrombocytopenia, hepatic function disorder, and administration site reactions did not differ significantly between treatment arms. No cases of the remaining AESIs were reported.

In Phase III study RGB19101, the following differences in AESIs were noted between groups:

- Nasopharyngitis: RGB-19 n=14, 7.7%, RoActemra n=26, 14.0%

- White blood cell count decreased: RGB-19 n=12, 6.6%, RoActemra n=21, 11.3%
- Neutrophil count decreased: RGB-19 n=3, 1.6%, RoActemra n=10, 5.4%
- Blood cholesterol increased: RGB-19 n=1, 0.5%, RoActemra n=6, 3.2%
- Stomatitis: RGB-19 n=27, 14.8%, RoActemra n=23, 12.4%
- Sinusitis: RGB-19 n=6, 3.3%, RoActemra n=2, 1.1%
- Hepatic function abnormal: RGB-19 n=8, 4.4%, RoActemra n=12, 6.5%
- Paronychia: RGB-19 n=2, 1.1%, RoActemra n=6, 3.2%

Diverticulitis/intestinal perforation was reported in one case in the RGB-19 group. Malignant tumours and unspecified tumours, heart failures, cerebrovascular disorders, and administration site reactions occurred only in the RoActemra treatment arm (1 case each). However, the follow-up time is too short to evaluate malignant and unspecified tumours. No cases of tuberculosis, HBV reactivation, pleurisy, or demyelinating disorders were reported.

Serious adverse events and deaths

There were no SAEs or deaths reported in phase I study RGB192101.

In phase III study RGB19101, a lesser proportion of participants in the RGB-19 group experienced SAEs (n=4, 2.2%) compared with the RoActemra group (n=14, 7.5%). This difference is noted, but not considered clinically relevant.

The SAEs in the RGB-19 arm were pneumocystis jirovecii pneumonia n=1, 0.5%, large intestine perforation n=1, 0.5%, cholecystitis acute n=1, 0.5%, and spinal compression fracture n=1, 0.5%.

The SAEs in the RoActemra arm were pneumocystis jirovecii pneumonia n=1, 0.5%, appendicitis n=1, 0.5%, pyelonephritis n=1, 0.5%, biliary tract infection n=1, 0.5%, colon cancer n=1, 0.5%, epilepsy n=1, 0.5%, nervous system disorder n=1, 0.5%, acute coronary syndrome n=1, 0.5%, hypotension n=1, 0.5%, shock hemorrhagic n=1, 0.5%, interstitial lung disease n=1, 0.5%, pulmonary toxicity n=1, 0.5%, hypersensitivity pneumonitis n=1, 0.5%, intervertebral disc protrusion n=1, 0.5%, and hematoma muscle n=1, 0.5%. One death occurred in the RoActemra arm in study RGB19101, unrelated to treatment. The cause of death was severe shock haemorrhagic due to a road traffic accident.

It is noted that two pneumocystis jirovecii pneumonia cases (one in each treatment arm) occurred during a relatively short timeframe in a study size which would be unlikely to detect the most rare adverse events. This is reported in the SmPC, where the incidence of all serious infections (bacterial, viral and fungal) is reported as 4.7 events per 100 patient-years.

ADRs of special interest, serious ADRs and deaths causally related to the medicinal product.

The majority of AESIs in phase I study RGB192101 were considered to be related to the study drug. The most reported ADR of special interest in the RGB-19 arm was neutrophil count decreased, followed by upper respiratory tract infection, and drug eruption. In the RoActemra arm, the most reported ADR of special interest was neutrophil count decreased, followed by upper respiratory tract infection, and alanine aminotransferase increased. It is agreed with the applicant that these adverse events of special interest likely were related to the study drug. There were no reported serious ADRs or deaths causally related to RGB-19.

In the RGB-19 arm in phase III study RGB19101, the most reported AESIs considered to be ADRs were white blood cell count decreased , hepatic enzyme increased, and liver function test increased. The most reported AESIs considered to be ADRs in the RoActemra arm were white blood cell count

decreased, neutrophil count decreased, and hepatic function abnormal. It is agreed with the applicant that these adverse events of special interest likely were related to the study drug.

