20 February 2014
EMA/CHMP/606295/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

RoActemra

International non-proprietary name: tocilizumab

Procedure No. EMEA/H/C/000955/X/0030

Note

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

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Product information

Name of the medicinal product:	RoActemra
Applicant:	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 3AY UNITED KINGDOM
Active substance:	Tocilizumab
International Nonproprietary Name:	Tocilizumab
Pharmaco-therapeutic group (ATC Code):	Pharmacotherapeutic group: Immunosupressants, Interleukin inhibitors (L04AC07)
Therapeutic indication(s):	RoActemra, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (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, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. RoActemra 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.
Pharmaceutical form(s):	Solution for injection
Strength(s):	162 mg
Route(s) of administration:	Subcutaneous use
Packaging:	Pre-filled syringe
Package size(s):	4 pre-filled syringes

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List of abbreviations

ACR	American College of Rheumatology
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the serum concentration-time curve
BMI	Body Mass Index
Cavg	Average concentrations
CBR	Cytokine binding region
CDR	Complementarity determining region
CHO	Chinese hamster ovary
CI	Confidence Interval
CIA	Collagen-induced arthritis
CL	Clearance
Cmax	Maximum Concentration
CMH	Cochran-Mantel Haenzsel
Cmin	Concentration at the End of the Dosing Interval (Trough Concentration)
COX	Cyclo-oxigenase enyzme
CPK	Creatine phosphokinase
CRP	C-reactive protein
Ctrough	trough concentrations
CYP450	Cytochrome P450
DAS	Disease Activity Score
DBP	Diastolic Blood Pressure
DC	Dendritic cells
DMARD	Disease modifying anti-rheumatic drug
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
EIA	Enzyme immunoassay
ELISA	Enzyme-Linked Immunosorbent Assay
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FcRN	Neonatal Fc receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
gp130	Glycoprotein 130 (signaling complex)
h	Hour
HAHA	Human Anti-Human Antibodies
HAQ-DI	Health Assessment Questionnaire – Disability Index
HDL	High density lipoprotein
IgG	Immunoglobulin G
IL-1β	Interleukin-1 beta
IL-2	Interleukin-2
IL-6	Interleukin-6
IL-6R	Interleukin-6 receptor

IM	Intra muscular
IR	Inadequate Responder
ITT	Intent-to-Treat
IV	Intravenous
Kd	Dissociation constant
KD	Equilibrium dissociation constant
LDL	Low density lipoprotein
LDL	Low-Density Lipoprotein
LLOQ	Lower Limit of Quantitation
mIL-6R	Membrane bound interleukin-6 receptor
MR16-1	Mouse specific interleukin-6 receptor antibody
MRA	Myeloma receptor antagonist, acronym for tocilizumab
MTX	Methotrexate
NA	Not applicable
ND	Not determined
NOAEL	Non observed adverse effect level
NSAID	Non-steroidal anti-inflammatory drug
NSD	Needle safety device
PBL	Peripheral blood leucocytes
PD	Pharmacodynamic(s)
PFS	Pre-filled syringe
PFP	Pre-filled pen
pJIA	Polyarticular juvenile idiopathic arthritis
PK	Pharmacokinetic(s)
PP	Per Protocol
PPI	Proton Pump Inhibitors
RA	Rheumatoid arthritis
RF	Rheumatoid factor
rh	Recombinant human
SAA	Serum Amyloid A
SBP	Systolic Blood Pressure
SC	Subcutaneous
SCID	Severe combined immunodeficiency disease
SD	Standard deviation
sgp130	Soluble glycoprotein 130
sIL-6R	Soluble interleukin-6 receptor
sJIA	Systemic Juvenile Idiopathic Arthritis
T½ (α)	Initial half-life
T½ (β)	Terminal half-life
TB	Tuberculosis
TCZ	Tocilizumab
tmax	Time to achieve Cmax
TNF	Tumor necrosis factor
ULN	Upper Limit of Normal
Vss	Volume of Distribution at Steady-State
WBC	White blood cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration Ltd submitted to the European Medicines Agency (EMA) on 20 December 2012 an extension application for the Marketing Authorisation for RoActemra, through the centralised procedure falling within Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I.

Roche Registration Ltd is the Marketing Authorisation Holder (MAH) for RoActemra 20 mg/ml concentrate for solution for infusion in vials (intravenous use) indicated in the following:

- RoActemra, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (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, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.
  RoActemra 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.
- RoActemra is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.
- RoActemra in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (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. RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

The MAH applied for a new strength 162 mg solution for injection in a pre-filled syringe and in a pre-filled pen (subcutaneous injection) for the following indication:

> *RoActemra, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (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, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.*
>
> *RoActemra 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.*

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0179/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0179/2012 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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 because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 24 May 2007, 19 January 2012 and 16 February 2012 (EMEA/CHMP/SAWP206914/2007, EMEA/CHMP/SAWP/9785/2012, EMEA/CHMP/SAWP/9787/2012 and EMEA/CHMP/SAWP/99262/2012). The Scientific Advices pertained to clinical aspects of the dossier.

Licensing status

RoActemra has been given a Marketing Authorisation in the European Union on 16 January 2009.

1.2. Manufacturers

Manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
D-79639 Grenzach-Whylen
Germany

1.3. Steps taken for the assessment of the product

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

Rapporteur: Jan Müller-Berghaus Co-Rapporteur: Ágnes Gyurasics

- The application was received by the EMA on 20 December 2012.
- The procedure started on 30 January 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 April 2013 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 April 2013 (Annex 2).

- During the meeting on 30 May 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 3 June 2013 (Annex 4).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 August 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 26 September 2013 (Annex 5).
- During the CHMP meeting on 24 October 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 6).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 November 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 26 November 2013 (Annex 7).
- During the meeting on 19 December 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting an extension of the Marketing Authorisation for RoActemra.
- On 20 December 2013, the MAH informed EMA of a clogging issue with the new pre-filled syringe presentation. During the meeting on 20-23 January 2014, the CHMP adopted a list of questions to the MAH requesting further information to which the MAH responded on 31 January 2013.
- On 31 January 2014 the MAH informed EMA and the CHMP of an out of specification issue with the new pre-filled pen presentation. On 11 February 2014 the MAH withdrew the new pre-filled pen presentation.
- During the meeting on 17-20 February 2014, the CHMP adopted a revised positive opinion for granting an extension to the Marketing Authorisation for RoActemra 162 mg solution for injection in a pre-filled syringe on 20 February 2014.

2. Scientific discussion

2.1. Introduction

Problem statement

This extension of the Marketing Authorisation for RoActemra concerns a new pharmaceutical form "solution for injection", a new strength 162 mg with two new presentations pre-filled syringe and pre-filled pen and a new route of administration for subcutaneous use.

Rheumatoid arthritis (RA) is a progressive, systemic auto-immune disease characterised by synovitis that damages diarthroidal joints and is accompanied by fatigue, anemia, and osteopenia. RA has a prevalence of 0.5% to 1.0% and a peak incidence between 40 and 60 years of age and affects primarily women.

Non-steroidal anti-inflammatory drugs (NSAIDs) provide only symptomatic relief. Disease-modifying anti-rheumatic drugs (DMARDs), the cornerstone of RA treatment throughout all

stages of the disease, maintain or improve physical function and retard radiographic joint damage. More recently, biologic compounds that target tumour necrosis factor alpha (TNF-α), B cells, or T cells have been used successfully to treat RA, but approximately 30% to 40% of patients fail to respond to these therapies.

IL-6 is a pleiotropic, pro-inflammatory, multifunctional cytokine produced by a variety of cell types, and it has been implicated in the pathogenesis of several inflammatory and autoimmune disorders, including RA. Elevated IL-6 levels have been observed in the serum and synovial fluid of RA patients, and levels correlate with disease activity.

About the product

TCZ is a recombinant humanised anti-human IgG1 monoclonal antibody directed against the interleukin-6 receptor (IL-6R) that binds specifically to both soluble and membrane-bound IL-6R, thereby inhibiting IL-6-mediated signalling.

The authorised formulation of TCZ is for IV administration given over 60 minutes. IV infusion requires administration by a healthcare professional (HCP) in a clinical setting. For the SC formulation, it is intended that after proper training in injection technique by an HCP, patients may self-inject at home if their physician determines that it is appropriate.

In several chronic conditions, including RA, in which patients are required to self-administer injectable drugs (e.g. diabetes, multiple sclerosis), a preference for an auto injector (AI) over a syringe has been reported (Korytkowski 2003, Summers 2004, Mikol 2005, Kivitz 2006).

Type of application and aspects on development

This Extension Application as referred to in Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I is to register the following:

- A new pharmaceutical form “solution for injection”
- A new strength 162 mg with two new presentations Pre-filled syringe and pre-filled pen
- A new route of administration for subcutaneous route.

The development program comprises six Phase I or Phase I/II clinical pharmacology studies (studies WP18097, BP22065, NP25539, BP21894, MRA227JP and NP22623) and two pivotal Phase III studies (studies WA22762 and NA25220) in patients with RA. The Phase III study MRA229JP, conducted exclusively in Japanese patients with RA, is supportive only of the efficacy and safety of TZC SC when given as monotherapy.

2.2. Quality aspects

2.2.1. Introduction

The formulation development program was to obtain a stable highly concentrated liquid formulation for subcutaneous (SC) administration of tocilizumab (RoActemra SC). A 180 mg/mL concentration was selected for SC administration of 162 mg/0.9 mL of tocilizumab in a single-use prefilled syringe (PFS) mounted with a needle safety device (NSD) or assembled as a single-use prefilled pen (also referred to as an “auto-injector” (AI)).

The RoActemra SC finished product formulation consists of 180 mg/mL tocilizumab in L-histidine/L-histidine hydrochloride, L-arginine/L-arginine hydrochloride, L-methionine, polysorbate 80, at a pH of approximately 6.0.

Tocilizumab for SC formulation was developed by modifying the latest tocilizumab G5 process version at the Chugai Utsunomiya (UT) facility (G5U).

To maintain the Phase III clinical supply and for future commercial supply, the manufacturing process for the G5.2 active substance was transferred to Genentech's Oceanside (OCN) facility.

2.2.2. Active Substance

Currently global commercial supply of active substance for IV administration is provided by the G5U fifth generation process in UT. For SC administration, active substance derived from the fifth generation process at OCN will be used. The initial G5U manufacturing process approved for tocilizumab active substance was validated to ensure consistent product quality.

The manufacturing process for subcutaneous (SC) administration (G5.2) was transferred from the clinical site in Vacaville (VV) to the Oceanside (OCN) facility. The OCN facility is the intended commercial manufacturing site for SC Active substance. The G5.2 manufacturing process is identical to the manufacturing process for the tocilizumab active substance for IV administration, except for higher bulk active substance concentration. Additional validation was required to support the changes, as well as to support the facility and equipment differences between the licensed UT site and the OCN site.

The process qualification (PQ) of the tocilizumab SC process was performed to qualify the manufacturing process at the OCN site.. The G5.2 qualification runs met the established ranges. Additionally, in-process testing and Certificate of Analysis (CofA) results were reviewed to demonstrate that the quality attributes of the qualification runs meet the quality control release criteria. Verification that the process parameters are maintained within the established acceptable ranges for all steps in common between the G5.2 and IV formulation process was demonstrated. The summary of the results indicate that the tocilizumab G5.2 manufacturing process is capable of consistently producing active substance that meets the established quality specifications and attributes.

To demonstrate the comparability of the tocilizumab G5.2 active substance manufactured at OCN facility to G5.2 active substance produced at Genentech Vacaville facility, G5.2 Active substance batches produced at the OCN facility (OCN G5.2 active substance batches) were compared to the Reference Standard (RS) and G5.2 active substance batches produced at the VV facility (VV G5.2 active substance batches). In addition to meeting the active substance specification, further characterisation was performed with respect to the primary structure of the G5.2 active substance and included an assessment of the heterogeneity of the G5.2 active substance with respect to glycosylation, size, and charge-based isoforms. It was demonstrated that, with respect to the structure of the tocilizumab molecule, the OCN G5.2 active substance batches are consistent with and comparable to the VV G5.2 active substance batches and the RS. Comparability data for batches manufactured with the currently approved G5U and the proposed G5.2 OCN process were also provided. Tocilizumab G5.2 batches were evaluated with respect to the removal of process- and product-related impurities. The results demonstrate that the levels of process- and product-related impurities are consistently removed to levels below or at the level of detection of the respective assay.

Specifications contain standard criteria for the acceptance or rejection of batches based on features that are important to assure the identity, purity, content, potency, and safety of G5.2 tocilizumab Active substance. The proposed specification is based upon knowledge from preclinical development as well as the approved tocilizumab intravenous (IV) active substance specification. Furthermore, the specification complies with current regulatory requirements. Appropriateness of the proposed specification was evaluated based on the results from batches of G5.2 tocilizumab active substance. The batch analysis data demonstrate that the G5.2 process is validated to produce tocilizumab that meets all current release specifications.

The results of the stability studies indicate consistency of tocilizumab manufactured at the commercial scale. Real-time and accelerated stability studies were initiated in accordance with ICH guidelines and per protocol (PP) to monitor the time-temperature stability of finished product. On the basis of the data provided, the approvable shelf life for the finished product is 30 months at 2-8°C.

2.2.3. Finished Medicinal Product

RoActemra (tocilizumab) is supplied as a sterile, colorless to slightly yellowish, preservative-free liquid solution in a single-use 1 mL prefilled syringe (PFS) for subcutaneous (SC) injection, delivering 162 mg tocilizumab in a 0.9 mL solution.

A) Finished product in prefilled syringe (PFS)

Galenical bulk production of RoActemra SC prefilled syringes (PFSs) 162 mg/0.9 mL is performed by Vetter Pharma-Fertigung GmbH & Co KG Schützenstrasse 87 and 99-101 D-88212 Ravensburg Germany.

RoActemra (tocilizumab) active substance is thawed in the primary container and stirred for homogenization. The filtered finished product bulk solution is sterile-filtered in-line and aseptically filled into 1 mL pre-sterilised syringes. Immediately after filling, the syringes are stoppered with sterilized plunger stoppers and stored at 2° C - 8° C prior to visual inspection. After the visual inspection is completed, syringes are bulk packaged and stored at 2° C - 8° C. Final automated assembly of the PFS with the plunger rod and needle safety device (NSD) is performed at the Roche Kaiseraugst facility on a fully automated assembly line. The final assembled PFS + NSD and patient leaflets are packaged together in a printed carton. After packaging, the final product is transferred to cold storage (2° C - 8° C) until final distribution.

Validation activities were conducted to ensure that appropriate process parameters and ranges are defined for the manufacture of the commercial batch sizes.

To validate the sterile filtration process, a microbial retention test was performed. Hold time study results support the proposed hold times.

In general the specifications are set according to the requirements of the ICH Q6B Guidance. The European Pharmacopoeia monograph “Monoclonal antibodies for human use” (2031) requires for appearance that liquid preparations are without visible particles, unless otherwise justified. The applicant was asked to set the specifications according to the monograph or to justify the proposed specification. The analytical procedures for RoActemra SC prefilled syringes have been established based on the validated analytical procedures previously submitted for RoActemra IV vials. The minor differences and adjustment have no impact on the test performance. The batch analysis data indicate that all acceptance criteria were met. The actual values for the potency

determination should be provided. The proposed RoActemra SC finished product release and end-of-shelf-life specifications are based upon knowledge from clinical development as well as the approved RoActemra IV.

The materials of the primary packaging material are in compliance with the Ph. Eur. requirements.

A maximum product expiry for the RoActemra PFS + NSD combination product of 30 months at the recommended storage condition of 2°C – 8°C was considered acceptable based on:

- Real-time and accelerated data for the PFS;

- Supportive Real-time and accelerated data for the PFS;

- Real-time and accelerated data for the PFS + NSD;

- Functionality data on PFS + NSDs assembled on the semi-automated assembly line at recommended storage conditions;

- Supportive container closure integrity (CCI) study of assembled media-filled syringes into the PFS + NSD.

On 20 December 2013, the MAH reported an issue affecting the PFS-NSD device: at the 9-month time point of the long term functionality testing performed in June 2013, one PFS-NSD device out of 60 units exceeded the acceptance criterion of peak force before the finished product is expelled from the syringe. Testing of the 0, 3, 6 and 12 month time points were successfully completed with all syringes meeting the acceptance criteria. The possible root cause is a clogged needle due to solidified finished product at the tip. The MAH already reported clogging as a possible root cause for a clinical complaint in the submission documentation.

As an immediate action the MAH proposed changes to the product information in sections 6.3 and 6.6 of the SmPC as well as in the Package Leaflet in sections 5 and 6 (Instructions for Use Steps 2 and 5). This is supported by CHMP.

Overall it was concluded that that clogging incidents, including clogging incidents prior to cap removal, are very rare events. Furthermore, the risk assessment provided by the MAH indicated that if in the very rare event a patient were to attempt to perform an injection using a PSF-NSD or PFP with a clogged needle, it is highly unlikely there would be any impact on clinical efficacy or safety.

It is concluded that there is no impact on clinical efficacy or safety due to clogging incidents when using the PFS-NSD device.

B) Finished product in prefilled pen (AI-auto injector)

An assessment of the potential influence of the assembly process on finished product performance was conducted. The degradation behaviour of tocilizumab at 2° C – 8° C and 25° C in the bulk PFS and in the AI configurations is considered very similar. Furthermore the results are well within specification limits for the recommended storage condition of 2° C – 8° C.

The AI delivers RoActemra to the patient by a mechanical spring that pushes the plunger stopper towards the needle, initiating the injection of the finished product solution. An additional risk assessment for the AI was performed in order to evaluate the influence of the assembly and

packaging process on CCI integrity. Supporting microbiological CCI testing on commercial representative media-filled syringes in the assembled system were additionally performed.

Galenical bulk production of RoActemra SC prefilled syringes (PFSs) 162 mg/0.9 mL: Vetter Pharma-Fertigung GmbH & Co KG. The autoinjector (AI) is composed of front and rear subassembly parts that are assembled to hold the prefilled syringe (PFS). Final assembly of the PFS into the AI is performed at the Roche Kaiseraugst facility on a fully automated assembly line in a controlled, non-sterile environment.

As part of validation, in-line controls and functionality were checked and the correct assembly of the AIs was demonstrated by a visual and functional test.