Differences between groups were noted for the following:

- White blood cell count decreased: RGB-19 n=12, 6.6%, RoActemra n=21, 11.3%
- Neutrophil count decreased: RGB-19 n=3, 1.6%, RoActemra n=10, 5.4%
- Blood cholesterol increased: RGB-19 n=1, 0.5%, RoActemra n=6, 3.2%

Two of the SAEs in the RGB-19 arm (pneumocystis jirovecii pneumonia and large intestine perforation) were considered related to study drug by the investigator and the sponsor. The outcomes for both cases were recovered. Since the pharmacological action of IL-6 inhibitors may cause a decrease in immune function, it is agreed that the pneumocystis jirovecii pneumonia was related to RGB-19. Likewise, intestine perforation is a known adverse event of RoActemra and the event was consistent with the duration of exposure of RGB-19. It is therefore agreed that the intestine perforation was related to RGB-19. Both pneumocystis pneumonia and intestine perforation are listed as adverse events in the RoActemra SmPC. One case of pneumocystis jirovecii pneumonia was also reported in the RoActemra arm. There were no reported deaths causally related to RGB-19.

Discontinuation due to adverse events

In phase I study RGB192101, 3 (2.8%) participants experienced AEs leading to study withdrawal, all after receiving RGB-19 treatment (motion sickness n=1, 0.9% and drug eruption n=2, 1.9%). Two cases were considered to be ADRs (drug eruption following the first dose administration). Based on the timing of the onset of these events, it is agreed with the applicant that they were related to the study drug.

In phase III study RGB19101, 3 events in 3 (1.6%) participants in the RGB-19 arm (all considered to be ADRs) led to discontinuation of investigational product administration. The events were large intestine perforation (severe, serious), hepatic function abnormal (mild), and hepatic enzyme increased (mild). In the RoActemra arm, 10 events in 10 (5.4%) participants (7 events in 7 (3.8%) subjects considered to be ADRs) led to discontinuation of investigational product administration. One event in 1 participant in the RGB-19 arm and 6 events in 6 participants in the RoActemra arm were reported as SAEs that led to discontinuation of investigational product administration. Out of these SAEs, 1 event in 1 participant in the RGB-19 arm and 3 events in 3 participants in the RoActemra arm were considered SADRs (RGB-19 arm: large intestine perforation; RoActemra arm: interstitial lung disease, pulmonary toxicity, and nervous system disorder).

Upon request, the applicant provided additional information regarding withdrawal, discontinuation or temporally disruption of drug and dose reduction. Overall, 25 subjects withdrew from study RGB19101, mostly during the second evaluation period. The proportion of patients withdrawing were slightly lower in the RGB-19 group than the RoActemra group (3.8% vs 9.7%). In addition, 32 subjects discontinued IP administration, 7.1% in the RGB-19 group and 9.7% in the RoActemra group. The numbers and reasons for discontinuation do not evoke any concerns and are rather similar between the two groups.

The numbers of patients who temporarily disrupted investigational product administration were also slightly lower in the RGB-19 group (9.9%) vs the RoActemra group (14.5%). This was mainly because of AE. No dose reductions of the IP were performed during the study. The provided information does not evoke any concerns regarding biosimilarity.

Laboratory findings

In study RGB192101, the following differences in laboratory measurements between the two treatment arms were reported:

- Total bilirubin: RGB-19 17/108, 15.7%, RoActemra 22/104, 21.2%
- Triglycerides: RGB-19 10/108, 9.3%, RoActemra 13/104, 12.5%
- White blood cell count: RGB-19 86/108, 79.6%, RoActemra 86/104, 86.7%
- Direct bilirubin: RGB-19 21/108, 19.4%, RoActemra 5/104, 17.3%
- Urinalysis protein (qualitative): RGB-19 3/108, 2.8%, RoActemra 18/104, 4.8%

Clinical laboratory abnormalities assessed as clinically significant by the Investigator were reported as AEs.

In phase I study RGB19101, there were differences in neutrophil count decreased between treatment arms. These differences are noted, but not considered clinically relevant. There were no clinically meaningful trends in changes in other haematology variables, clinical chemistry variables, or urinalysis variables between the two treatment groups. Clinically significant results from clinical laboratory evaluations were reported as AEs.