The degradation behaviour of tocilizumab at 2° C – 8° C and 25° C in the bulk PFS and in the AI configurations is considered very similar. Furthermore the results are well within specification limits for the recommended storage condition of 2° C – 8° C. The shelf life for the RoActemra AI combination product is further supported by the results from all assembled AI batches and available studies for the components and will be assigned to each assembled AI batch based on the component having the shortest remaining shelf life.

On 29 January 2014, the applicant reported several out-of-specification results with the PFP at the 24 month time point of the long-term functionality testing: several examples exceeded the injection time limit. This acceptance limit for the injection time into air is based on the performance capability of the spring-driven PFP auto-injector to deliver the full dose of RoActemra 162 mg/0.9 mL. The possible root cause of these events is not fully understood. As a consequence, on 11 February 2014 the MAH decided to remove the PFP presentation from the scope of this line extension. The MAH also confirmed their ability to ensure commercial supply of the PFS to all rheumatoid arthritis patients once approved and to subjects enrolled in on-going clinical studies.

C) Adventitious agents safety evaluation

The G5U manufacturing process of tocilizumab was used as the basis for the initial manufacture of RoActemra SC. Modifications to the G5U purification process were made to accommodate facility-related differences, including larger mass produced in Genentech bioreactors relative to those used in the G5U process. No new TSE risk material has been introduced. For all viral clearance steps that did not change from G5U to G5.2 virus removal and inactivation studies have not been repeated.

In summary, the virus safety for the new G5.2 active substance manufacturing process is considered sufficiently demonstrated.

2.2.4. Conclusions on the chemical, pharmaceutical and biological aspects

The overall Quality of RoActemra in a pre-filled pen syringe equipped with needle safety device (PFS+NSD) is considered acceptable.

2.2.5. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Tocilizumab is a recombinant humanized monoclonal antibody of the immunoglobulin G1 (IgG1) class that binds both soluble and membrane-bound human interleukin-6 receptor (IL-6R). Tocilizumab has been shown to be pharmacologically active in cynomolgus monkeys. To support the original marketing authorisation application (MAA), an extensive number of pharmacology, pharmacokinetics and toxicities studies were conducted. Authorisation of the IV route of administration was mainly based on pharmacology, pharmacokinetics and toxicology data using this route of exposure in cynomolgus monkeys. Pharmacology, PK and toxicity data (reproductive toxicity and juvenile toxicity studies) were also provided using a murine surrogate antibody MR16-1 with IV infusion in the mouse.

To bridge this comprehensive dataset to the subcutaneous (SC) route of administration, a PK study was conducted in the minipig to assess the absorption behavior from the high concentration SC formulation of tocilizumab (180 mg/mL) intended for clinical use. An IV dose arm allowed for the estimation of the bioavailability of tocilizumab after SC dosing. The minipig was selected for this purpose as this species represents an animal model with skin and subcutaneous tissue texture similar to humans making it appropriate to study the absorption of SC formulations.

Further, the safety of tocilizumab SC with respect to any local reactions at the site of injection, the effects on the draining lymphatic system specific to this site of administration, a comparison of exposure and an assessment of anti-drug antibody formation with this subcutaneous mode of administration versus the IV route, the elimination phase of tocilizumab and the possible reversibility of any observations in a treatment-free phase of the study were assessed in a 9-week SC repeat-dose toxicity study in the cynomolgus monkey, which included a 16-week treatment-free observation period.

These studies were conducted with the high concentration preparation of 180 mg/mL tocilizumab that is also used for the human SC formulation. Thus, these data also bridge the non-clinical kinetic and safety data to the human preparation including the excipients used.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The pharmacodynamics studies performed with tocilizumab in support of the original application showed that tocilizumab specifically binds to the IL-6 binding site of both sIL-6R and mIL-6R with similar affinity. Therefore, tocilizumab is able to block IL-6 from binding to both receptors and thereby blocks the activity of IL-6. *In vitro* studies demonstrated that tocilizumab can inhibit IL-6 binding to and displace already bound IL-6 from sIL-6R and that tocilizumab has a strong anti-IL-6 effect. Tocilizumab is specific to the IL-6R with no binding to other receptors associated with gp130 or to receptors for other cytokines. Pre-clinical studies showed specificity of tocilizumab to the IL-6R with no direct cross-reactive inhibitory effect on TNF-α, IL-1β, IL-15 or IL-2 *in vitro*.

2.3.3. Pharmacokinetics

A non-GLP PK study (study No 165.001) was conducted in the minipig to assess the absorption behavior of the high concentration SC formulation of tocilizumab (180 mg/mL) intended for clinical use. An IV dose arm allowed for the estimation of the relative bioavailability of tocilizumab after SC dosing. The bioavailability was estimated at 83.5%, which indicates a very good absorption of tocilizumab SC from this formulation.

No repeated dose PK studies have been performed with tocilizumab SC. Information on the repeated dose PK of tocilizumab SC was obtained in a repeated dose SC toxicology study in cynomolgus monkeys (study 1029905).

Method of analysis

Assay for quantification of tocilizumab in cynomologus monkey plasma

Concentrations of tocilizumab after repeated doses in cynomolgus monkey plasma were determined with a validated sandwich enzyme-linked immunosorbent assay (ELISA).

The ELISA used for analysis of tocilizumab concentrations in the single SC dose study in cynomolgus monkey was already described in the original MAA for the tocilizumab IV formulation.

Assay for quantification of tocilizumab in minipig plasma

Concentrations of tocilizumab in minipig plasma were determined with an exploratory sandwich ELISA which was adapted from the assay validated for cynomolgus monkey plasma. The assay closely followed the procedure for cynomolgus monkey plasma, with calibration and quality control samples made up in minipig plasma.

Assay for detection of anti-tocilizumab antibodies in cynomologus monkey plasma

A validated sandwich ELISA was used to detect and confirm the presence of antitocilizumab antibodies after repeated doses in cynomolgus monkey plasma. This assay uses a mouse anti-human IL-6R monoclonal antibody (mPM- 1) which has the same CDR as tocilizumab. This assay system only detects monkey antibodies that bind to the CDR of tocilizumab.

Absorption

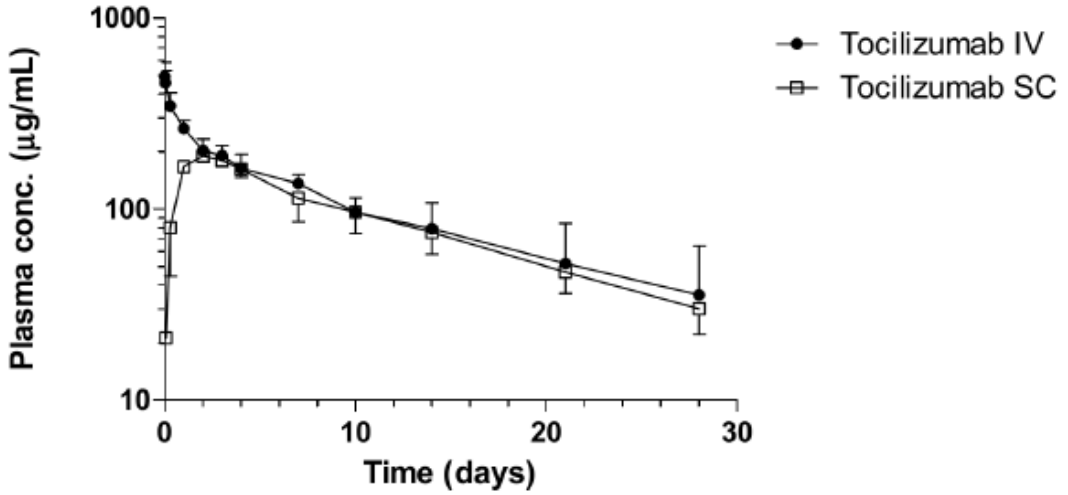
Single-dose intravenous and subcutaneous administration in minipigs (study No. 165.001)

A PK study was conducted with tocilizumab SC in minipigs to explore the PK of the high concentration SC formulation of tocilizumab (concentration 180 mg/mL). The study included an IV dosing arm to allow estimation of absolute bioavailability. In additional dose arms, the PK of two alternative formulations was studied containing different concentrations of recombinant human hyaluronidase (rHuPH20) as a permeation enhancer. The tocilizumab SC formulations containing rHuPH20 are not relevant for this application, as the clinical tocilizumab SC formulation does not contain rHuPH20. Therefore the results for the rHuPH20 containing formulations will not be discussed further.

Female Göttingen minipigs (n=3 and 5 for IV and SC administration, respectively) received a single IV dose of tocilizumab at 20.3 mg/kg or a single SC dose at 180 mg/animal (about 20.2 mg/kg). The SC injection volume was 1 mL. Plasma concentrations of tocilizumab were analyzed

with a specific ELISA. PK analysis was conducted by both non-compartmental and compartmental methods. The figure below shows the average plasma concentration-time profiles after IV and SC dosing.

Figure 1. Time Course of Tocilizumab Plasma Concentrations in Female Göttingen Minipigs Following a Single iV (at 20.3 mg/kg) or SC (at 180 mg/animal. Equivalent to ca. 20.2 mg/kg) Administration of Tocilizumab (n = 3 or 5, respectively) (mean ± SD)



After IV administration, the plasma concentration-time curve showed a biphasic disposition of TCZ. Non-compartmental PK analysis indicated a terminal half-life of 286 ± 182 hours. Clearance was estimated at 0.00435 ± 0.00179 mL/min/kg (equivalent to 6.26 ± 2.58 mL/day/kg), and the volume of distribution at steady-state (Vss) was estimated to be 84.9 ± 19.2 mL/kg (mean ± SD).

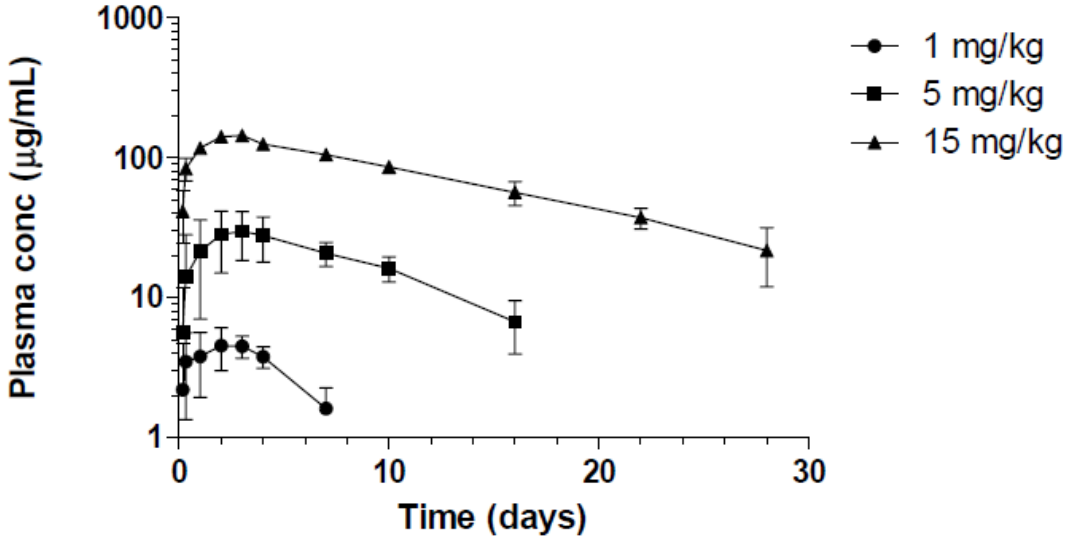
After SC administration, maximum TCZ plasma concentrations were 190 ± 14 µg/mL (mean ± SD). They were reached after 48 hours (median value; range: 24 to 72 hours). The terminal half-life (262 ± 40 hours; mean ± SD) was similar to that after IV administration. The SC bioavailability from non-compartmental PK analysis was 83.5 ± 23.1%. Compartmental PK modeling revealed a first order absorption rate constant ka of 0.0359 h-1 and a fraction absorbed of 81.2% (population estimates).

Single-dose subcutaneous administration in cynomolgus monkeys (study No ADM04-0014)

This SC PK study in male cynomolgus monkeys was already described in the original MAA for the tocilizumab IV formulation. The results of this study were used to support the planning of the SC GLP toxicology study in cynomolgus monkeys. Therefore, the results of this study are again briefly summarized.

Male cynomolgus monkeys (n=4/dose group) received a single SC tocilizumab dose at a dose level of 1, 5, or 15 mg/kg. Plasma concentrations of tocilizumab were analyzed with a specific ELISA. PK analysis was conducted by non-compartmental analysis. The figure below shows the average plasma concentration-time profiles.

Figure 2. Time Course of Tocilizumab Plasma Concentrations in Cynomolgus Monkeys Following a Single Subcutaneous Administration of Tocilizumab at Various Dose levels (n = 4/dose group) (mean ± SD)



PK parameters are summarized in the table below.

Table 1. Noncompartimental Pharmacokinetic Parameters for Tocilizumab in Cynomolgus Monkeys Following Single Subcutaneous Administration of Tocilizumab at Various Dose Levels (mean ± SD)

Parameter	Dosing Regimen (n=4/dose group)		
	1 mg/kg	5 mg/kg	15 mg/kg
C_{max} (µg/mL)	4.88 ± 1.29	30.1 ± 11.8	145 ± 8
T_{max} (h)	50.0 ± 30.2	72.0 ± 19.6	66.0 ± 12.0
$AUC_{0\text{-}inf}$ (h·µg/mL)	737 ± 210	7860 ± 2260	55200 ± 10200
$T_{1/2}$ (h)	68.1 ± 26.1	112 ± 9	229 ± 42
F (%)	NC	72.1	NC

C_{max}: Maximum plasma concentration
T_{max}: Time to maximum plasma concentration
AUC: Area under the plasma concentration-time curve
F: Bioavailability
NC: not calculated

Following SC administration maximum tocilizumab plasma concentrations were reached at about 2 to 3 days post dose at all dose levels. Cmax and AUC values increased more than dose-proportionately, which is in line with the non-linear PK of tocilizumab in cynomolgus monkeys observed after IV administration. At the 5 mg/kg dose level the SC bioavailability was estimated at 72.1%.

Repeated-dose subcutaneous administration

Information on the repeated-dose PK of tocilizumab SC was obtained in a repeated dose toxicology study (study 1029905). Cynomolgus monkeys (n=5/gender) received weekly doses of tocilizumab SC at 100 mg/kg over 9 weeks. Average maximum plasma concentrations of tocilizumab increased from 1110 µg/mL after the first dose to 3280 µg/mL after the 8th dose, while average AUC(0-168h) values increased from 151,000 to 478,000 µg·h/mL.

Anti-tocilizumab antibodies were measured in the recovery animals (n=2/gender) during and at the end of the 16-week recovery phase. No anti-tocilizumab antibodies were detected in any cynomolgus monkeys during the recovery phase.

Metabolism (interspecies comparison)

No dedicated studies on the metabolism/catabolism of tocilizumab SC have been performed. Tocilizumab is expected to undergo catabolism similar to that of other IgGs. There is broad evidence in the literature that IgG is cleared from the body predominantly via catabolism. The neonatal Fc receptor (FcRn) plays a key role in maintaining IgG homeostasis by protecting IgG from catabolism.

The FcRn mediated protection process is also relevant during the SC absorption process. Studies in mice have shown a marked reduction in SC bioavailability for an IgG in FcRn knockout mice relative to wild-type mice. It is known that most of IgGs given subcutaneously are absorbed into blood flow through lymph.

Dedicated studies to assess the fate of tocilizumab in the subcutaneous interstitial space and the lymphatic system were not considered to be necessary. This was supported by the CHMP. Uptake of IgGs from the interstitial space into the lymphatic system and subsequent back transport into blood circulation also occurs following IV administration as part of the normal distribution and re-circulation process of IgGs. Therefore, catabolic processes unique to SC administration are quite unlikely.

Overall, the catabolism processes of tocilizumab administered SC are expected to be similar to those after IV administration.

Pharmacokinetic drug interactions

No PK drug interaction studies have been performed with tocilizumab SC. The potential for PK drug interaction with tocilizumab SC is not expected to differ from that of the tocilizumab IV formulation, since after having reached systemic circulation tocilizumab will behave the same irrespective of the administration route. This was considered acceptable by the CHMP.

2.3.4. Toxicology

Tocilizumab has been extensively characterized in the cynomolgus monkey in single and repeat-dose toxicity studies with intravenous (IV) administration of this antibody. In order to bridge the IV toxicity study program to the new subcutaneous (SC) formulation program, a single 9-week SC repeat-dose toxicity study followed by a 16-week recovery phase in the cynomolgus monkey was conducted. The treatment duration of this study and the recovery phase was based on steady state and elimination expectations.

Any concerns regarding systemic toxicity of tocilizumab are sufficiently characterized using the IV route of exposure in cynomolgus monkey studies and in studies using MR16-1, a surrogate antibody blocking the mouse IL-6 receptor. Hence, the toxicology bridging program for the SC route focused on the following objectives:

- any local reactions at the site of injection
- the effects on the draining lymphatic system specific to this site of administration
- a comparison of exposure and an assessment of anti-drug antibody formation with this subcutaneous mode of administration versus the intravenous route
- the elimination phase of tocilizumab and the possible reversibility of any observations in a treatment-free phase of the study.

One high dose of 100 mg/kg weekly was administered subcutaneously for this purpose. This dose was also used as a high dose in the IV toxicity program with tocilizumab in the cynomolgus monkey with weekly administrations for six months. The exposure and clearance of tocilizumab did not substantially differ between the two modes of administration. The somewhat higher trough values with SC administration are related to a slower absorption with this route compared to the IV route but otherwise the two administration routes had similar elimination kinetics. No evidence for anti-drug antibodies was found in the animals investigated during and at the end of the treatment free phase of the SC study (n=2/gender). The low levels of tocilizumab towards the end of the treatment-free period together with the high drug tolerance of the anti-drug antibody assay allowed a reliable assessment of recovery animals for presence of antidrug antibodies. Hence, the formation of anti-drug antibodies did not have an impact on the study data. There were no specific reactions to the local SC administration of tocilizumab in the area of administration or in the draining lymphatic system, in this 9- week cynomolgus monkey SC study followed by a 16-week recovery period. Thus, this study bridges the previously characterized acute and chronic dosing animal safety program of tocilizumab using the IV route with the new intended route of a SC administration. No new safety concerns, which can be addressed by animal studies using tocilizumab, have emerged from this change in the route of administration.

Repeat dose toxicity

Study 1029905: a 9-week subcutaneous administration toxicity study in the cynomolgus monkey with a 16-week recovery phase

The objective of the repeat-dose toxicity study was to determine the toxicity of tocilizumab, following weekly SC administrations to cynomolgus monkeys for 9 weeks and to assess the reversibility of the adverse effects during a 16-week recovery phase.

Assessment of toxicity was based on observation of mortality, clinical signs, injection sites, and on measurement of body weight, testicular volume, haematology, clinical chemistry, urine analysis, toxicokinetics, and on terminal procedures (organ weights, macroscopic findings and histopathology) and on bone marrow evaluation.

The dosing design was as follows in the table below.

Table 2. Dose and number of animals in the repeat-dose SC toxicity study with tocilizumab

Group number	Group description	Treatment code	Dose level (mg/kg/week)	Animals/group		Necropsy	
				Male	Female	Main animals	Recovery animals
1	control	G1	0	5	5	3M / 3F	2 M / 2 F
2	dose	G2	100	5	5	3M / 3F	2 M / 2 F

Consistent high systemic exposure to tocilizumab was seen in this study. Mean Cmax concentrations of 3410 and 3140 µg/mL and mean AUC (0-168h) of 507000 and 448000 h.µg/mL were reached in this study in males and females respectively, after the 8th administration on day 50.

Systemic exposure was characterized by a normal inter-individual variability with no relevant gender differences. As expected from the long plasma half-life, exposure to tocilizumab, accumulated during the course of the treatment period with an overall average day 50 to day 1 ratio of 3.16 for AUC(0-168h) and 2.96 for Cmax. Due to the slow plasma clearance of tocilizumab, 3 of the 4 animals were continuously exposed to tocilizumab during the entire recovery period of 16 weeks, with terminal tocilizumab plasma concentrations between 2.9 and 43.1 µg/mL.

Tocilizumab demonstrated no immunogenic potential in this study. Anti-tocilizumab antibodies, measured under non-GLP conditions were not detected in any sample taken during the treatment period or during the recovery period. Accelerated clearance of tocilizumab was neither observed during the treatment phase nor was it observed during the 16-week treatment free period in the 4 recovery sub-group animals.

Exposure to tocilizumab by weekly SC injections did not induce any noteworthy or significant adverse effects. Similar to the repeat-dose studies with IV administration, there was in particular no effect on absolute neutrophil counts or any other hematological dyscrasia observed at any phase of the study. A slight decrease in serum fibrinogen as the only potential treatment-related observation was considered to be of minor physiological relevance. All values were within or close to normal ranges.

The histological examination of organs and tissues, including the axillary lymph node as the injection site draining lymph node, did not reveal any histopathological differences between the control and treated animals.

Local reactions at the injection sites were clinically insignificant and macroscopically comparable between control and dosed animals. The injection site reactions were histologically seen as mild focal and predominantly mononuclear and perivascular inflammatory reactions. Such reactions were found in control and treated animals of both sexes with insignificant differences in the severity between the two groups. Control animals were injected with physiological saline.

Toxicokinetic data

Consistent high systemic exposure to tocilizumab was seen in the 9-week SC toxicity study. Mean Cmax concentrations of 3410 and 3140 µg/mL and mean AUC (0-168h) of 507000 and

448000 h.µg/mL were reached in this study in males and females respectively, after the 8th administration on day 50.

As expected from the long plasma half-life, tocilizumab accumulated over time with an overall average day 50 to day 1 ratio of 3.16 for AUC(0-168h) and 2.96 for Cmax, respectively. Due to the slow plasma clearance of tocilizumab, 3 of the 4 animals were continuously exposed to tocilizumab during the entire recovery period of 16 weeks, with terminal tocilizumab plasma concentrations between 2.9 and 43.1 µg/mL.

Comparison of different administration routes

The dose level of 100 mg/kg chosen for the 9-week SC study was equivalent to that was used previously in a 6-month repeat-dose IV toxicity study. C_{min} exposure at 168 h (7 days) after the eighth weekly dose in the SC study is approximately 40 % higher than the exposure at 168 h (7 days) after the eighth weekly dose in the 6-month IV study.

Table 3. C_{min} exposures attained at 100 mg/kg tocilizumab given intravenously or subcutaneously in monkey toxicity studies

Study	Time point	Dose (mg/kg)	No. of animals	C_{min} (µg/mL)	CV[1] or SD[2]
9-week monkey subcutaneous study (Report No.1029905)	168h after 8th weekly dose (samples taken before 9th weekly dose)	100	5 males 5 females	2580 2230	18% 17.7%
6-month monkey intravenous study (Report No. TOX02-0169)	168h after 8th weekly dose (samples taken before 9th weekly dose)	100	5 males 5 females	1436.2 1594.9	135.8 87.7

[1] CV – coefficient of variation used as the parameter in the SC study;

[2] SD – standard deviation used as the parameter in the IV study.

Local Tolerance

The local tolerance of the SC formulation was assessed as part of the repeat-dose toxicity study in the cynomolgus monkey carried out to bridge the previous IV animal toxicity program to support a SC administration of tocilizumab.

Local reactions at the injection sites were clinically insignificant and macroscopically comparable between control and treated animals. The histological findings were mild focal and predominantly mononuclear and perivascular inflammatory reactions.

The SC formulation of tocilizumab was well tolerated, so this result supports the SC administration of tocilizumab.

2.3.5. Ecotoxicity / environmental risk assessment

No dedicated ecotoxicity/environmental risk assessment was performed for this medicinal product, which is in accordance with the applicable guidance. The active substance is a protein, the use of which is unlikely to result in significant risk to the environment. Therefore, tocilizumab is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Pharmacokinetics

The PK of tocilizumab after SC administration was studied in minipigs and cynomolgus monkeys. The studies focused on the absorption behavior of tocilizumab after SC administration, since the disposition PK of tocilizumab after IV administration has been well characterized previously during the development of tocilizumab for IV administration.

The species selection served the needs of the non-clinical SC development program.

The SC PK data in cynomolgus monkeys supported the planning of the GLP cynomolgus monkey toxicology study.

Minipigs were used to assess the absorption behavior of the high concentration tocilizumab formulation. The minipig was chosen for this study because its skin and the texture of the SC tissue are considered to be similar to those of humans with a fibrous tissue network connecting dermis and deep fascia/muscle. It was not assessed whether the minipig is a responder species to tocilizumab. This was considered irrelevant for the interpretation of the present study, as this focused on the absorption behavior rather than on the general disposition PK of tocilizumab.

Tocilizumab showed high SC bioavailability in both species, i.e. 83.5 and 72.1% in minipigs and cynomolgus monkeys, respectively, estimated by non-compartmental PK analysis. Time to maximum plasma concentration was in the expected range for SC administration of IgGs.

As a result of above studies, the PK of tocilizumab were well characterized after SC administration to animals. The data provided a basis for planning of the SC toxicology study and gave support for the clinical development program of tocilizumab SC.

Toxicology

The evaluation of the potential toxicity of tocilizumab SC extends previous evaluations following an IV administration. The bridging strategy to non-clinical safety data focused on the elements specific to the SC route of administration versus the IV route, i.e. local tolerance at the injection site, effects on the local and draining immune system via assessment of the draining lymph nodes, an assessment of the exposure, and possible formation of anti-drug antibodies in relationship to the IV route at the same dose.

Furthermore, the reversibility of any changes, if observed, was assessed.

One high dose level of 100 mg/kg weekly given subcutaneously was chosen for this purpose. This is the same high dose that was used previously in a 6-month repeat-dose toxicity study using the IV route of administration in cynomolgus monkeys. C_{min} exposure at 168 h (7 days) after the eighth weekly dose in the 9-week cynomolgus monkey SC study (100 mg/kg) is approximately

40% higher than the exposure at 168 h (7 days) after the eighth weekly dose in the 6-month cynomolgus monkey IV study (100 mg/kg).

Hence, taking into account the high subcutaneous bioavailability and the generally slower absorption phase for SC mode of administration compared to the IV route, the somewhat higher C_{min} values for the SC dose in this sub-chronic study are to be expected. Overall, taking variability into account, comparable exposures between the same nominal doses used for IV and SC administration to cynomolgus monkeys have been observed. This justifies a complete bridging of systemic effects observed between these two modes of administration.

As local reactions and effects on the draining lymphatic system specific to the SC administration of tocilizumab were not apparent from the study with SC administration, no additional safety concerns have emerged from this administration mode of tocilizumab. Further, there was no evidence of formation of anti-drug antibodies in the animals of the 16 weeks recovery phase of the study.

In the submitted 9-week subcutaneous administration toxicity study in the cynomolgus monkey with a 16-week recovery phase, only a very rough reference to the IV study was made. Higher trough values for the subcutaneous dose were observed with comparable elimination kinetics in a sub-chronic study. Since a lot of data from clinical studies using the SC administration are available no further animal studies are considered required. Nevertheless the applicant was requested during the evaluation to review the PK data from IV and SC administration in cynomolgus monkeys.

The MAH argued that comparable exposures between the same nominal doses used for IV and SC administration to cynomolgus monkeys in repeat dose toxicity studies cannot be concluded from the measured data alone. This is mainly due to the fact that the chronic IV toxicity study included trough sampling only for toxicokinetic (TK) assessment and hence no full profile is available for this study. Full profiles are available for the (newer) 9 week SC toxicity study. To bridge these two data sets, the MAH simulated the full profile for the 6 month IV toxicity study and compared it with the measured values in the 9 week SC toxicity study. The simulation of IV PK profiles was done using a non-linear PK model. The non-linear PK model was fitted to data from a single dose PK study in cynomolgus monkeys (IV dose levels of 0.5, 5, and 50 mg/kg) and from the 6 months IV toxicity study. Contrary to the 6 months IV toxicity study, in the single dose IV PK study, the full PK profiles were available.

The simulated PK after weekly IV dosing of 100 mg/kg tocilizumab to cynomolgus monkeys over 26 weeks were in agreement with both the observed trough levels and levels in the recovery phase from the 6 months IV toxicity study. This match between PK model-projected plasma levels and measured levels indicates that the PK model captures tocilizumab levels during the 6 months IV toxicity study in an adequate manner. A comparison of the average post-hoc estimated clearance and population clearance indicates a maximal mismatch of 20%.

AUC(0-168h) values are nearly identical after IV and SC administration at 100 mg/kg/week for each dosing route. As expected both Cmax and Cmin data differ between both dosing routes. Cmax levels are slightly lower after SC administration, while Cmin values tended to be higher after SC administration. These differences are consistent with the relatively slow SC absorption of immunoglobulins, as was also evident in the 9 week SC toxicity study. This was indicated by times to maximum plasma concentrations ranging from 24 to 72 h. The justification provided by the MAH was considered acceptable by the CHMP. The data provided indicate a comparable

exposure to tocilizumab in terms of AUC after SC and IV administration at the dose level of 100 mg/kg/week used in both the SC and IV toxicity studies.

2.3.7. Conclusion on the non-clinical aspects

Tocilizumab and its murine surrogate antibody MR16-1 have been extensively characterized in the cynomolgus monkey and in the mouse in pharmacology, PK and toxicity studies using the IV route of administration. These data have been the basis for approval of the IV formulation.

In order to bridge the IV non-clinical study program to the new SC formulation program, a bridging program consisting of a single-dose SC PK study in the minipig and a 9-week SC repeat-dose toxicity study followed by a 16-week recovery phase in the cynomolgus monkey was conducted. These studies were conducted using the same dose strength (180 mg/mL) formulations as in humans containing the same excipients.

The bridging strategy to non-clinical safety data focused on the safety elements specific to the SC route of administration versus the IV route, i.e. local tolerance at the injection site, effects on the local and draining immune system via assessment of the draining lymph nodes and an assessment of the exposure, and possible formation of anti-drug antibodies in relationship to the IV route at the same dose. Furthermore, the reversibility of any changes, if observed, was assessed.

One high dose level of 100 mg/kg weekly given subcutaneously was chosen for this purpose. This was the same high dose used previously in a 6-month repeat-dose toxicity study using the IV route of administration in cynomolgus monkeys. SC weekly dosing of tocilizumab to cynomolgus monkeys at 100 mg/kg for nine weeks was well tolerated, without any relevant tocilizumab-induced finding. The NOAEL was considered to be at the dose of 100 mg/kg. Exposure at 168 h (7 days) after the eighth weekly dose in the 9-week cynomolgus monkey SC study (100 mg/kg) was approximately 40% higher than the exposure at 168 h (7 days) after the eighth weekly dose in the 6 month cynomolgus monkey IV study (100 mg/kg). Hence, taking into account the high subcutaneous bioavailability and the generally slower absorption phase for the subcutaneous route of administration compared to the intravenous route, the slightly higher trough values for the subcutaneous dose are to be expected with comparable elimination kinetics in a sub-chronic study. Overall, taking variability into account, comparable exposures between the same nominal doses used for IV and SC administration to cynomolgus monkeys have been observed. This justifies a complete bridging of systemic effects observed between these two modes of administration.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH. The MAH has provided a statement to the effect that clinical trials conducted outside the Union were carried out in accordance with the ethical standards of Directive 2001/20/EC.

In study WA22762, critical GCP issues were identified in one centre in Lithuania following an unscheduled Health Authority and Ethics Committee inspection. These included: 1) late reporting

of serious adverse events (SAEs) and adverse events of special interest (AESI) for one patient, and 2) instances of non-compliance with the study protocol requirements (failure to use the 24-hour medical line for support, failure to examine the patient and perform necessary tests per protocol requirements, and failure to include an unscheduled visit). Corrective and preventative actions were undertaken, including the appointment of a new site principal investigator. This was considered acceptable by the CHMP.

The clinical development program comprises six Phase I or Phase I/II clinical pharmacology studies (studies WP18097, BP22065, NP25539, BP21894, MRA227JP and NP22623) and two pivotal Phase III studies (studies WA22762 and NA25220) in patients with RA. The Phase III study MRA229JP, conducted exclusively in Japanese patients with RA, is supportive only of the efficacy and safety of TZC SC when given as monotherapy.

Table 4. Tabular overview of clinical studies

Protocol	Study Design	Patient Population	Dose, Route, Regimen	Number of Patients
Pivotal Phase III Studies				
WA22762	Randomized, active-controlled, parallel-group non-inferiority study of TCZ + DMARD 24-week double-blind period followed by 72-week open-label extension	Adult patients with moderate to severe active RA who had an inadequate response to current DMARD therapy that may have included one or more TNF antagonists	First 24 weeks: 162 mg SC TCZ qw (via PFS) + placebo IV q4w or Placebo SC qw (via PFS) + 8 mg/kg IV TCZ q4w Open-label extension: 162 mg SC TCZ qw (via PFS) or 8 mg/kg IV TCZ q4w	N=1262 SC TCZ qw: n=631 IV TCZ q4w: n=631 SC TCZ qw: n=524 IV TCZ q4w: n=377 IV TCZ q4w→SC qw: n=186 SC TCZ qw→IV q4w: n=48
NA25220	Randomized, placebo-controlled, parallel-group study of TCZ + DMARD 24-week, double-blind period followed by 72-week open-label extension	Adult patients with moderate to severe active RA who had an inadequate response to current DMARD therapy that may have included one or more TNF antagonists	First 24 weeks: 162 mg SC TCZ q2w (via PFS) or Placebo SC q2w (via PFS) Open-label extension: 162 mg SC TCZ q2w (PFS) or 162 mg SC TCZ q2w (AI) Escape therapy (from Week 12): 162 mg SC TCZ qw	N=656 SC TCZ q2w PFS: n=438 Pl SC q2w PFS: n=218 TCZ PFS q2w: n=167 TCZ PFS q2w → AI q2w: n=167 Pl PFS q2w→TCZ PFS q2w: n=60 Pl PFS q2w→TCZ AI q2w: n=59 n=162 (including 90 placebo patients before week 24)

Protocol	Study Design	Patient Population	Dose, Route, Regimen	No. of Patients
Supportive Studies				
MRA229JP (Phase III)	Randomized, double-blind, parallel-group comparative study of SC TCZ monotherapy	Adult patients with RA with inadequate response to DMARDs (including TNF antagonists)	162mg SC TCZ q2w + placebo IV q4w vs 8 mg/kg IV TCZ q4w + placebo SC q2w for 24 weeks followed by open-label SC TCZ for up to 84 weeks	N=348
MRA227JP (Phase I/II)	Randomized, open-label, multiple-dose, inter-individual dose escalation study of SC TCZ monotherapy	Adult patients with RA	81 mg SC TCZ q2w for 35 weeks vs 162 mg SC TCZ q2w for 35 weeks vs 162 mg SC TCZ qw for 28 weeks	N=32
NP22623 (Phase Ib)	Open-label, randomized, parallel-group	Adult patients with RA	Part 1: 7.5-25 mg MTX (PO or IV) plus 162 mg SC TCZ qw or q2w for 12 weeks Part 2: (optional post-study phase) 8 mg/kg IV TCZ q4w for up to one year	N=29
WP18097 (Phase I)	Single-dose, single-blind, randomized, double dummy	Adult healthy volunteers	160 mg SC TCZ + IV placebo vs 160 mg IV TCZ + SC placebo	N=20
BP22065 (Phase I)	Single-dose, open-label, single-center, parallel four-group study of PK, PD, safety of SC TCZ vs IV	Adult healthy volunteers	81 or 162 mg SC TCZ, or 81 or 162 mg IV TCZ	N=48
NP25539 (Phase I)	Single-dose, randomized, open-label, parallel 2-group, 2-center relative bioavailability study (PFS vs AI)	Adult healthy volunteers	162 mg SC TCZ via PFS vs 162 mg SC TCZ via AI	N=261
BP21894 (Phase I)	Single-dose, open-label, parallel-group study of PK, PD, safety of SC TCZ	Adult healthy volunteers	single dose of 162, 324, or 648 mg with or without rHuPH20	N=48

AI=autoinjector; DMARDs=disease-modifying anti-rheumatic drugs; IV=intravenous; MTX=methotrexate; PD=pharmacodynamics; PFS=prefilled syringe; PK=pharmacokinetics; PI: Placebo; PO=orally; q2w=every two weeks; q4w=every four weeks; qw=every week; RA=rheumatoid arthritis; rHuPH20=recombinant human hyaluronidase; SC=Subcutaneous; TCZ=Tocilizumab; TNF=tumor necrosis factor

2.4.2. Pharmacokinetics

The clinical pharmacology program was designed to characterize the PK and PD profiles of TCZ following IV and SC administration and to evaluate the immunogenicity of TCZ when administered subcutaneously.