Immunogenicity

In phase I study RGB192101, pre-dose ADA positivity was observed in 3.6% of study participants. In Period 1 on Day 43, 26/52 (50.0%) participants who received RGB-19 and 23/53 (43%) participants who received RoActemra were ADA positive. Combining the results for the two treatment periods, the proportion of ADA positive RGB-19-treated participants was 61/105 (58%) (26 at Day 43 and 35 at Day 85) compared to 62/102 (60.8%) (23 at Day 43 and 39 at Day 85) RoActemra-treated participants. Hence, the incidence of ADA positivity was similar between treatment groups. In addition, the time course for the proportions who were ADA positive was similar for Period 1 and Period 2 regardless of treatment order.

Regarding NAb positivity, in Period 1 on Day 43, 18 participants receiving RGB-19 and 16 participants receiving RoActemra were NAb positive. Combining the results for the two treatment periods, i.e. at Day 43 following administration of either IP in Period 1 or Period 2, the number of NAb positive participants was 44 (18 at Day 43 and 26 at Day 85) amongst RGB-19-treated participants compared to 48 (16 at Day 43 and 32 at Day 85) amongst RoActemra-treated participants. Hence, the incidence of NAb positivity was similar between treatment groups.

Only a few hypersensitivity reactions were reported, and there was no relevant difference between treatment arms .

In phase III study RGB19101, 12/182 (6.6%) participants in the RGB-19 group and 12/186 (6.5%) participants in the RoActemra group were ADA positive at baseline. In the RGB-19 group, 4/182 (2.2%) participants had a treatment-emergent (treatment induced + treatment boosted) ADA response up to and including Week 24. The corresponding proportion in the RoActemra group was 6/186 (3.2%). Of the ADA positive participants, 9/10 were also classified as NAb positive. Hence, treatment-emergent ADA incidence and NAb positivity was generally low and there was no clinically meaningful difference between the treatment groups. The frequency of reported hypersensitivity reactions was also similar for RGB-19 and RoActemra.

In summary, the incidence of ADA and NAb positivity was higher in study RGB192101 compared with study RGB19101. In the latter, only a small number of participants were ADA positive in each treatment group. Concomitant treatment with methotrexate in study RGB19101 could partly explain

the difference in ADA positivity between studies. There were no clinically meaningful differences in the incidence of ADA or NAb positivity nor hypersensitivity reactions between treatment arms in any of the studies.

Vital signs and physical findings

In phase I study RGB192101, 24 (22.2%) participants receiving RGB-19 and 20 (18.9%) participants receiving RoActemra had clinically significant abnormal physical examination findings which were reported as AEs. There were no clinically meaningful trends in changes in body weight and no clinically significant abnormal 12-lead ECG findings. There were few cases of injection site reactions in both treatment groups, and all injection site reactions were mild and resolved.

In phase III study RGB19101, there were no clinically meaningful trends in changes in vital signs or body weight between the two treatment groups. The proportions of subjects with abnormal clinically significant physical examination findings were similar for both treatment groups, as well as the proportions of subjects with abnormal 12-lead ECG findings. Clinically significant values for vital signs, physical examinations, and other observations related to safety were reported as AEs.

5.4.14.1.1. Adverse drug reactions (ADRs) in the SmPC

The adverse drug reactions in the SmPC are line with the ones of the originator RoActemra.

5.4.14.2. Conclusions on clinical safety

The most frequent adverse drug reactions for both RGB-19 and RoActemra were decreased neutrophil count followed by increased hepatic enzymes and hepatic function abnormal. Upper respiratory tract infection was also reported in both treatment arms in one of the studies.

Differences in adverse drug reactions between treatment arms included white blood cell count decreased (more frequently reported in the RoActemra arm), neutrophil count decreased (more frequently reported in the RoActemra arm), and blood cholesterol increased (more frequently reported in the RoActemra arm). These differences are noted but not considered clinically relevant and therefore not further pursued. There were no clinically meaningful differences in the incidence of ADA or NAb positivity nor hypersensitivity reactions between treatment arms in any of the studies.

The overall safety profile of RGB-19 appears to be in line with known safety profile of the reference product EU-RoActemra.

Biosimilarity is supported from a safety perspective.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP:

Table 55: Summary of safety concerns in the proposed RMP

Summary of safety concerns	
Important identified risks	• Serious infection * • Complications of diverticulitis * • Neutropenia • Hepatotoxicity
Important potential risks	• Thrombocytopenia and the potential risk of bleeding • Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events • Malignancies • Demyelinating disorders • Immunogenicity
Missing information	• None

COVID = coronavirus disease 19; TCZ = tocilizumab

* The safety concerns "serious infection" and "complications of diverticulitis" are considered important identified risks for chronic TCZ dosing, but are assessed as important potential risks for the indication of COVID-19

6.1.2. Discussion on proposed safety specification

The proposed summary of safety concerns is in line with that of the reference product RoActemra. The provided safety specification is considered acceptable.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan

As routine pharmacovigilance activities beyond adverse reactions reporting and signal detection, eight specific adverse reaction follow-up questionnaires are utilised to collect information in a standardised manner and monitor the frequency and nature of adverse events (AEs) emerging during post-marketing use. These targeted follow-up questionnaires are related to the following safety concerns:

- Serious infections (including neutropenia)
- Complications of diverticulitis (including gastrointestinal [GI] perforation)
- Thrombocytopenia and the potential risk of bleeding
- Hepatotoxicity
- Elevated lipid levels and potential risk of cardiovascular/cerebrovascular events (2)
- Malignancies
- Demyelinating disorders

The applicant did not propose any additional pharmacovigilance activities.

6.2.2. Discussion on the pharmacovigilance plan

6.2.2.1. Routine pharmacovigilance activities

With the proposed routine pharmacovigilance activities, the safety concerns from Module SVIII are considered to be sufficiently addressed. The number and content of the targeted follow-up questionnaires correspond to those of the originator RoActemra.

RMP Annex 4 includes eight specific adverse drug reaction follow-up forms which refer to infections (including opportunistic infections), gastrointestinal perforation and related events, medically significant hepatic event, spontaneous serious/non-serious bleeding event, myocardial infarction/acute coronary syndrome, stroke, malignancy, and demyelination events.

Overall conclusion on the pharmacovigilance plan: The PRAC, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product. The PRAC also considered that routine pharmacovigilance remains sufficient to monitor the effectiveness of the risk minimisation measures.

6.2.2.2. Additional pharmacovigilance activities

The applicant does not plan any additional pharmacovigilance activities. This is considered acceptable.

6.3. Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are planned. This is considered acceptable.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

Table 56: Planned routine risk minimisation measures

Safety concern	Routine risk minimisation activities
Important identified risk	
Serious infections*	**Routine risk communication** SmPC Section 4.3 Contraindications: • Active, severe infections with the exception of COVID-19 (see Section 4.4) Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient information leaflet Section 2 Warnings and precautions Section 4 Possible serious side effects **Routine risk minimisation activities recommending specific clinical measures to address the risk** None **Other risk minimisation measures beyond the product information**

	Pack size: None Medicine's legal status: Tuyory is a prescription only medicine.
Complications of diverticulitis*	**Routine risk communication** SmPC Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient information leaflet Section 2 Warnings and precautions Section 4 Possible side effects **Routine risk minimisation activities recommending specific clinical measures to address the risk** None **Other risk minimisation measures beyond the product information** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine.
Neutropenia	**Routine risk communication** SmPC Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient information leaflet Section 4 Possible side effects **Routine risk minimisation activities recommending specific clinical measures to address the risk** None **Other risk minimisation measures beyond the product information** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine.
Hepatotoxicity	**Routine risk communication** SmPC Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient information leaflet Section 2 Warning and precautions Section 4 Possible side effects **Routine risk minimisation activities recommending specific clinical measures to address the risk** In patients with RA, GCA, pJIA, sJIA, ALT, and AST should now be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. **Other risk minimisation measures beyond the product information** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine.
Important potential risk	