PK characteristics of TCZ SC

The PK of TCZ following multiple IV and SC administration in RA patients was best described by a two-compartment PK model with first-order absorption (following SC administration) and parallel linear and Michaelis-Menten (non-linear) eliminations. The population estimate of bioavailability following SC administration of TCZ was 79.5%, and the absorption half-life was approximately 4 days.

The total clearance of tocilizumab was concentration-dependent and is the sum of linear clearance and non-linear clearance. Exposure following the administration of a single dose of TCZ to healthy volunteers increased in a greater than proportional manner when the SC dose was increased from 81 mg to 162 mg; AUC_{inf} increased 6.4-fold and C_{max} increased 4-fold as the dose was doubled.

For both the 162 mg qw SC and 8 mg/kg q4w IV regimens, nearly complete target saturation was achieved at steady state during the entire dosing interval. The contribution of non-linear CL to total CL was small, and the average steady-state concentration (AUC/dosing interval) was similar for both dose regimens. By virtue of the different routes of administration and the extended absorption following SC dosing, C_{max} was higher following IV dosing, whereas C_{trough} was higher following SC administration.

For the 162 mg q2w SC dosing regimen, the target-mediated elimination pathway was not saturated at steady state, which led to high total clearance and high fluctuation of clearance over

the dosing interval. The nonlinear clearance led to a more than dose-proportional increase in exposure following the 162 mg qw dosing regimen compared with the q2w SC dosing regimen.

After multiple dosing with 162 mg qw and q2w SC, steady-state for AUC and C_{trough} was achieved after the 12th injection for the qw regimen and the 6th injection for the q2w regimen. For 162 mg qw SC, the accumulation ratio was high for AUC, C_{max}, and C_{trough} (6.83, 5.47, and 6.37 respectively).Ffor 162 mg q2w SC, the accumulation was small for AUC and C_{max} (2.67 and 2.12 respectively) but higher for Ctrough (5.6).

Based on parameter estimates from the population PK model, the effective $t_{1/2}$ at steady-state ranged from 12.1 to 13.0 days for 162 mg qw SC and from 1.8 to 4.9 days for 162 mg q2w SC.

Comparison of the pharmacokinetics of PK of TCZ following IV and SC administration

The PK profile of TCZ following SC and IV dosing differed as expected on the basis of the different route of administration and dosing frequency. IV administration of TCZ is infused over a short period of time (i.e. over 1 hour) directly into the venous system, which leads to a high C_{max} followed by the disposition phase. After SC administration, TCZ is absorbed from the subcutaneous tissue into the venous system, resulting in lower bioavailability, lower C_{max}, and longer T_{max} compared with IV administration. At steady-state after multiple dosing, the fluctuation of TCZ concentration for SC regimens is small over the dosing interval and the peak-to-trough TCZ ratios of SC regimens are much lower than those of corresponding IV regimens. IV dosing was also based on body weight–adjusted dosing regimens, whereas SC administration applied flat dosing regimens.

In study WA22762, the average steady-state concentration (C_{mean}) was similar for the 162 mg SC qw and IV 8 mg/kg q4w regimens. However, C_{max} was three times lower for the SC regimen compared with the IV regimen, whereas C_{trough} was 2.4 times higher with the SC regimen (see table below). The exposure level of the IV 8 mg/kg regimen in this study is comparable to historical IV 8 mg/kg data, with the exception of a 2-fold higher C_{trough} value that was highly variable (CV% of approximately 80%).

In study NA25220, the average steady-state concentration (C_{mean}) following TCZ SC q2w administration was 1.9 times lower than historical IV 4 mg/kg q4w data (see table below). The C_{max} values for the SC q2w regimen were 6.8 times lower than the IV 4 mg/kg regimen, but C_{trough} values were four times higher with SC q2w.

In study MRA229JP, the observed C_{trough} was comparable between the SC q2w and 8 mg/kg IV q4w groups from Week 4 onwards (~11–12 µg/mL at Week 24). The observed C_{trough} levels at Week 24 in these Japanese patients following SC q2w dosing were higher than those observed in similarly treated, but comparatively heavier, patients (54 kg vs. 70 kg) from study NA25220 (approximately 11 µg/mL vs. approximately 7 µg/mL).

Table 5. Summary Statistics – Mean (SD) of Predicted Steady-State Exposure Parameters for Different SC and IV Dose Regimens

Dose Regimen	N	AUC_T (µg/mL•h) over 4 weeks	C_{mean} (µg/mL)	C_{max} (µg/mL)	T_{max} (days)	C_{trough} (µg/mL)
WA22762 162 mg SC qw	621	33000 (15320)	49.1 (22.8)	51.3 (23.2)	2.8 (0.2)	45.3 (22.2)
WA22762 8 mg/kg IV q4w	629	39500 (14500)	58.7 (21.6)	152.7 (42.1)	-	18.8 (14.8)
Historical 8 mg/kg IV q4w	[a]	35000 (15500)	52.1 (23.1)	183 (85.6)	-	9.74 (10.5)
NA25220 162 mg SC q2w	509	6920 (5060)	10.3 (7.5)	13.0 (8.3)	4.7 (0.5)	5.9 (6.3)
Historical 4 mg/kg IV q4w	[a]	13000 (5800)	19.3 (8.6)	88.3 (41.4)	-	1.49 (2.13)

[a] simulation performed with 48 weeks of treatment and the two doses tested in Phase III (4 and 8 mg/kg q4w) with 10 studies (replicates) (n=1793 patients per replicate).

Effect of intrinsic factors on the pharmacokinetics of TCZ

The following intrinsic covariates were found to have a statistically significant influence on the PK parameters of TCZ:

- Body weight and HDL cholesterol on CL
- Body weight, total protein, and albumin on central and peripheral volume of distribution
- Normalized creatinine clearance on the maximum elimination rate, and age on the absorption rate constant.

Among all identified covariate relationships, the only strong covariate dependence was the influence of body size on TCZ clearance and volume parameters. No other covariate influence had a clinically relevant effect on TCZ PK.

Body weight was identified as the best predictor among three body size parameters (body weight, body surface area, and body mass index). TCZ clearance and volumes increased with increasing body weight. For IV administration, the effect of body weight was accounted for with a body weight–adjusted dosing regimen (maximum of 800 mg for patients with a body weight of ε100 kg); however, this body-weight adjustment resulted in a higher exposure for patients of high body weight. For SC administration, flat dosing regimens were applied and TCZ exposure decreased with increasing body weight. For the 162 mg SC qw and q2w regimens, steady-state exposure was consistently low for patients of ε100 kg and higher for patients of <60 kg compared with the majority of patients with body weight of 60 to <100 kg. In study WA22762, the steady-state C_{mean} for the 162 mg SC qw regimen was slightly lower for patients with body weight of 60 to 100 kg compared with the 8 mg/kg IV regimen, whereas C_{trough} was 2.3-fold higher. For patients of ε100kg, steady-state C_{mean} and C_{trough} for 162 mg SC qw were 3-fold and 30% lower than those of 8 mg/kg IV, respectively; whereas steady-state C_{mean} and C_{trough} for 162 mg SC qw were 30% and 4.7-fold higher than those of 8 mg/kg IV for patients of <60kg, respectively.

Effect of extrinsic factors on the pharmacokinetics of TCZ

Neither smoking nor the route of administration had a noticeable effect on the TCZ PK parameters and thus were not included in the final PK model. Among three tested injection sites for SC regimens (arm, abdomen, and thigh), the effect of administration into the thigh on bioavailability was greater than those of arm and abdomen. However, the difference was small (11%) and not clinically relevant.

Pharmacokinetics of TCZ following administration with an autoinjector or prefilled syringe

Study NP25539

The relative bioavailability of TCZ in healthy subjects following a single SC dose of 162 mg administered via a disposable AI or PFS was assessed in study NP25539.

The data showed similar PK parameters of TCZ following administration via PFS and AI. Although the bioequivalence criterion was met for the secondary PK parameter, AUC_{inf}, the bioequivalence of the AI compared with the PFS could not be claimed because the upper 90% CIs for geometric mean ratios (GMRs) for the primary PK parameters C_{max} and AUC_{last} (1.27 for both) fell slightly above the prospectively defined upper bound of the bioequivalence range (0.80, 1.25).

Although the primary analyses did not show the two devices to be bioequivalent, the results showed that the time course for TCZ was very similar following administration of TCZ via the PFS and AI. The estimated GMRs (AI compared to PFS) for C_{max}, AUC_{last}, and AUC_{inf} were approximately 1.09, 1.07, and 1.04, respectively. These values, along with the 90% CIs for GMRs, indicated slightly higher average exposure to TCZ following administration via the AI. It was noted, however, that all individual exposure values following AI administration were within the range of values observed with PFS, with the exception of the maximal C_{max} value following AI (33.1 µg/mL, compared with 29.2 µg/mL following PFS). Furthermore, safety results from both treatment groups were comparable.

Study NA25220

Study NA25220 also evaluated administration of TCZ SC via a PFS or AI in the LTE phase (i.e. from Week 24 onwards). Regardless of treatment up to Week 24, C_{trough} levels were comparable between the PFS and AI from Weeks 24 through 36, indicating that both devices delivered a comparable dose of TCZ with each injection up to that point. Compared with the PFS, the Week 40 and Week 48 C_{trough} values for the AI were lower in patients who switched from placebo and higher in those who switched from active TCZ treatment. Interpretation of this finding was limited by the low numbers of evaluable patients compared with available data up to Week 36.

2.4.3. Pharmacodynamics

Mechanism of action

Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit sIL-6R and mIL-6R-mediated signalling. 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 diverse physiological processes such as T-cell

activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis and neoplasia.

Primary pharmacology

In clinical studies with tocilizumab, rapid decreases in CRP, erythrocyte sedimentation rate (ESR) and serum amyloid A (SAA) were observed. Consistent with the effect on acute phase reactants, treatment with tocilizumab was associated with reduction in platelet count within the normal range. Increases in haemoglobin levels were observed, through tocilizumab decreasing the IL-6 driven effects on hepcidin production to increase iron availability. In tocilizumab-treated patients, decreases in the levels of CRP to within normal ranges were seen as early as week 2, with decreases maintained while on treatment.

Effect of TCZ SC on CRP and sIL-6R Levels

The sIL-6R-bound TCZ complex and CRP are two key PD markers for the TCZ mechanism of action. Greater increases in sIL-6R levels suggest more binding of TCZ to sIL-6R. CRP levels are suppressed after blockade of the IL-6 pathway by TCZ.

The profiles of sIL-6R (see figure below) and CRP (see figure below) for RA patients receiving TCZ 162 mg SC qw closely mirrored those receiving TCZ 8 mg/kg IV, with respect to both the rate and magnitude of change. For patients on the TCZ SC qw regimen, there was a substantial increase in sIL-6R levels which were comparable to those achieved with the 8 mg/kg IV q4w regimen (study WA22762). An increase in sIL-6R levels was also observed with the SC q2w regimen, but to a lesser extent than was observed with the SC qw regimen. However, sIL-6R levels were notably higher for TCZ SC q2w compared with historical TCZ 4 mg/kg IV q4w data.

The SC qw regimen provided complete suppression of CRP from Week 2 onwards, with mean CRP levels slightly lower than those achieved with 8 mg/kg IV from Weeks 4 to 24, consistent with higher trough TCZ concentrations in this group (see figure below). The SC q2w regimen also provided suppression of CRP from Week 2 onwards, but CRP levels remained higher than those achieved with SC qw or 8 mg/kg IV, but lower than those seen with historical 4 mg/kg IV data. These results indicate that the SC q2w regimen provides adequate suppression of CRP, but to a lesser extent than with the qw regimen.

Figure 3. Studies WA2762, NA25220, and Historical 4 and 8 mg/kg IV Data: Mean (± SEM) sIL-6R Levels over Time

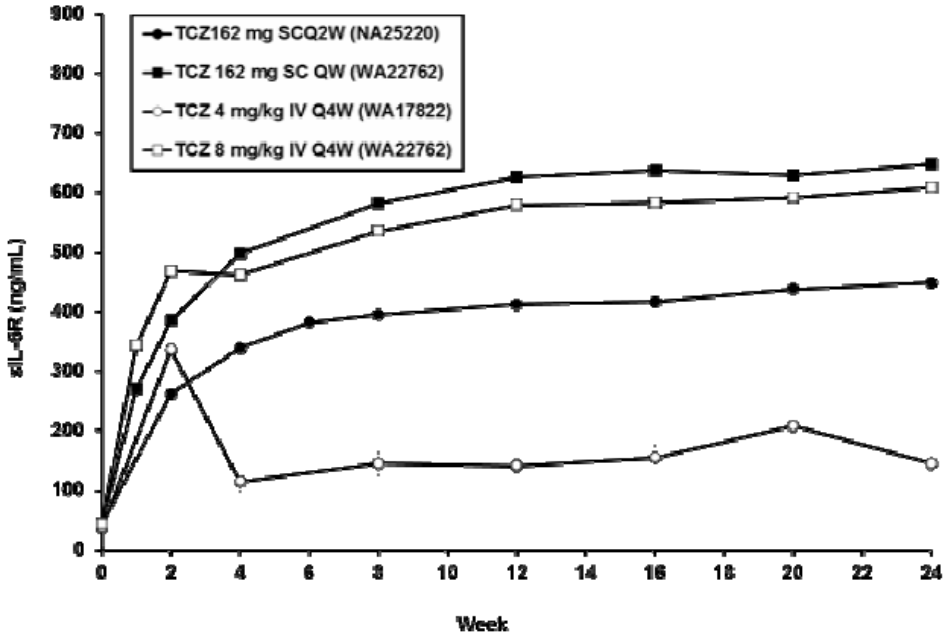
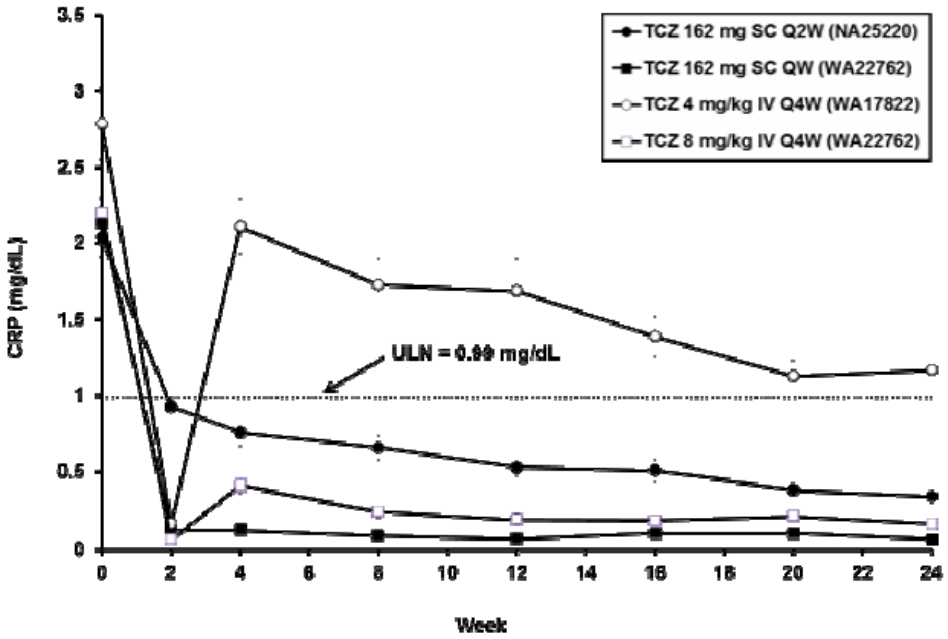


Figure 4. Studies WA22762, NA25220 and Historical 4 and 8 mg/kg IV Data: Mean (± SEM) CRP Levels over time



Pharmacodynamic effects following administration of TCZ with an autoinjector or prefilled syringe in study NA25220

In study NA25220, following re-randomization, and irrespective of treatment up to Week 24, the levels of the various PD markers (sIL-6R, CRP, and ESR) were comparable between the PFS and AI from Weeks 24 through 48. This indicates that the differences in TCZ exposure noted at

Weeks 40 and 48 did not translate into a discernible difference in PD effect. However, the low numbers of patients at Weeks 40 and 48 limits this analysis.

Immunogenicity

The overall immunogenicity rate (defined as the development of a confirmed postbaseline anti-TCZ antibody response) with TCZ SC was low and comparable to that previously reported for TCZ IV.

At Week 24, the proportion of patients who developed anti-TCZ antibodies was 0.8% with the SC qw regimen, 0.8% with the 8 mg/kg IV regimen, and 1.6% with the SC q2w regimen. The proportion of patients who developed neutralizing anti-TCZ antibodies was 0.8% with both the SC qw and 8 mg/kg IV regimens, and 1.4% with the SC q2w regimen. These rates are consistent with those previously reported for TCZ IV (0.6% and 1.0%, respectively).

In the SC qw and q2w studies, data from the LTE phase showed that the proportion of patients who developed anti-TCZ antibodies was consistent with the Week 24 results.

It should be noted with the 162 mg TCZ SC qw regimen used in study WA22762, there was the possibility for interference with the immunogenicity assay (because of high Ctrough TCZ levels); this could potentially have led to an underestimation of the incidence of immunogenicity. As a consequence, the protocol for study WA22762 was amended (amendment C), to allow the collection of an additional serum sample to analyze anti-TCZ antibodies in patients who had prematurely withdrawn from the study, completed the study, or missed TCZ treatment during the study. The data for the 162 mg TCZ SC q2w regimen used in study NA25220 are considered robust, as the TCZ Ctrough levels were lower and were not expected to interfere with the immunogenicity assay.

Effect of anti-TCZ antibodies on the pharmacokinetics of TCZ

Anti-TCZ antibodies had no impact on the PK profiles of TCZ, except for one patient in study NA25220 for whom anti-TCZ antibodies may be related to the change in PK/PD profile for this particular patient.

In the population PK covariate analysis, anti-TCZ antibodies were not identified as a covariate influencing the PK of TCZ. Neutralizing anti-TCZ antibodies did not affect the evaluated exposure−safety and exposure−efficacy relationships.

2.4.4. Discussion on clinical pharmacology

Central to the PK/PD assessment are the two pivotal studies (studies WA22762 and NA25220), which provide data on SC dosing at the fixed dose of 162 mg administered via the prefilled syringe (PFS). The dose regimen proposed by the MAH i.e. q1w was studied in WA22762 only. In study NA25220 a q2w regimen was investigated.