Thrombocytopenia and the potential risk of bleeding	**Routine risk communication** SmPC Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk** None **Other risk minimisation measures beyond the product information** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine.
Elevated lipid levels and potential risk of cardiovascular/ cerebrovascular events	**Routine risk communication** SmPC Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient information leaflet Section 2 Warnings and precautions Section 4 Possible serious side effects **Routine risk minimisation activities recommending specific clinical measures to address the risk** None **Other risk minimisation measures beyond the product information** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine.
Malignancies	**Routine risk communication** SmPC Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient information leaflet Section 2 Warnings and precautions **Routine risk minimisation activities recommending specific clinical measures to address the risk** None **Other risk minimisation measures beyond the product information** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine.
Demyelinating disorders	**Routine risk communication** SmPC Section 4.4 Special warnings and precautions for use **Routine risk minimisation activities recommending specific clinical measures to address the risk** None **Other risk minimisation measures beyond the product information** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine.
Immunogenicity	**Routine risk communication**

	SmPC Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk** None **Other risk minimisation measures beyond the product information** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine.

*The safety concerns "serious infection" and "complications of diverticulitis" are considered important identified risks for chronic tocilizumab dosing, but are assessed as important potential risks for the indication of COVID-19.

In addition, the applicant proposes the following additional risk minimisation measures:

Table 57: Planned additional risk minimisation measures

Safety concern	Additional risk minimisation activities
Important identified risk	
Serious infections*	Patient card; Guide for risk minimisation for patients; Guides for risk minimisation for healthcare professionals (brochure, dosing guide)
Complications of diverticulitis*	Patient card; Guide for risk minimisation for patients; Guides for risk minimisation for healthcare professionals (brochure, dosing guide)
Neutropenia	Guide for risk minimisation for patients; Guides for risk minimisation for healthcare professionals (brochure, dosing guide)
Hepatotoxicity	Guide for risk minimisation for patients; Guide for risk minimisation for healthcare professionals (Brochure); Patient Card
Important potential risk	
Thrombocytopenia and the potential risk of bleeding	Guide for risk minimisation for patients; Guide for risk minimisation for healthcare professionals (Brochure)
Elevated lipid levels and potential risk of cardiovascular/ cerebrovascular events	Guide for risk minimisation for patients; Guides for risk minimisation for healthcare professionals (brochure, dosing guide)
Malignancies	Guide for risk minimisation for patients; Guides for risk minimisation for healthcare professionals (brochure, dosing guide)
Demyelinating disorders	Guide for risk minimisation for healthcare professionals (Brochure)
Immunogenicity	None

*The safety concerns "serious infection" and "complications of diverticulitis" are considered important identified risks for chronic tocilizumab dosing, but are assessed as important potential risks for the indication of COVID-19.

Additional risk minimisation measures are targeted for the indications of RA, GCA, pJIA, and sJIA. CRS, an acute life-threatening condition treated in the hospital setting by oncologists, has a different benefit-risk profile relative to previously approved indications. Given this therapeutic context, no additional risk minimisation measure is required for treatment of CRS. Use of tocilizumab for CRS and its risk profile are specified in the SmPC. The additional risk minimisation measures listed in Table 57 are not applicable for the COVID-19 indication.

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

The proposed routine risk minimisation measures are considered acceptable.

6.4.2.2. Additional risk minimisation measures

The proposed additional risk minimisation measure include a patient card, which is considered acceptable. A Guide for risk minimisation for patients and a Guide for risk minimisation for healthcare professionals (brochure and dosing guide) were previously included but later deleted at the end of the procedure following a concomitant update of the originator (RoActemra)'s Risk Management Plan. Tuyory will need to update their RMP to follow the originator at the earliest possibility. This is considered acceptable. The patient card address all safety concerns and is in line with the originator. This is considered appropriate. For the originator product and the safety concern of hepatotoxicity, there was, as a one-time additional risk minimisation measure, a direct healthcare professional communication in June 2019, which is not planned for the biosimilar Tuyory. This is accepted as appropriate measures should have been implemented in the clinical routine by now.

6.5. RMP summary and RMP annexes overall conclusion

The RMP Part VI and the Annexes are considered acceptable.

6.6. Overall conclusion on the Risk Management Plan

☒The CHMP and PRAC consider that the risk management plan version 0.2 is acceptable.

In addition, the following minor revisions are recommended to be taken into account with the next RMP update:

- Alignment with the reference medicinal product (RoActemra, Tocilizumab)'s RMP whenever available

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic safety update reports (PSURs) submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

8. Product information

8.1. Summary of Product Characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

In this biosimilar application, the applicant is seeking all indications of the reference product RoActemra. The SmPC is aligned with the SmPC of RoActemra.