The use of single-use auto-injector (AI) was investigated in study NA25220 open-label extension part (q2w). Additional data on the comparison of PFS versus AI are derived from the single dose study NP25539 in healthy volunteers.

Study WA22762 directly compared the already approved IV posology (8 mg/kg q4w) with the 162 mg SC fixed q1w dose that the MAH applied for as part of this extension application.

Of note, the observed Ctrough level was approximately 18 µg/mL in the IV arm which is nearly twice as high as the historical value (9.74 µg/mL) currently reflected in the SmPC. The MAH shall submit a variation to align section 5.2 of the SmPC for the IV and the SC route of administration with the corrected Ctrough value.

For both the IV and SC route of administrations steady state was reached around week 12. The increase from baseline was in the SC group 5-fold and in the IV group 2-fold. Ctrough level were approximately 40 µg/mL in the SC qw arm and approximately 18 µg/mL in the IV q4w arm. With a KD value of about 1nM (corresponding to 0.15 µg/ml) for the binding of tocilizumab to IL-6R, this corresponds to 267 and 120 times the KD value respectively.

Ctrough is highest at low body weight and decreases with body weight. This is mainly due to the flat dose in contrast to the weight adjusted IV dose, which led to a relative increase in exposure in patients with low body weight. In comparison to IV dosing at comparable body weight, Ctrough after SC administration in the low body weight category is 4-fold higher, in the mid body weight group 2-fold higher and about equal in patients with high body weight. This means that, in patients with a body weight below 100 kg, steady state exposure to tocilizumab is at least twice as high as with the approved IV posology. Even in patients with body weight > 100 kg, the Ctrough at week 24 after q1w SC application is as high as in the IV group corresponding to 120 times the KD value.

The results indicate that for patients >100 kg, the SC qw dose is required to achieve an adequate response to therapy. Study NA25220 demonstrated that as expected lower Ctrough level are observed with the q2w SC dose regimen compared to weekly SC dosing. Steady state is reached later at week 20 with a 3.9-fold increase around week 24. The mean steady-state predose TCZ concentration at Week 24 was approximately 7.4 µg/mL following SC dosing q2w (higher than previously reported in the small sized study NP22623). This corresponds to 49 times KD value for the binding of tocilizumab to IL6-R.

Similar to the q1w SC regimen, increasing exposure with decreasing body weight is also observed with the SC q1w 162 fixed dose. Ctrough increases by 2-fold in patients <60kg compared to patients with average body weight (60-100kg). In contrast to the weekly dose regimen, however, the results indicate a steeper decline of Ctrough in patients >100kg. Given the low number of patients in this body weight category (5.8%), the results may be interpreted with cautions. However, they could also be related to the low serum concentration level, where non-linear clearance manifests, and thus indicate that the q2w SC dose regimen may not be appropriate for obese patients in providing reliably a sufficient Ctrough level for target saturation.

In patients with body weight > 100 kg, the variability of Ctrough was also high, which may further explain why despite a mean Ctrough at wk24 after q2w SC application of 2.0 µg/mL corresponding to 13 times the KD value.

A similar pattern arises with the q2w dosing as seen with q1w or IV dosing with regard to CRP, sIL-6R and ESR response. The drop in CRP below the ULN is observed also at wk2. A level below the ULN is maintained throughout treatment, which is only slightly higher than after IV or 2wq SC administration.

SC bioavailability derived by population PK modelling (79.5%) is higher than previously reported from single dose studies (48.8% and 56.5% for the respective dose range of 162 mg). However, the CHMP is of the view that the most reliable assessment of bioavailability, which is affected by

clearance, is the population PK approach, since it takes the concentration-dependent variability of the clearance into account. When applying compartmental modelling to the single dose study results to address clearance more properly, the bioavailability is estimated as 77% (95% CI: 69% to 85%).

With regard to Ka and elimination half-life, since it could not be determined what definitely caused the discrepancy (of ~2 days) between the two pivotal studies (sampling intervals, differences in elimination between the dose regimens), Tmax instead of absorption half-life has been included in section 5.2 of the SC SmPC and also the bioavailability is expressed in %.

While there was no clear correlation between Ctrough and incidence of AEs there is a reduction of overall AEs and of infection/infestations in the q2w SC dose group compared to the q1w SC dose regimen and IV dosing. This could be related to the reduced incidence of grade 1-2 neutropenia observed with SC q2w dosing. These data suggest a trend towards reduced infection/infestation risk with 162 mg q2w SC dos regimen. There was no apparent association between concentrations of tocilizumab and the occurrence of SAEs. This observation is consistent with the analysis of pooled IV data from four Phase III studies. The incidence of SAE was comparable between the treatment regimens

In general, the model parameters are similar to the estimates obtained earlier with the IV data suggesting that there are no major differences between exposure-response relationships between the IV and SC formulations.

There was a slight covariate effect of the injection site (arm, abdomen, thigh or “unknown”) on bioavailability with an increase in Fsc after injection into the thigh by 11%. There are however differences in the covariate effects. Previously identified influences on the population PK-safety analysis were only partially confirmed (CRP, PCOR, gender, IL-6 level). Age was a newly identified effect on Kout in the current model, resulting in increased neutrophil reduction rate in older patients. Nevertheless, in none of the dose regimens did this result in a clinical meaningful difference.

Overall, the influence of covariates on neutrophil counts over time depicted in simulations was small and clinically not significant.

With regard to immunogenicity, albeit the same DP was used in all three phase III studies (WA22762, NA25220, MRA229JP), there is discrepancy between the studies in the incidence of ADA development after SC (0.8(q1w), 1.6(q2w), 15% (q2w)) as well as after IV dosing (0.8, na., 5% respectively). The MAH clarified that the differences observed were due to different immunogenicity assay strategies, and were not related to assay methodology or other influences. This was considered acceptable by the CHMP.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of TCZ following single multiple SC administrations were studied in six Phase I and II studies in healthy volunteers and RA patients. In addition PK data have been collected from the two pivotal phase III studies (studies NA25220 and WA22762) for population PK modelling.

The PK profile of TCZ following SC and IV administration differed as expected based on the different route of administration and dosing regimen. IV administration of TCZ is infused over a short period of time leading to a high Cmax followed by a disposition phase. After SC

administration, TCZ is absorbed through the lymphatic system into the venous system resulting in a lower bioavailability, lower Cmax and longer Tmax compared with IV administration. The inter-subject variability of plasma levels significantly increased but is more pronounced after single administration than at steady-state. Steady state was reached after 12 weeks for AUC, C_{min}, and C_{max} like with the IV route of administration.

After a single dose, the mean AUCinf for the 162-mg SC dose was approximately 6.4-fold higher than the AUCinf for the 81 mg SC dose while the corresponding ratio for Cmax was 4. The non-linear clearance of TZC was more marked in the SC route than in the IV route.

In conclusion, though the predefined margins for bioequivalence between the AI and PFS were not met for primary PK parameters (AUC_{last} and C_{max}), the bioequivalence criterion was met for the secondary PK parameter (AUC_{inf}). In addition, the mean TCZ concentration–time profiles of PFS and AI were near superimposable, which indicated that the rate and extent of absorption are comparable following AI and PFS administrations. Considering the variability in PK parameters, the fact that the pre-specified margins for the upper 90% CIs for AUC_{last} and C_{max} were exceeded by 2%, this is not considered to be clinically relevant.

In the population PK, among all identified covariate relationships, the only strong covariate was body size impacting on TCZ clearance and volume parameters. No other covariate influence had a clinically relevant effect on TCZ PK. The strong influence of body weight was already observed with the IV route hence the dosing regimen is expressed per body weight. In contrast, the TZC dose is a flat one at 162 mg for the SC route.

The mechanism of action of TCZ administered via the SC route is not expected to differ from TCZ administered via the IV route. Therefore no new PD studies were submitted by the MAH with this extension application which is considered acceptable by the CHMP. The relationships between concentration and effect and also concentration and safety have been satisfactorily discussed by the MAH for the new SC route of administration.

2.5. Clinical efficacy

2.5.1. Dose response studies

No formal exposure-response evaluation has been performed by the MAH to register the SC route of administration. This was considered acceptable by the CHMP.

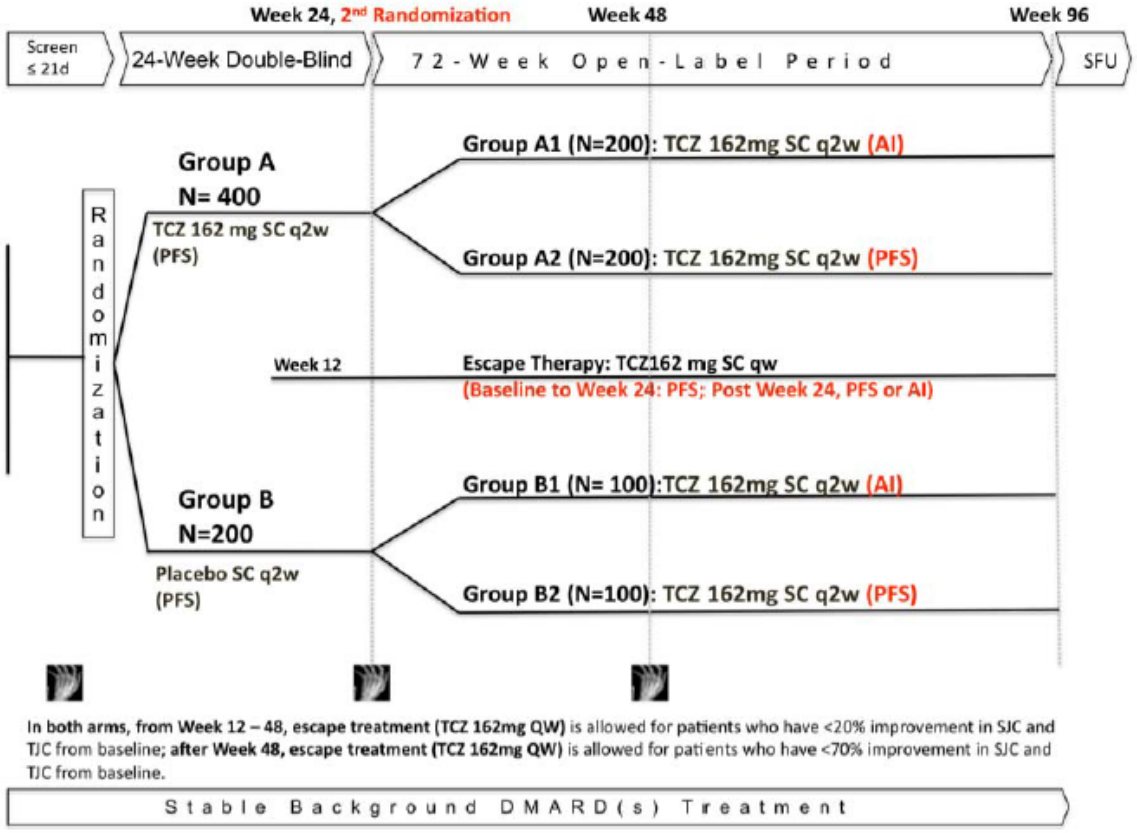
2.5.2. Main studies

Study NA25220

Study NA25220 was a phase III, two arms, two years, randomized, double-blind, placebo controlled, parallel-group, multi-center study in patients with moderate to severe active RA who had an inadequate response to DMARD(s) that may have included one or more anti–TNF-α agents (with the percentage of patients who had failed one or more anti–TNF biologic agents being capped at approximately 20%). The primary endpoint was evaluated at 24 weeks.

The overall study design is shown in the figure below.

Figure 5. Study Design



AI=autoinjector; IV=intravenous; q2w=every 2 weeks; qw=once weekly; PFS=pre-filled syringe; SC=subcutaneous; SJC=swollen joint count; TCZ=tocilizumab; TJC=tender joint count.

Methods

Study participants

The target population for this study was patients with moderate to severe RA who were inadequate responders to DMARDs that may include one or more anti−TNF-α agents.

The percentage of patients who had failed one or more anti-TNF-α agents was capped at approximately 20%.

Inclusion criteria

Patients were eligible for the study if they met all of the following criteria:

1. Able and willing to give written informed consent and comply with the requirements of the study protocol (e.g. willing to take oral folate at a minimum dose of 5 mg/wk if on methotrexate [MTX] treatment.)
2. Age ≥ 18 years

3. RA of ≥ 6 months duration, diagnosed according to the revised 1987 ACR (formerly American Rheumatism Association criteria)
4. Receiving treatment on an outpatient basis
5. SJC ≥ 6 (66 joint count) and TJC ≥ 8 (68 joint count) at screening and baseline
6. Prior to randomization, had discontinued etanercept for ≥ 2 weeks, infliximab, certolizumab, golimumab, abatacept or adalimumab for ≥ 8 weeks, anakinra for ≥ 1 week
7. Had to be on permitted DMARD(s) (see Section 4.4.2 of the protocol), at a stable dose for at least 8 weeks prior to baseline
8. At screening, either C-reactive protein (CRP) ≥ 1 mg/dL (10 mg/L) or erythrocyte sedimentation rate (ESR) ≥ 28 mm/hr
9. At screening, radiographic evidence of at least one joint with a definite erosion attributable to rheumatoid arthritis, as determined by the central reading site. Any joint of the hands, wrist, or feet was considered, with the exception of the DIP joints of the hands
10. Oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and NSAIDs (up to the maximum recommended dose) were permitted if on a stable dose regimen for ≥ 4 weeks prior to baseline
11. Females of childbearing potential and males with female partners of childbearing potential participated in this trial only if using a reliable means of contraception (e.g., physical barrier [patient or partner], contraceptive pill or patch, spermicide and barrier, or intrauterine device)
12. If female of childbearing potential, the patient had to have a negative pregnancy test at screening and baseline visit.

Exclusion criteria

Patients were ineligible for the study if they met any of the following criteria:

General

1. Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery within 6 months following randomization
2. Rheumatic autoimmune disease other than RA, including systemic lupus erythematosus, mixed connective tissue disease, scleroderma, polymyositis, or significant systemic involvement secondary to RA (e.g., vasculitis, pulmonary fibrosis, or Felty syndrome).
3. Secondary Sjögren syndrome with RA was allowed.
4. Functional class IV as defined by the ACR Classification of Functional Status in Rheumatoid Arthritis
5. Diagnosed with JIA or juvenile RA and/or RA before the age of 16

6. History of or current inflammatory joint disease other than RA (e.g., gout, Lyme disease, seronegative spondyloarthropathy, including reactive arthritis, psoriatic arthritis, arthropathy of inflammatory bowel disease).

Excluded Previous or Concomitant Therapy

1. Treatment with any investigational agent within 4 weeks (or 5 half-lives of the investigational drug, whichever was longer) of screening
2. Previous treatment with any cell-depleting therapies, including investigational agents or approved therapies, some examples of which are CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19, and anti-CD20
3. Treatment with IV gamma globulin, plasmapheresis within 6 months of baseline
4. Intra-articular (IA) or parenteral corticosteroids within 4 weeks prior to baseline
5. Immunization with a live/attenuated vaccine within 4 weeks prior to baseline
6. Previous treatment with TCZ (an exception to this criterion could have been granted for single-dose exposure upon application to the Sponsor on a case-by-case basis)
7. Any previous treatment with alkylating agents such as chlorambucil or with total lymphoid irradiation.

Treatments

During the double-blind period, a fixed dose of 162 mg TCZ or matching placebo was administered by SC injection q2w until Week 24. The open-label period began at Week 24, when all patients who did not initiate escape therapy received a fixed dose of 162 mg of SC TCZ q2w.

Escape therapy:

- From Weeks 12 to 48, patients initially randomized to receive either TCZ or placebo could move to escape therapy with TCZ 162 mg SC qw if there was < 20% improvement in SJC and TJC from baseline. Such patients could receive open label treatment until the completion of the trial.
- After Week 48, if a ≥ 70% improvement from baseline in SJC and TJC was not reached, patients could be switched to treatment with TCZ 162 mg SC qw.

If a patient discontinued for any reason from the study prior to Week 12, he or she was not eligible to receive escape therapy. All patients who received escape therapy had radiographic assessments scheduled at Weeks 24 and 48.

Study drug was supplied in a 1-mL ready-to-use, single-use PFS, with a needle safety device, delivering either 162 mg/0.9 mL solution of TCZ or matching placebo and stored at 2ºC−8ºC. One PFS was used for each SC administration that was warmed to room temperature before use.

Objectives

The primary objectives of the study were to assess the following:

- The efficacy of treatment with TCZ 162 mg SC given every other week versus placebo, in combination with DMARDs, at Week 24 using American College of Rheumatology (ACR) 20
- The safety of treatment with TCZ 162 mg SC given every other week versus placebo, in combination with DMARDs, with regard to adverse events and laboratory assessments.

The secondary objectives of the study were to assess the following:

- Prevention of progression of structural joint damage at Week 24 and Week 48 (addressed in the Open-label Extension Report 105275)
- Improvement of physical function
- Long-term safety and efficacy (addressed in the Open-label Extension Report 105275)
- Pharmacokinetics and pharmacodynamics of TCZ following SC administration
- Immunogenicity of TCZ following SC administration
- Specimens stored in the Roche Clinical Repository (RCR) are to be used to:
    - Study the association of biomarkers with efficacy and/or adverse events associated with medicinal products; and/ or
    - Increase our knowledge and understanding of disease biology; and/or
    - Develop biomarker or diagnostic assays; establish the performance characteristics of these assays TCZ pharmacokinetic (PK)−safety and PK−efficacy relationships were also explored.

Outcome / endpoints

Primary endpoint

The primary endpoint was identified as the percentage of patients with an ACR20 response at Week 24. The primary comparison was between the group of patients who received TCZ 162 mg SC q2w (Group A) and the group who received placebo SC q2w (Group B).

Main efficacy secondary endpoints

The main secondary efficacy endpoints were the following:

1. Proportion of patients with ACR50 response at Week 24
2. Proportion of patients with ACR70 response at Week 24
3. Change in Disease Activity Score 28 (DAS28) from baseline at Week 24
4. Proportion of patients with DAS28 < 2.6 (DAS28 remission) at Week 24

Sample size

The primary analysis was based on the intent-to-treat (ITT) population. Based on previous ACR20 response rates of patients in the placebo and 4-mg/kg groups in the Phase III TCZ IV studies, OPTION (study WA17822), LITHE (study WA17823), and RADIATE (study WA18062), the expected ACR20 response was 23% in the placebo arm and 46% in patients treated with IV TCZ. These assumptions were used to generate the sample size for this trial. A sample size of 600 patients, randomized at a ratio 2:1 (400:200 patients), would ensure at least 90% power to detect this difference with a significance level of 5%.

The analysis of the progression of structural damage was a critical secondary objective.

Assuming that patients treated with TCZ 162 mg SC q2w showed the same response as patients treated with TCZ 4 mg/kg IV in the LITHE study, and the response of the placebo SC arm was identical to the placebo IV arm in the LITHE study, then 600 patients randomized in a 2:1 ratio provided a power > 90% to detect a treatment difference between both arms.

The power calculation of the radiographic analysis was based on simulations of the Week 24 LITHE data followed by analysis with the van Elteren test. This non-parametric statistical test provides a p-value but not an estimate of the treatment effect.

Randomisation

Eligible patients who fulfilled the inclusion and exclusion criteria were randomly assigned at a ratio of 2:1 to either 162 mg SC q2w or placebo at baseline for the double-blind period and subsequently re−randomized at a 1:1 ratio within each treatment group at Week 24 for the open-label period, utilizing an interactive voice response system (IVRS).

The two sets of randomization numbers were generated by Perceptive Informatics, Inc. and were linked to a unique patient identification number through the IVRS. At baseline, randomization was by minimization, stratified by geographic region (Europe, North America, South America, and rest of world) and body weight category (< 60 kg, 60 to < 100 kg, and ≥ 100 kg). The minimization procedure was implemented by Perceptive Informatics. This involved maintaining an updated record of treatment assignments by stratification factors and was used to determine the treatment of choice for a newly recruited patient. The minimization procedure was based on an 80:20 random element (i.e. a patient was assigned to the treatment of choice with a probability of 0.8).Randomization at Week 24 was implemented by permuted block.

Blinding (masking)

This study was blinded during the first 24 weeks and a “dual assessor” approach was used to evaluate first efficacy and then safety data to prevent potential unblinding because of observed efficacy or laboratory changes. The efficacy assessor was a rheumatologist or other skilled arthritis assessor but could not be the Principal Investigator. The efficacy assessor was responsible for assessing the joint counts and the Physician’s Global Assessment of Disease visual analog scale (VAS) components but was not allowed access to other patient data. The safety assessor was a rheumatologist or medically qualified physician with access to both the safety and efficacy data and was permitted to be the Principal Investigator.

Assessments completed by the patient and by the efficacy assessor were to be made before the assessments by the safety assessor.

The study centers, Roche monitors, project statisticians, and the project team were blinded to specific laboratory data (i.e., TCZ, IL-6, sIL-6R, and CRP) before the primary analysis.

Blinding of the treatment received was maintained for patients and site personnel until all patients completed Week 48 and all data for all patients up to that time point had been collected and reported. Unblinding by the Sponsor occurred at the time of the Week 24 primary analysis.

Per regulatory requirements, study treatment was to be unblinded for all unexpected serious adverse events that were considered by the investigator to be related to study drug. There were no cases of treatment code breaks during the double-blind period of the study.

After the Week 48 data analysis and following specific instructions from the Sponsor, a single assessor approach (using a qualified physician to perform all efficacy and safety assessments) could be used for subsequent visits during the open-label part of the study.

Statistical methods

The primary analysis tested the null hypothesis that the percentage of patients with an ACR20 response at Week 24 in Group A (TCZ 162 mg SC q2w) was the same as the percentage of patients with an ACR20 response at Week 24 in Group B (placebo SC q2w). The null hypothesis was rejected if the percentage of ACR20 responders in Group A differed from Group B.

To test whether treatment assignment by minimization did not affect the outcome of the study, the primary and secondary analyses were re-analyzed by the re-randomization or permutation

Results

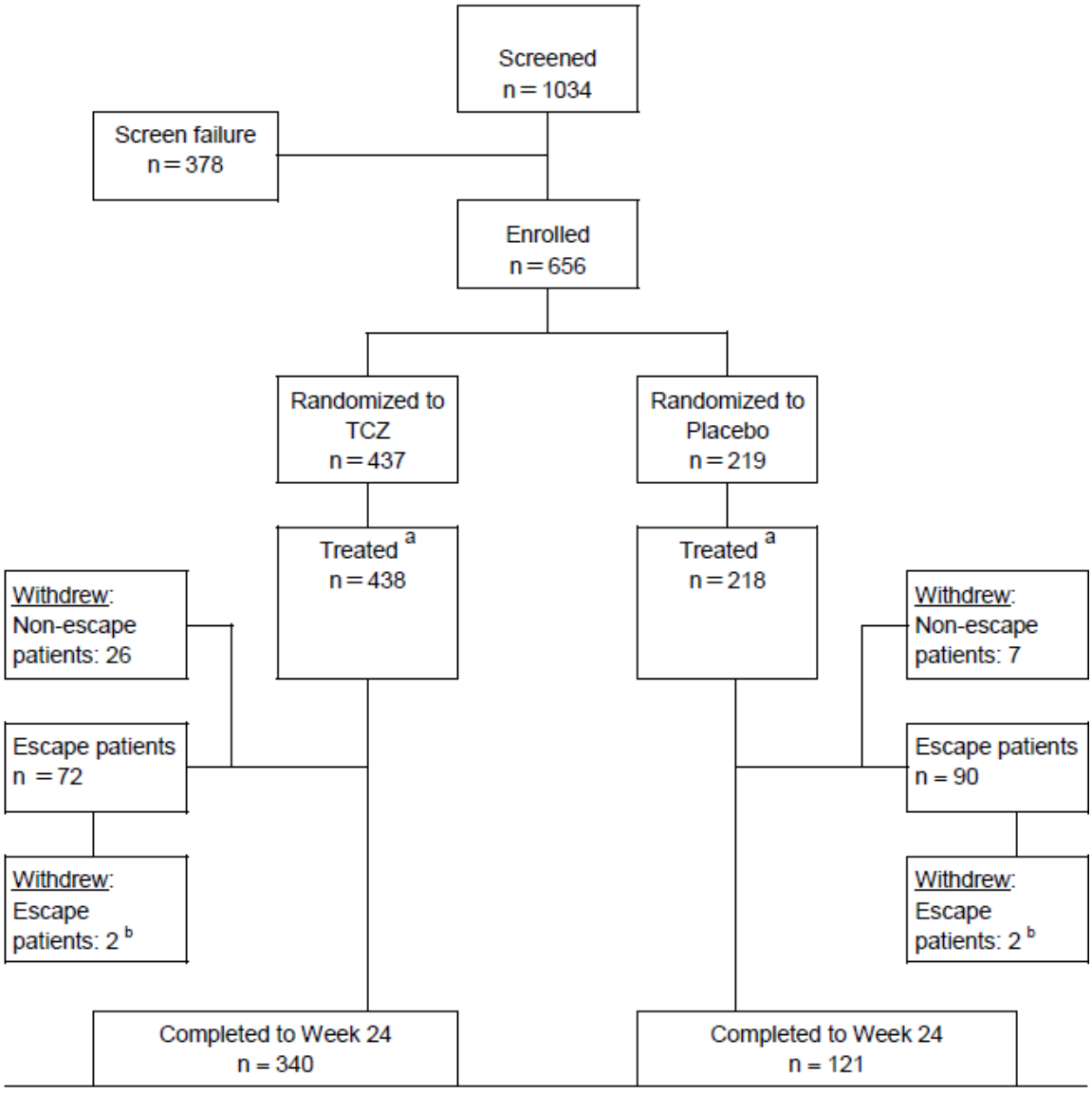
Participants flow

Of the 1034 patients screened, a total of 656 patients were randomized into the study. The main reason for screen failure was a lack of radiographic evidence of at least one joint with a definite erosion attributable to RA, as determined by the central reading site.

Of the 656 patients enrolled into the study, 437 patients were randomized to receive TCZ and 219 patients were randomized to receive placebo (see figure below).

All patients received at least one dose of study drug. However, 1 patient inadvertently received the wrong treatment. Patient 12001 received TCZ instead of placebo at baseline.

Figure 6. Overview of Patient Disposition



Note: Percentages are based on the number of randomized patients.

[a] All patients received at least one dose of study drug; however, 1 patient (12001) inadvertently received the wrong treatment. Patient 12001 received TCZ instead of placebo at baseline.

[b] Patients who withdrew after Escape

Source: Table 5, Table 6, Table 7, page 276.

Recruitment

Patients were enrolled at 124 active centres in 21 countries including South America, Europe, and North America.

The first patient was screened on 23 February 2011, and the first patient was randomized on 14 March 2011. The last patient was randomized on 28 November 2011, and the clinical cut-off for the 24-week analysis was 28 May 2012.

Conduct of the study

There were two amendments of the protocol.

Amendment B (24 February 2011):

- A TCZ AI was made available for use in the open−label portion of the study.
- Additional details for the analyses of the radiographic endpoint were included.
- The required tests for the liver profile were clarified, liver profile testing was added at Week 36, and vital sign measurements were added at Weeks 10 and 36.
- The adjustment of the random element used to ensure a baseline randomization ratio of 2:1 was clarified.
- To prevent any potential unblinding, a dual assessor approach was used until the completion of Week 48 data analysis.
- The reporting period for AESI, including nonserious AESI to Roche Drug Safety was clarified (i.e. within 24 hours of learning of the event).
- The requirement for an X−ray image at the initiation of escape therapy was clarified.

Amendment C (26 April 2011)

- An optional ease-of-use substudy was added to the open-label period for the sites in Canada and the United States in order to evaluate the ability of patients, caregivers and healthcare professionals to handle and use the PFS or AI.

These two amendments of the protocol did not impact on the safety and efficacy analysis of the study.

The change in the planed analysis (sensitivity analyses) was implemented prior to the unblinding, and had no impact on the efficacy and safety analysis.

Baseline data

Demographic data

The study population comprised predominantly Caucasian (72.1%) females (84.7%), with a mean age of approximately 52 years (range 18−82 years, see table below). The two treatment arms were balanced with respect to all baseline demographic characteristics recorded. The majority of the patients (67%) weighed between 60 and < 100 kg, with 27% weighing < 60 kg and 5.6% weighing ≥ 100 kg. The maximum weight was capped at 150 kg (per the exclusion criterion).

The baseline demographic characteristics of patients in the ITT population were consistent with those observed in the safety population. A listing of baseline demographic characteristics for all patients randomized is provided.

Table 6. General Demographic Variables (Safety Population)

	TCZ PFS q2w N = 437	Placebo PFS q2w N = 218
Sex		
MALE	62 (14.2%)	38 (17.4%)
FEMALE	375 (85.8%)	180 (82.6%)
n	437	218
Race		
AMERICAN INDIAN / ALASKA NATIVE, WHITE	-	1 (0.5%)
AMERICAN INDIAN / ALASKA NATIVE	3 (0.7%)	1 (0.5%)
WHITE	321 (73.5%)	151 (69.3%)
AMERICAN INDIAN / ALASKA NATIVE, BLACK /	1 (0.2%)	-
ASIAN-INDIAN SUBCONTINENT	1 (0.2%)	-
ASIAN-OTHER THAN INDIAN SUBCONTINENT	19 (4.3%)	13 (6.0%)
ASIAN-OTHER THAN INDIAN SUBCONTINENT,	1 (0.2%)	-
BLACK / AFRICAN AMERICAN	22 (5.0%)	13 (6.0%)
OTHER RACE	66 (15.1%)	38 (17.4%)
WHITE, OTHER RACE	3 (0.7%)	1 (0.5%)
n	437	218
Age in years		
Mean	52.1	52.0
SD	11.49	11.67
SEM	0.55	0.79
Median	53.0	54.0
Min-Max	18 - 82	18 - 76
n	437	218
Weight in kg		
Mean	70.33	70.04
SD	16.623	15.800
SEM	0.795	1.070
Median	67.00	68.80
Min-Max	37.1 - 130.9	40.0 - 129.0
n	437	218
Height in cm		
Mean	161.116	161.740
SD	8.9256	9.4313
SEM	0.4284	0.6388
Median	160.000	161.000
Min-Max	132.00 - 200.00	124.00 - 193.00
n	434	218
Baseline Weight Category (kg)		
<60	119 (27.2%)	58 (26.6%)
60-100	292 (66.8%)	149 (68.3%)
>=100	26 (5.9%)	11 (5.0%)
n	437	218

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
For reproductive status, NA stands for Not Applicable and Con. Prot. stands for Contraceptive Protection.
Escape patients are included.
Output : $MARSOUT/cr11935a/r25220a/stdm11_gen.dat
DM11 20JUL2012:16:14:49 (1 of 2)

	TCZ PFS q2w N = 437	Placebo PFS q2w N = 218
Ethnicity		
HISPANIC	165 (37.8%)	90 (41.3%)
NON-HISPANIC	272 (62.2%)	128 (58.7%)
n	437	218
Geographic Region		
Europe	101 (23.1%)	49 (22.5%)
North America	88 (20.1%)	45 (20.6%)
South America	177 (40.5%)	88 (40.4%)
Rest of World	71 (16.2%)	36 (16.5%)
n	437	218
Female Reproductive status		
CHILDBEARING POTENTIAL WITH CONTRACEPTIVE PROTECTION	98 (26.1%)	42 (23.3%)
CHILDBEARING POTENTIAL WITHOUT CONTRACEPTIVE PROTECTION	1 (0.3%)	2 (1.1%)
NON CHILDBEARING POTENTIAL	13 (3.5%)	8 (4.4%)
POSTMENOPAUSAL	190 (50.7%)	98 (54.4%)
PRE-MENARCHAL	-	1 (0.6%)
SURGICALLY STERILIZED	73 (19.5%)	29 (16.1%)
n	375	180
Smoking status		
CURRENT	71 (16.2%)	32 (14.7%)
NEVER	286 (65.4%)	149 (68.3%)
PREVIOUS	80 (18.3%)	37 (17.0%)
n	437	218
Family history of Chronic Heart Disease		
YES	52 (12.0%)	26 (11.9%)
NO	351 (80.9%)	177 (81.2%)
UNK	31 (7.1%)	15 (6.9%)
n	434	218

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
For reproductive status, NA stands for Not Applicable and Con. Prot. stands for Contraceptive Protection.
Escape patients are included.
Output : $MARSOUT/cr11935a/r25220a/stdm11_gen.dat
DM11 20JUL2012:16:14:49 (2 of 2)

Baseline RA disease characteristics

Overall, the treatment arms were balanced with respect to RA disease characteristics.

The duration of RA was 11.1 years in both arms (see table below).

As part of the study eligibility criteria, patients were required to take DMARDs (only those permitted) at a stable dose for at least 8 weeks prior to baseline. Oral NSAIDs were permitted if a patient was on a stable dose regimen for ≥ 4 weeks prior to baseline.

Patients enrolled in the study had been on a mean of 1.3 and 1.4 previous DMARDs in the TCZ and placebo arms, respectively, prior to baseline. Patients had been on a mean of 1.1 and 1.2 previous NSAIDs, respectively. Approximately 20% of the patients in each treatment arm had failed prior anti-TNF treatment.

Approximately 65% of patients in the TCZ arm and 56% of patients in the placebo arm were treated with oral corticosteroids at baseline, for which the dose was similar (median dose of 5 mg/day in both arms). The majority of patients tested positive for rheumatoid factor (81% in the

TCZ arm and 82% in the placebo arm) and were anti–cyclic citrullinated peptide positive at baseline (84% TCZ arm vs. 83% placebo arm).

The percentage of the patients who failed prior anti-TNF treatment was 20.4% and 21.6% in the TCZ and placebo arms, respectively, which was reflective of the capping rule (the protocol stipulated the percentage of patients who failed one or more anti–TNFs should be approximately 20%). The baseline RA disease characteristics of the ITT population were consistent with those observed in the safety population.

Table 7. RA Disease Characteristics at Baseline (Safety Population)

	TCZ PFS q2w N = 437	Placebo PFS q2w N = 218
Duration of RA (years)		
Mean	11.1	11.1
SD	8.23	8.41
SEM	0.39	0.57
Median	9.3	9.7
Min-Max	1 - 43	1 - 49
n	437	217citru
No. of previous DMARDS		
Mean	1.3	1.4
SD	0.70	0.76
SEM	0.03	0.05
Median	1.0	1.0
Min-Max	1 - 6	0 - 4
n	437	218
Baseline Oral Corticosteroid Use (y/n)		
NO	153 (35.0%)	95 (43.6%)
YES	284 (65.0%)	123 (56.4%)
n	437	218
Baseline Oral Corticosteroid Dose (mg/day)		
Mean	6.50	6.31
SD	2.879	3.835
SEM	0.171	0.347
Median	5.00	5.00
Min-Max	0.0 - 25.0	0.0 - 40.0
n	282	122
Baseline RF Positivity		
NO	83 (19.2%)	40 (18.4%)
YES	349 (80.8%)	177 (81.6%)
n	432	217
Baseline Anti-CCP Positivity		
NO	69 (16.1%)	37 (17.1%)
YES	360 (83.9%)	179 (82.9%)
n	429	216
IVRS Failed Prior anti-TNF Treatment?		
NO	348 (79.6%)	171 (78.4%)
YES	89 (20.4%)	47 (21.6%)
n	437	218

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
Escape patients are included.
Output : $MARSOUT/cr11935a/r25220a/stdm11_ra.dat
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Numbers analysed

All patients who received at least one dose of study drug were included in the ITT population and safety population.

Table 8. Analysis population

Population	TCZ PFS q2w	Placebo PFS q2w
Randomized	437	219
Randomized treatment received at baseline [a]	438	218
ITT [b]	437	219
Completed [c]	410	209
Completer [d]	347	124
Safety [e]	437 [f]	218

ITT = intent-to-treat; PFS = pre-filled syringe; q2w = every 2 weeks; TCZ = tocilizumab.

[a] Patient 12001 inadvertently received TCZ instead of placebo as the first study drug dose; the patient had been randomized to receive placebo.

[b] For analysis purposes, patients were assigned to the ITT population as randomized, irrespective of the treatment actually received (escape patients are included).

[c] Total completing treatment is up to Week 24 (escape patients are excluded).

[d] Completer population includes patients with a valid efficacy assessment at Week 24 (escape patients are excluded)..

[e] For analysis purposes, patients were assigned to the safety population according to the treatment they received at baseline.