8.1.2. SmPC section 4.2 justification

The wording in 4.2 has been modified compared to the originator. The added wording in 4.2 under Method of administration for Tuyory compared to RoActemra is to avoid exposure to DEHP from PVC infusion bags. It is indeed recommended to use DEHP-free PVC, polypropylene (PP) or polyethylene (PE) infusion bags to reduce potential risks from DEHP.

8.2. Labelling

8.2.1. Package leaflet (PL) and labelling text

The package leaflet is in line with the originator, with a few improvements made in the user instructions.

8.2.2. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

8.2.3. Quick Response (QR) code

A request to include a QR code in the labelling and package leaflet for the purpose of providing statutory information has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code: package leaflet, instructions for use and educational materials.

8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tuyory (tocilizumab) is included in the additional monitoring list since it is a biological product that is not covered by the previous category and is authorised after 1 January 2011.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

9. Biosimilarity assessment

9.1. Comparability exercise and indications claimed

Indications claimed:

Tuyory is being developed as a biosimilar candidate to approved RoActemra (tocilizumab). The applicant applied for all approved therapeutic indications of the reference product RoActemra:

Rheumatoid arthritis (RA) (IV and SC formulation)

Tuyory, in combination with methotrexate (MTX), is indicated for:

- the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Tocilizumabhas been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

Coronavirus disease 2019 (COVID-19) (IV formulation only)

Tuyory is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

Systemic juvenile idiopathic arthritis (sJIA) (IV and SC formulations)

Tuyory is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older (for the IV formulation, 1 year and older in case of using the pre-filled syringe and 12 years and older in case of using the pre-filled pen), who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. Tuyory can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Polyarticular juvenile idiopathic arthritis (pJIA) (IV and SC formulations)

Tuyory in combination with methotrexate (MTX) is indicated for the treatment of polyarticular juvenile idiopathic arthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older (for the IV formulation and in case of using the pre-filled syringe, 12 years and older in case of using the pre-filled pen), who have responded inadequately to previous therapy with MTX.

Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Cytokine release syndrome (CRS) (IV formulation only)

Tuyory is indicated for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older.

Giant cell arteritis (SC formulations only)

Tuyory is indicated for the treatment of Giant Cell Arteritis (GCA) in adult patients.

Comparability exercise

Quality

The applicant has evaluated the similarity between RGB-19 SC and IV finished product to RoActemra SC and IV finished product in a comprehensive comparability program, evaluating relevant quality attributes by a panel of state-of-the-art and standard analytical methods. The overall approach to assess analytical similarity is found acceptable.

The number of batches included in the biosimilarity study are found acceptable, both with respect to RGB-19 and EU approved RoActemra. The analytical similarity assessment has been performed with a combination of methods assessing primary and higher order structures, post-translational modifications including charge variants and glycosylation profile, purity and impurities, particles and aggregates, and product variants. In addition, biological functional activities and biological binding were measured by several methods and results from a comparative stability testing study has been presented as well.

Overall, the provided data indicates a high degree of similarity between RGB-19 SC and IV finished product to RoActemra SC and IV finished product with respect to the physicochemical and biological characterizations. In addition, further characterization studies performed have shown comparable degradation profiles as well as similar lack of ADCC- and CDC-activity in support of the biosimilarity claim. Some minor differences are noted, and they are described in detail, for instance in LMWs, NGHC, level of basic variants, C-terminal lysine and proline amidation as well as in the levels of mono-glycated, galactosylated and sialylated forms. The applicant justifies all differences noted and provides arguments related to tocilizumab mode of action, highly similar functional activities and biological bindings, information in the literature as well as results obtained in the non-clinical and clinical studies, implying that these differences are not expected to have any impact on efficacy, safety, PK and immunogenicity and therefore not considered as clinically meaningful, hence not impacting the biosimilarity claim.