[f] Patient 58201 had no post-baseline safety data and, consequently, was excluded from the safety population (escape patients are included).

Outcomes and estimation

Table 9. Primary efficacy endpoint: ACR 20 response rate at Week 24 and secondary endpoints presented as per hierarchical testing

	TCZ 162mg SC q2w + DMARD (n=437)	Placebo + DMARD (n=219)	
Primary Endpoint: Percentage of ACR20 Responders at Week 24			
Percentage of ACR20 responders	n=437 60.9%	n=219 31.5%	
Weighted difference (95% CI)	29.5 (22.0, 37.0)		p < 0.0001
Sensitivity analysis: completer population	n=347	n=124	
Percentage of ACR20 Responders	76.7%	55.6%	
Weighted difference (95% CI)	22.4 (12.8, 31.9)		p < 0.0001
Secondary Endpoints at Week 24			
Secondary endpoints presented as per hierarchical testing			
1. ACR50 responders	n=437 39.8%	n=219 12.3%	
Weighted difference (95% CI)	27.9 (21.5, 34.4)		p < 0.0001
2. ACR70 responders	n=437 19.7%	n=219 5.0%	
Weighted difference (95% CI)	14.8 (9.8, 19.9)		p < 0.0001
3. Change in DAS28, mean	n=344 −3.1	n=123 −1.7	
Weighted difference (95% CI)	−1.4 (−1.7, −14.1)		p < 0.0001
4. DAS28 <2.6 (DAS28 remission), %	n=347 32%	n=124 4%	
Weighted difference (95% CI)	28.6 (22.0, 35.2)		p < 0.0001
5. Change in TJC, mean	n=432 −14.2	n=219 −7.8	
Weighted difference (95% CI)	−6.4 (−8.5, −4.3)		p <0.0001

	TCZ 162mg SC q2w + DMARD (n=437)	Placebo + DMARD (n=219)	
Secondary Endpoints at Week 24 (cont.)			
6. Change in SJC, mean	n=432 −9.3	n=219 −5.6	
Weighted difference (95% CI)	−3.7 (−5.1, −2.3)		p < 0.0001
7. Change in CRP, mean	n=345 −1.6	n=124 −0.4	
Weighted difference (95% CI)	−1.2 (−1.4, −1.0)		p < 0.0001
8. Change in ESR, mean	n=347 −35.6	n=124 −12.0	
Weighted difference (95% CI)	−23.6 (−26.7, −20.5)		p < 0.0001
9. DAS LDA (≤3.2)	n=347, 45.2%	n=124, 15.3%	
Weighted difference (95% CI)	30.3 (22.0, 38.6)		p < 0.0001
10. DAS Categorical Responders (good), %	n=374 41.7%	n=138 13.8%	p < 0.0001
11. Change in van der Heijde modified Sharp radiographic score to Week 24			
mTSS at Week 24 (Campaign 1)			
Mean change mTSS (SD) linear extrapolation method	n= 391 0.62 (2.692)	n=186 1.23 (2.816)	p=0.0149 [a] p=0.0145 [b]
12. Median time to onset of ACR20	57 Days	86 Days	p<0.0001
13. Change in hemoglobin, mean	n = 344 8.7	n = 123 0.2	
Difference (95% CI)	8.5 (6.6, 10.3)		p<0.0001
14. Change in Patient's Global VAS, mean	n=346 −29.3	n=123 −19.8	
Weighted difference (95% CI)	−9.4 (−14.0, −4.9)		p<0.0001
15. Mean change in Pain VAS	n=346 −24.9	n=123 −13.6	
Weighted difference (95% CI)	−11.2 (−15.6, −6.9)		p<0.0001
16. Change in Physician's Global VAS, mean	n=348 −34.3	n=124 −28.7	
Weighted difference (95% CI)	−5.6 (−9.4, −1.7)		p=0.0048
17. Change in HAQ-DI, mean	n=348 −0.4	n=124 −0.3	
Weighted difference (95% CI)	−0.2 (−0.3, 0.0)		p=0.0054

	TCZ 162mg SC q2w + DMARD (n=437)	Placebo + DMARD (n=219)	
Secondary Endpoints at Week 24 (cont.)			
18. Decrease ≥0.3 in HAQ	n = 348 58.0%	n = 124 46.8%	
Weighted difference (95% CI)	12.1 (2.2, 22.0)		p = 0.0170
19. Change in SF-36 (Physical), mean	n=347 5.3	n=123 2.9	
Difference (95% CI)	2.4 (1.0, 3.8)		p=0.0006
20. Change in SF-36 (Mental), mean	n=347 6.5	n=123 3.8	
Difference (95% CI)	2.7 (0.7, 4.6)		p=0.0068
21. Median time to onset of ACR50	115 days	Not computable [c]	p<0.0001
22. Median time to onset of ACR70	174 days		p<0.0001

ACR = American College of Rheumatology; CI = confidence interval; CRP = C-reactive protein; DAS = disease activity score; DMARD = disease-modifying anti-rheumatic drug; HAQ-DI = Health Assessment Questionnaire Disability Index; ITT = intent-to=treat; IV = intravenous; LOCF = last observation carried forward; mTSS = modification of the Sharp score; SC = subcutaneous; SF-36 = Short Form 36; VAS = visual analog scale.

Van der Heijde modified total sharp radiographic score (mTSS)

The mean change from baseline in the van der Heijde modified total Sharp radiographic score at Week 24 was less for TCZ (0.62 ± 2.692) than with placebo (1.23 ± 2.816), suggesting there was less joint damage following TCZ treatment.

Table 10. Change from baseline in TSS at week 24 linear extrapolation method using van Elteren analysis and ANOVA analysis (ITT population)

	TCZ PFS q2w (N = 437)	Placebo PFS q2w (N = 219)
Modified Total Score		
Baseline		
N	391	186
MEAN	59.01	60.38
STD	65.897	66.466
MEDIAN	33.00	32.75
MIN-MAX	0.0-355.0	0.0-337.5
Week 24		
N	391	186
MEAN	59.63	61.61
STD	66.329	66.580
MEDIAN	35.00	35.00
MIN-MAX	0.0-358.0	0.0-338.5
Change from Baseline at Week 24		
N	391	186
MEAN	0.62	1.23
STD	2.692	2.816
MEDIAN	0.00	0.00
MIN-MAX	-11.0-19.7	-6.0-12.4
p-value (van Elteran Analysis)	0.0149	
ANOVA	0.0145	

Campaign 1 consists of the evaluations of Baseline, Week 24, early withdrawal or escape therapy readings taken up to the Week 24 visit.
Analysis carried out by van Elteren's test and ANOVA separately stratified by region and weight category.
Missing Week 24 data is imputed using linear extrapolation.
Patients will be extrapolated if they have a baseline assessment and at least one post baseline assessment. Escape and withdrawal patients are excluded from the time they withdraw or escape (regardless of assigned visit label).
A 30 day window is allowed for, any assessment greater than this 30 day window will not be included.

Program : $PROD/cs11935c/c25220a/etscble52.sas / Output :
$PROD/cr11935a/r25220a/reports/etscble52_scn1_1.out
07AUG2012 16:56 Page 1 of 1

Escape data

During the 24-week double-blind treatment period, patients who experienced less than a 20% improvement in their SJC and TJC from baseline could receive open-label escape therapy from Week 12 with TCZ 162 mg SC qw using the PFS, if requested and deemed necessary by the investigator. A total of 90 (41.1%) patients in the placebo arm and 72 (16.4%) in the TCZ arm received escape therapy.

Table 11. ACR response following escape therapy

	TCZ 162 mg SC q2w → TCZ 162 mg SC qw + DMARD N=72	Placebo SC q2w → TCZ 162 mg SC qw + DMARD N=90
12 weeks after escape	n=67	n=79
ACR20	39 (58.2%)	57 (72.2%)
ACR50	12 (17.9%)	30 (38.0%)
ACR70	4 (6.0%)	12 (15.2%)
24 weeks after escape	n=31	n=32
ACR20	18 (58.1%)	25 (78.1%)
ACR50	9 (29.0%)	14 (43.8%)
ACR70	4 (12.9%)	8 (25.0%)

ACR = American College of Rheumatology; TCZ = tocilizumab; SC = subcutaneous; DMARD = disease modifying anti-rheumatic drug; qw = once weekly.

Source: NA25220-LTE:eteprsp01_pstesc_acrsp_wk24_10

Ancillary analyses

Subgroup analysis

Table 12. ACR 20, ACR 50 and ACR 70 response rates at week 24 by body weight (ITT population)

ACR Response by Body Weight	No. of Patients (%)	
	TCZ PFS q2w (n=437) Number of Responders/n (%)	Placebo PFS q2w (n=219) Number of Responders/n (%)
ACR20 response		
All patients	266/437 (60.9)	69/219 (31.5)
<60 kg	75/119 (63.0)	17/58 (29.3)
60 to < 100 kg	181/292 (62.0)	49/150 (32.7)
≥100 kg	10/26 (38.5)	3/11 (27.3)
ACR50 response		
All patients	174/437 (39.8)	27/219 (12.3)
<60 kg	52/119 (43.7)	6/58 (10.3)
60 to < 100 kg	119/292 (40.8)	19/150 (12.7)
≥100 kg	3/26 (11.5)	2/11 (18.2)
ACR70 response		
All patients	86/437 (19.7)	11/219 (5.0)
<60 kg	28/119 (23.5)	2/58 (3.4)
60 to < 100 kg	57/292 (19.5)	8/150 (5.3)
≥100 kg	1/26 (3.8)	1/11 (9.1)

ACR=American College of Rheumatology; ITT=intent to treat; PFS = pre-filled syringe; q2w=every 2 weeks; TCZ=tocilizumab.

Region

Table 13. ACR 20, ACR 50 and ACR 70 response rates at week 24 by region (ITT population)

ACR Response by Region	Number of Patients (%)	
	TCZ PFS q2w (n=437) Number of Responders/n (%)	Placebo PFS q2w (n=219) Number of Responders/n (%)
ACR20 response		
All patients	266/437 (60.9)	69/219 (31.5)
Europe	71/101 (70.3)	21/49 (42.9)
Rest of world	46/71 (64.8)	9/36 (25.0)
North America	34/89 (38.2)	7/45 (15.6)
South America	115/176 (65.3)	32/89 (36.0)
ACR50 response		
All patients	174/437 (39.8)	27/219 (12.3)
Europe	45/101 (44.6)	7/49 (14.3)
Rest of world	28/71 (39.4)	1/36 (2.8)
North America	21/89 (23.6)	4/45 (8.9)
South America	80/176 (45.5)	15/89 (16.9)
ACR70 response		
All patients	86/437 (19.7)	11/219 (5.0)
Europe	21/101 (20.8)	2/49 (4.1)
Rest of world	15/71 (21.1)	1/36 (2.8)
North America	11/89 (12.4)	1/45 (2.2)
South America	39/176 (22.2)	7/89 (7.9)

ACR=American College of Rheumatology; ITT=intent to treat; PFS = pre-filled syringe; q2w=every 2 weeks; TCZ=tocilizumab.

Study NA25220 LTE

Results

Participant flow

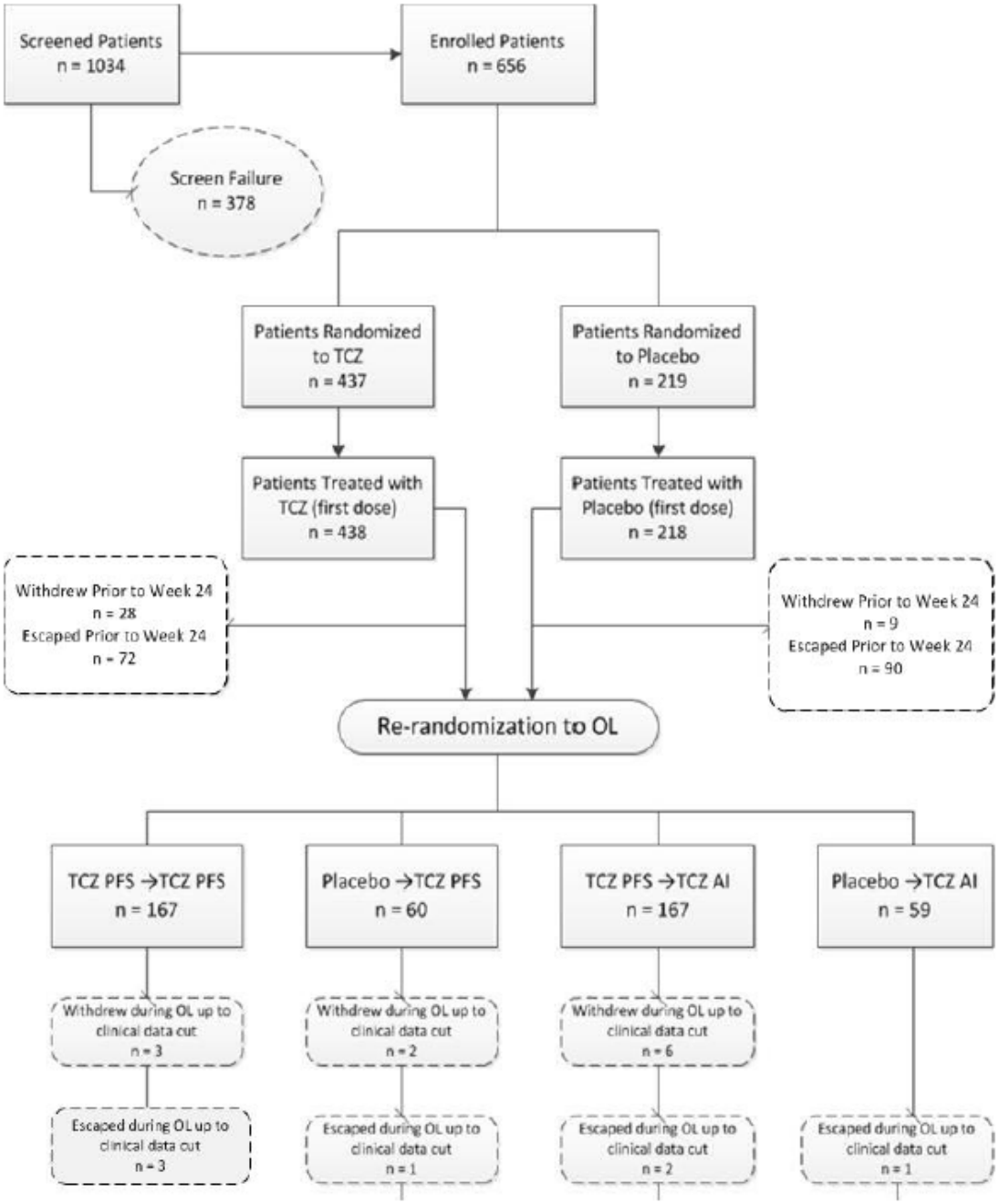
A total of 410 patients in the TCZ arm and 209 patients in the placebo arm (including 70 and 88 of the patients, respectively, who received escape therapy prior to Week 24) completed the 24-week treatment period. As specified in the protocol, patients who withdrew prior to Week 24 and those who received escape therapy prior to Week 24 were not re-randomized at Week 24.

An additional 7 patients received open-label treatment in the extension, although they had no re-randomized dates in IVRS.

As of the clinical cut-off date (28 May 2012), a total of 11 patients withdrew from the study after Week 24, including 3 (1.8%) patients from the TCZ PFS arm, 6 (3.6%) patients from the TCZ PFS-to-AI switch arm and 2 (3.3%) patients from the placebo to TCZ PFS switch arm. The most common reasons for withdrawal were AEs (5 patients overall).

Among the escape patients who received escape therapy as early as Week 12, 14 patients withdrew from the study: 3 were assigned to the TCZ q2w arm at baseline and 11 were assigned to the placebo arm at baseline. The most common reasons for withdrawal among escape patients were withdrawn consent (5 patients overall) and AEs (4 patients overall).

Figure 1. Overview of Patient Disposition



Baseline data

Safety Population

The study population was comprised predominantly of Caucasian (>70%) females (>80%) with a mean age of approximately 52 years (range 18-82 years). The four re-randomization treatment arms were balanced with respect to all baseline demographic characteristics. The majority of patients (>65%) weighed between 60 and 100 kg, with <30% weighing 60 kg and less, and <5% of patients weighing 100 kg or more. The maximum weight was capped at 150 kg (per the exclusion criterion).

Generally, the four treatment arms were balanced with respect to RA disease characteristics. The mean duration of RA disease was approximately 11 years in all treatment arms. Median oral corticosteroid dose at baseline was 5.0 mg/day for each arm. The majority of patients were positive for rheumatoid factor (ranging from 78% to 81% in the treatment arms), and the proportion of patients with a positive baseline for anti-cyclic citrullinated peptide (CCP) ranged from 76% to 85% in the treatment arms.

Consistent with the capping rule imposed in the protocol, the proportion of the patients with inadequate response to anti-TNFs prior to study participation was 20.3% for the placebo to TCZ AI switchers treatment arm and was <20% in all other treatment arms.

There were no noteworthy differences between the treatment arms with respect to the ACR core set (the number of swollen and tender joints, the functional status [HAQ-DI] at baseline, the patient and physician's assessment of global disease status and patient pain rating, and CRP and ESR levels). The study population had moderate to severe RA disease, as reflected by the mean DAS28 ranging from 6.3 to 6.7 in the treatment arms.

Escape Patients

As mentioned previously, only those patients who initiated escape therapy between Week 12 and Week 24 are summarized and described in this report. Data for the seven patients who initiated escape therapy after Week 24 are included only in the listings.

The baseline demographics of patients who received escape therapy were generally consistent with that of the overall safety population. The proportion of patients in each body weight category was similar in the prior TCZ and placebo arms. Approximately 68% of patients in each treatment arm weighed between 60 and 100 kg; <30% weighed less than 60 kg; and approximately 6% of patients weighed more than 100 kg. More patients from North America and Rest of World received escape therapy compared with patients from Europe.

The RA disease characteristics of the escape patients showed that the proportion of patients who were RF positive, anti-CCP positive, and who had failed one or more previous anti-TNF therapies was higher among patients who received escape therapy as compared to the overall safety population. The ACR core set and DAS28 characteristics for escape patients at the initiation of escape therapy were generally unchanged from baseline (with the exception of ESR and CRP in the prior TCZ arm) and reflected the inadequate response in these patients.