Clinical program

The clinical development program supporting the biosimilarity of RGB-19 to the reference product EU-RoActemra consists of two clinical studies: one phase I study in healthy males, and one phase III study in RA-patients. The phase I study, RGB192101, is a randomised, double-blind, 2-treatment, 2-period, 2-sequence crossover study to compare the PK, PD, and safety of a single subcutaneous dose of RGB-19 and RoActemra 162 mg in healthy Japanese male volunteers. The primary objective was to demonstrate PK equivalence between RGB-19 and RoActemra 162 mg following a single SC dose in healthy adult men. The phase III study, RGB19101, is an randomised, double-blind, active control, parallel-group multicentre clinical study conducted in patients with active RA who have experienced an inadequate clinical response to methotrexate (MTX) and currently receiving a stable dose of MTX. The overall aim was to evaluate efficacy, safety, and immunogenicity similarity of RGB-19 to RoActemra administered as 8 mg/kg intravenous drip infusion once every 4 weeks.

The clinical development program generally followed the applicable guidelines and the received CHMP advices.

9.2. Results supporting biosimilarity

Quality

The applicant has evaluated the similarity between RGB-19 SC and IV finished product to RoActemra SC and IV finished product in a comprehensive comparability program, evaluating relevant quality attributes by a panel of state-of-the-art and standard analytical methods. The overall approach to assess analytical similarity is found acceptable.

Overall, the provided data indicates a high degree of similarity between RGB-19 SC and IV finished product to RoActemra SC and IV finished product. Some minor differences are noted, and they are described in detail, for instance in LMWs, NGHC, level of basic variants, C-terminal lysine and proline amidation as well as in the levels of mono-glycated, galactosylated and sialylated forms. The applicant justifies all differences noted and provides arguments related to tocilizumab mode of action, highly similar functional activities and biological bindings, information in the literature as well as results obtained in the non-clinical and clinical studies, implying that these differences are not considered as clinically meaningful.

Pharmacokinetics

PK equivalence was demonstrated between RGB-19 and EU-RoActemra for C_{max} and AUC_{inf} as the 90% CIs for the GMRs were contained within the predefined 80.00-125.00% equivalence range. Also, the secondary PK endpoints were comparable between RGB-19 and EU-RoActemra.

Analyses of ADA positive/negative status indicated that ADA status did not impact C_{max} and AUC_{inf} for either RGB-19 or RoActemra treatment.

Clinical efficacy

The treatment effect of interest on the efficacy (primary estimand) was the treatment effect as determined by the change from baseline in DAS28-ESR in the hypothetical scenario that all subjects receiving IP had continued treatment up to Week 12 as planned in the protocol (hypothetical strategy). Two types of intercurrent events were defined: discontinuation of investigational treatment administration and violation or conflict with the rules regarding prohibited and permitted concomitant therapies. A secondary estimand was defined to estimate the treatment effect regardless of whether or not the intercurrent events had occurred up to 12 weeks assuming the situation in clinical practice (treatment policy strategy).

The primary endpoint, mean change from baseline in DAS28-ESR at week 12 was -3.62 (SE 0.09) for RGB-19 and -3.41 (SE 0.09) for RoActemra. The adjusted mean difference was -0.21 with 95% CI of -0.43, 0.02. The point estimate and two-sided 95% CIs for the between-group differences were within the predefined equivalence range of -0.6 to 0.6, thus the equivalence claim was met. The outcome from the secondary estimand primary endpoint aligned analysis was almost identical: -0.21, 95% CI:-0.44, 0.02. In this analysis using a treatment policy strategy, there were only a few patients with missing primary endpoint values at week 12 (3 patients in each group). Neither was there any significant differences in the analysis based on the PPS nor in the supplementary analysis adjusting for the stratification variable "site". In addition, a tipping point was planned and has been presented which support the robustness of the primary conclusion.

Clinical safety

The character and frequency of AEs, ADRs, AESI and SAEs were in general in line with tocilizumab in both phase I study RGB192101 (healthy males) and phase IIII study RGB19101 (patients with rheumatoid arthritis).

Immunology:

There were no clinically meaningful differences in the incidence of ADA or NAb positivity nor hypersensitivity reactions between treatment arms in any of the studies.

9.3. Uncertainties and limitations about biosimilarity

Quality

The overall approach to assess analytical similarity is found acceptable.

Some minor differences are noted, for instance in LMWs, NGHC, level of basic variants, C-terminal lysine and proline amidation as well as in the levels of mono-glycated, galactosylated and sialylated forms. The applicant justifies most differences and provides arguments related to tocilizumab mode of action, results from biological characterisation, information in the literature as well as results obtained in non-clinical and clinical studies, implying that these differences are not clinically meaningful.

Pharmacokinetics

The available PK/PD data supports biosimilarity versus the EU reference product.

PK similarity has been demonstrated between RGB-19 and EU-RoActemra in the pivotal PK study in healthy subjects. PK data from the phase III study in patients with rheumatoid arthritis is supportive.

There are no remaining uncertainties.

Clinical efficacy

No major issues were identified in the efficacy data reported up to Week 52 that questions biosimilarity. Secondary endpoint was however only presented descriptively and additional analyses regarding the ACR20/50/70 response were requested to fully evaluate the findings. In general efficacy were similar between the two products at all time points. The numbers were slightly in favour of RGB-19 especially at week 8 and week 52, however this finding does not preclude biosimilarity since they are considered as a result of normal variability.

Clinical safety

Overall, 25 subjects withdrew from phase III study RGB19101, mostly during the second evaluation period. The proportion of patients withdrawing were slightly lower in the RGB-19 group than the RoActemra group (3.8% vs 9.7%). In addition, 32 subjects discontinued IP administration, 7.1% in the RGB-19 group and 9.7% in the RoActemra group. The numbers and reasons for discontinuation do not evoke any concerns and are rather similar between the two groups. The numbers of patients who temporarily disrupted investigational product administration were also slightly lower in the RGB-19 group (9.9%) vs the RoActemra group (14.5%). This was mainly because of AE. No dose reductions of the IP were performed during the study. The provided information does not evoke any concerns regarding biosimilarity but are rather the results of normal variability.

9.4. Discussion on biosimilarity

From a quality perspective, an extensive biosimilarity exercise has been performed, evaluating relevant quality attributes by a panel of state-of-the-art and standard analytical methods. The overall approach to assess analytical similarity is found acceptable. Overall, the provided data indicates a high degree of similarity between RGB-19 SC and IV finished product to RoActemra SC and IV finished product. Some minor differences are noted, and they are described in detail, for instance in LMWs, NGHC, level of basic variants, C-terminal lysine and proline amidation as well as in the levels

of mono-glycated, galactosylated and sialylated forms. The applicant justifies all differences noted and provides arguments related to tocilizumab mode of action, highly similar functional activities and biological bindings, information in the literature as well as results obtained in the non-clinical and clinical studies, implying that these differences are not considered as clinically meaningful.

From a pharmacokinetic perspective, PK similarity has been demonstrated between RGB-19 and EU-RoActemra in the pivotal PK study in healthy subjects. PK data from the phase III study in patients with rheumatoid arthritis is supportive.

From a clinical efficacy perspective, the results show evidence of therapeutic equivalence between RGB-19 and EU-RoActemra in this sensitive clinical model of rheumatoid arthritis and therefore supports biosimilarity.

From a clinical safety perspective, the results demonstrate evidence of biosimilarity between RBG-19 and RoActemra.

9.5. Extrapolation of safety and efficacy

Tuyory has been developed as a biosimilar to the reference medicinal product RoActemra. The applicant has applied for the same therapeutic indications as those currently authorised for RoActemra, namely: rheumatoid arthritis, Coronavirus disease 2019, systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis, cytokine release syndrome and giant cell arteritis. The applicant has applied for the same pharmaceutical forms and strengths as RoActemra, namely: a 20 mg/ml concentrate for solution for infusion, a 162 mg solution for injection in pre-filled syringe and a 162 mg solution for injection in pre-filled pen.

The choice of rheumatoid arthritis as the study population is considered appropriate, indeed, inflammatory diseases for which RoActemra is approved are associated with enhanced IL-6 production. Tocilizumab binds to soluble and membrane bound IL-6 receptors, blocking IL-6 from exerting its pro-inflammatory effects. Thus, extrapolation to all indications of RoActemra is acceptable.

9.6. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Tuyory can be considered biosimilar to RoActemra and a benefit/risk balance comparable to the reference product can be concluded.