Numbers analysed

Table 14. Summary of analysis Population

	TCZ PFS	TCZ PFS to TCZ AI Switch	Placebo to TCZ PFS Switch	Placebo to TCZ AI Switch	Placebo (provided as reference)[b]
Safety	437[a]	168[c]	61[d]	59	218
ITT	167	167	60	59	N/A

AEs = adverse events; AI = autoinjector; PFS = prefilled syringe

[a] The TCZ-PFS arm included all patients who were treated with TCZ 162 mg SC by PFS for their first dose. AE and immunogenicity data include all data up to Week 24 and data for patients re-randomized to TCZ PFS from the open-label period up to the date of the data cut.

[b] Placebo data from baseline to re-randomization at Week 24 provided as reference for safety analyses.

[c] Patient 57451 received TCZ PFS and then received AI but had no re-randomization date; hence is not included in lab outputs, but is in AE outputs (ie n=167 for labs and 168 for AEs)

[d] Patient 37310 received placebo and then received TCZ PFS but had no re-randomization date; hence not included in lab outputs, but is in AE outputs (ie n= 60 for labs and 61 for AEs)

Efficacy data are also summarized for a population of escape patients who met escape criteria from Week 12 up to Week 24 (per protocol) and are receiving weekly injections of TCZ. These escape patients (n=72 in the prior TCZ arm and 90 in the prior placebo arm) are analysed separately from the ITT and safety populations.

Data for the 7 patients who initiated escape therapy after Week 24 are presented only in the listings.

Outcomes and estimation

The data presented are based on the analysis of data up to the clinical cut-off date of 28 May 2012.

Table 15. Summary of efficacy at weeks 24, to 48 (ITT population)

	Study Week					
	24	28	32	36	40	48
ACR20 Responder (%)						
TCZ PFS →TCZ PFS	79.0 (n=167)	80.0 (n=165)	73.7 (n=114)	81.1 (n=74)	70.5 (n=44)	78.9 (n=19)
TCZ PFS → TCZ AI	77.2 (n=167)	75.9 (n=166)	72.8 (n=114)	67.5 (n=77)	69.8 (n=43)	73.7 (n=19)
ACR50 Responder (%)						
TCZ PFS → TCZ PFS	53.9 (n=167)	51.5 (n=165)	56.1 (n=114)	51.4 (n=74)	50.0 (n=44)	52.6 (n=19)
TCZ PFS → TCZ AI	49.1 (n=167)	49.4 (n=166)	50.0 (n=114)	48.1 (n=77)	53.5 (n=43)	57.9 (n=19)
ACR70 Responder (%)						
TCZ PFS → TCZ PFS	25.7 (n=167)	29.7 (n=165)	30.7 (n=114)	39.2 (n=74)	36.4 (n=44)	31.6 (n=19)
TCZ PFS → TCZ AI	24.6 (n=167)	25.9 (n=166)	28.9 (n=114)	28.6 (n=77)	23.3 (n=43)	10.5 (n=19)
Mean DAS28						
TCZ PFS → TCZ PFS	3.41 (n=167)	3.29 (n=162)	3.23 (n=106)	3.20 (n=69)	3.10 (n=39)	2.85 (n=16)
TCZ PFS → TCZ AI	3.31 (n=167)	3.32 (n=161)	3.28 (n=104)	3.10 (n=71)	2.74 (n=36)	3.08 (n=18)
Mean change in DAS28 from baseline						
TCZ PFS → TCZ PFS	-3.34 (n=165)	-3.48 (n=160)	-3.46 (n=105)	-3.52 (n=68)	-3.57 (n=38)	-3.78 (n=16)
TCZ PFS → TCZ AI	-3.24 (n=116)	-3.27 (n=160)	-3.36 (n=105)	-3.53 (n=71)	-3.84 (n=36)	-3.42 (n=18)
DAS28 < 2.6 (%)						
TCZ PFS → TCZ PFS	29.3 (n=167)	35.2 (n=162)	39.6 (n=106)	36.2 (n=69)	41.0 (n=39)	62.5 (n=16)
TCZ PFS → TCZ AI	36.5 (n=167)	34.8 (n=161)	36.5 (n=104)	47.9 (n=71)	52.8 (n=36)	44.4 (n=18)
Mean change in HAQ-DI						
TCZ PFS → TCZ PFS	-0.58 (n=166)	-0.59 (n=163)	-0.65 (n=107)	-0.69 (n=69)	-0.84 (n=39)	-0.52 (n=16)
TCZ PFS → TCZ AI	-0.43 (n=167)	-0.43 (n=165)	-0.52 (n=108)	-0.45 (n=72)	-0.52 (n=36)	-0.40 (n=18)
HAQ-DI decrease ≥ 0.3 (%)						
TCZ PFS → TCZ PFS	63.3 (n=166)	62.6 (n=163)	68.2 (n=107)	69.6 (n=69)	79.5 (n=39)	62.5 (n=16)
TCZ PFS → TCZ AI	53.9 (n=167)	51.5 (n=165)	54.6 (n=108)	52.8 (n=72)	61.1 (n=36)	38.9 (n=18)

ACR = American College of Rheumatology; DAS28 = disease activity score 28; HAQ-DI = Health Assessment Questionnaire Disability Index; TCZ = tocilizumab; PFS = pre-filled syringe; AI autoinjector.

Ancillary analyses

Subgroup analysis

Table 16. ACR20, ACR 50 and ACR 70 response rates at week 36 by bodyweight (ITT population)

ACR Response by Body Weight	No. (%) of Patients			
	TCZ PFS q2w (N = 167) No. of Responders/n (%)	TCZ PFS q2w → TCZ AI q2w (N = 167) No. of Responders/n (%)	Placebo PFS q2w → TCZ PFS q2w (N = 60) No. of Responders/n (%)	Placebo PFS q2w → TCZ AI q2w (N = 59) No. of Responders/n (%)
ACR20 response				
<60 kg	12/15 (80.0)	15/20 (75.0)	7/8 (87.5)	5/6 (83.3)
60 to < 100 kg	46/56 (82.1)	33/50 (66.0)	10/17 (58.8)	16/21 (76.2)
≥100 kg	2/3 (66.7)	4/7 (57.1)	3/3 (100)	1/1 (100.0)
ACR50 response				
<60 kg	9/15 (60.0)	13/20 (65.0)	6/8 (75.0)	3/6 (50.0)
60 to < 100 kg	29/56 (51.8)	23/50 (46.0)	8/17 (47.1)	7/21 (33.3)
≥100 kg	0/3 (0.0)	1/7 (14.3)	2/3 (66.7)	1/1 (100.0)
ACR70 response				
<60 kg	6/15 (40.0)	9/20 (45.0)	2/8 (25.0)	2/6 (33.3)
60 to < 100 kg	23/56 (41.1)	13/50 (26.0)	4/17 (23.5)	2/21 (9.5)
≥100 kg	0/3 (0.0)	0/7 (0.0)	2/3 (66.7)	1/1 (100.0)

ACR20 = American College of Rheumatology 20% response; ACR50 = American College of Rheumatology 50% response; ACR70 = American College of Rheumatology 70% response; AI = Autoinjector; CRP = C-reactive protein; PFS = Pre filled syringe; q2w = Every 2 weeks.

Source: page 450.

Table 17. Summary of efficacy at 8 and 12 weeks following escape therapy

Efficacy Endpoint Study Week	No. of Patients (%)	
	TCZ PFS qw (prior TCZ q2w) N = 72	TCZ PFS qw (prior Placebo q2w) N = 90
ACR20 response rate		
8 Weeks after Escape	37/69 (53.6)	54/87 (62.1)
12 Weeks after Escape	39/67 (58.2)	57/79 (72.2)
ACR50 response rate		
8 Weeks after Escape	10/69 (14.5)	27/87 (31.0)
12 Weeks after Escape	12/67 (17.9)	30/79 (38.0)
ACR70 response rate		
8 Weeks after Escape	4/69 (5.8)	12/87 (13.8)
12 Weeks after Escape	4/67 (6.0)	12/79 (15.2)
DAS LDA (<3.2)		
8 Weeks after Escape	21/66 (31.8)	32/79 (40.5)
12 Weeks after Escape	19/60 (31.7)	33/76 (43.4)
DAS responders (good EULAR response)		
8 Weeks after Escape	18/66 (27.3)	32/79 (40.5)
12 Weeks after Escape	18/60 (30.0)	33/76 (43.4)

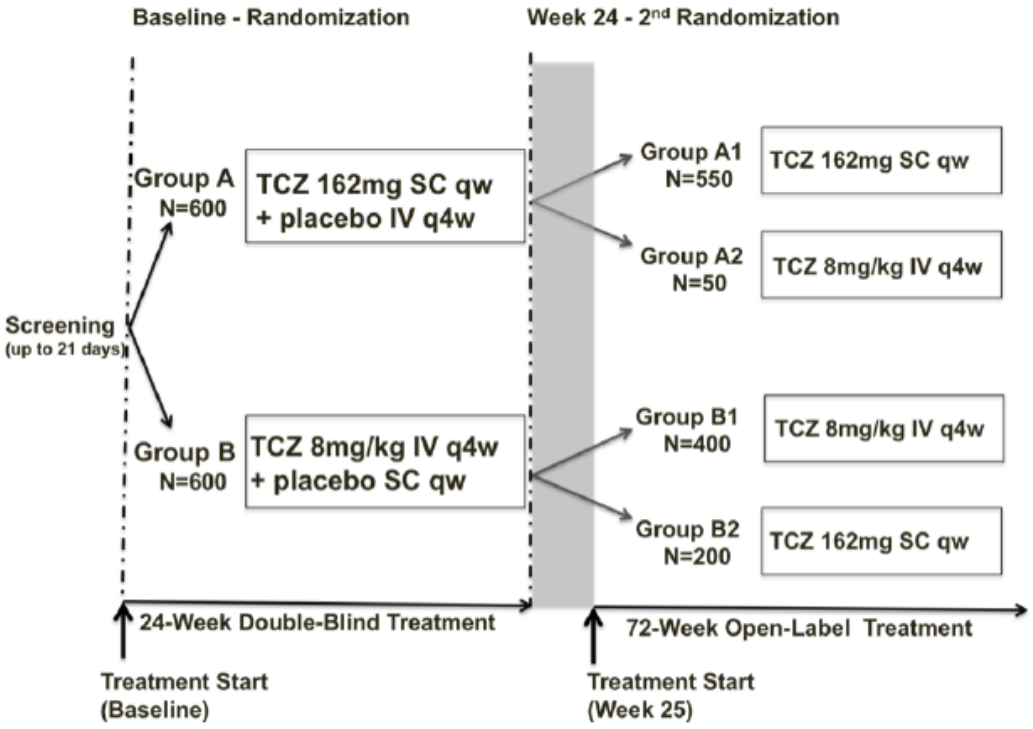
ACR20 = American College of Rheumatology 20% response; ACR50 = American College of Rheumatology 50% response; ACR70 = American College of Rheumatology 70% response; DAS = Disease Activity Score; LDA = Low disease activity; PFS = Pre filled syringe; qw = Every week; q2w = Every 2 weeks; TCZ = Tocilizumab.

Study WA22762

Methods

Study WA22762, otherwise known as SUMMACTA, was a Phase III, two-arm, 2-year, randomized, double-blind, double-dummy, active-controlled, parallel-group, multicentre trial in patients with moderate to severe active RA who had an inadequate response to a stable dose of DMARDs that may have included one or more anti-TNF biologic agents (with the percentage of patients who had failed one or more anti-TNF biologic agents capped at approximately 20%). The primary endpoint was evaluated at 24 weeks.

Figure 7. Study Design



IV = intravenous; q4w = every 4 weeks; qw = once weekly; SC = subcutaneous; TCZ = tocilizumab.

Study participants

Inclusion criteria

Patients were eligible for the study if they met all of the following criteria:

1. Able and willing to give written informed consent and comply with the requirements of the study protocol (e.g., willing to take oral folate at a minimum dose of 5 mg/wk if on methotrexate [MTX] treatment)
2. Age ≥ 18 years
3. RA of ≥ 6 months' duration, diagnosed according to the revised 1987 ACR (formerly, the American Rheumatism Association) criteria

4. Received treatment on an outpatient basis
5. Swollen joint count (SJC) ≥ 4 (66 joint count) and tender joint count (TJC) ≥ 4 (68 joint count) at screening and baseline
6. Prior to randomization, had discontinued etanercept for ≥ 2 weeks, infliximab, certolizumab, golimumab, abatacept, or adalimumab for ≥ 8 weeks, or anakinra for ≥ 1 week
7. Had to be on at least one permitted DMARD (see Section 4.4.2 of the protocol, which had been at a stable dose for at least 8 weeks prior to baseline
8. At screening, either C-reactive protein (CRP) ≥ 10 mg/L (≥ 1 mg/dL) and/or erythrocyte sedimentation rate (ESR) ≥ 28 mm/hr
9. Oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and NSAIDs (up to the maximum recommended dose) were permitted if on a stable dose regimen for ≥ 4 weeks prior to baseline
10. Females of childbearing potential and males with female partners of childbearing
11. potential participated in this trial only if using a reliable means of contraception (e.g., physical barrier [patient or partner], contraceptive pill or patch, spermicide and barrier, or intrauterine device)
12. If female of childbearing potential, the patient had to have a negative pregnancy test at screening and baseline visit.

Exclusion criteria

Patients were ineligible for the study if they met any of the following criteria:

General

1. Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery within 6 months following randomization
2. Rheumatic autoimmune disease other than RA, including systemic lupus erythematosus, mixed connective tissue disease, scleroderma, polymyositis, or significant systemic involvement secondary to RA (e.g., vasculitis, pulmonary fibrosis, or Felty syndrome).

   Secondary Sjögren syndrome with RA was allowed.
3. Functional class IV as defined by the ACR Classification of Functional Status in Rheumatoid Arthritis
4. Diagnosed with JIA or juvenile RA and/or RA before the age of 16
5. History of or current inflammatory joint disease other than RA (e.g., gout, Lyme disease, sero-negative spondyloarthropathy, including reactive arthritis, psoriatic arthritis, arthropathy of inflammatory bowel disease).

Excluded Previous or Concomitant Therapy

6. Treatment with any investigational agent within 4 weeks (or 5 half-lives of the investigational drug, whichever was longer) of screening
7. Previous treatment with any cell-depleting therapies, including investigational agents or approved therapies, some examples of which are Campath, anti-CD4, anti-CD5, anti-CD3, anti-CD19, and anti-CD20
8. Treatment with IV gamma globulin, plasmapheresis within 6 months of baseline
9. Intra-articular (IA) or parenteral corticosteroids within 4 weeks prior to baseline
10. Immunization with a live/attenuated vaccine within 4 weeks prior to baseline
11. Previous treatment with TCZ (an exception to this criterion could have been granted for single-dose exposure upon application to the Sponsor on a case-by-case basis)
12. Any previous treatment with alkylating agents such as chlorambucil or with total lymphoid irradiation.

Treatments

IV Tocilizumab / Placebo

During the double-blind period, patients received an IV infusion of 8 mg/kg of TCZ or placebo q4w on an outpatient basis for a total of six infusions (baseline [Week 0, Day 1], Weeks 4, 8, 12, 16, and 20). The last recorded body weight of a patient was used for calculating the TCZ dose for each infusion. No study treatment was scheduled at Week 24. All patients were to be re-randomized for the open-label period at Week 24.

After a 1-week dose interruption, patients assigned to receive 8 mg/kg of IV TCZ were to receive this dose q4w, starting at Week 25 until Week 93. Infusions were administered under close supervision of the investigator in a setting where medications and resuscitation facilities were available.

SC Tocilizumab / Placebo

During the double-blind period, a fixed dose of 162 mg of TCZ or matching placebo was administered by SC injection qw until Week 23. No study treatment was scheduled at Week 24. SC injections of study drug (TCZ or placebo) were given using a pre-filled syringe (PFS) with a needle safety device. The recommended injection sites were the front of the middle part of the thigh and the lower part of the abdomen below the navel (belly button), except for the 2-inch area directly around the navel. If a caregiver was giving the injection, the outer area of the upper arms could also be used. Injections were not to be made into areas where the skin was not intact or was tender, bruised, red, or hard. All patients were re-randomized for the open-label period at Week 24. After a 1-week dose interruption, patients assigned to receive 162 mg of SC TCZ were to receive this dose qw, starting at Week 25 until Week 96.

Objectives

The primary objectives of the study were to assess:

- The efficacy of treatment with 162 mg TCZ given subcutaneously weekly versus 8 mg/kg TCZ given intravenously every 4 weeks with regard to non-inferiority of the proportion of patients who achieved American College of Rheumatology (ACR) 20 response at Week 24
- The safety of treatment with 162 mg TCZ given subcutaneously weekly versus 8 mg/kg TCZ given intravenously every 4 weeks, with regard to adverse events (AEs) and laboratory assessments.

The secondary objectives of the study were to assess:

- Long-term safety and efficacy
- Pharmacokinetics and pharmacodynamics of TCZ following SC administration
- Immunogenicity of TCZ following SC administration
- Effect of IV to SC switch on the safety, efficacy, pharmacokinetics, and pharmacodynamics of TCZ.

Specimens stored in the Roche Clinical Repository (RCR) were to be used to:

- Study the association of biomarkers with efficacy and/or AEs associated with medicinal products; and/or
- Increase the knowledge and understanding of disease biology; and/or
- Develop biomarker or diagnostic assays; establish the performance characteristics of these assays TCZ pharmacokinetic (PK)−safety and PK−efficacy relationships were also explored.

Outcome / endpoint

The primary efficacy endpoint was the ACR20 response rate at Week 24.

For the ACR20 response to be considered positive, a ≥ 20% improvement (i.e. reduction) compared with baseline was required for both TJC68 and SJC66, as well as for three of the additional five ACR core set variables: patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, Health Assessment Questionnaire (HAQ), and acute-phase reactant (either CRP or ESR).

The secondary efficacy endpoints were the following:

- Proportion of patients with an ACR50 response at Week 24
- Proportion of patients with an ACR70 response at Week 24
- Proportion of patients with a Disease Activity Score 28 (DAS28) < 2.6 (DAS remission) at Week 24
- Proportion of patients achieving a decrease of ≥ 0.3 in the HAQ-DI from baseline to Week 24

- Proportion of patients who withdrew because of lack of therapeutic response at Week 24.

Sample size

The primary analysis was based on the PP population. Data from the initial three pivotal Phase III studies (studies WA17823, WA17822, and WA18063), evaluating 8 mg/kg of TCZ in combination with MTX versus placebo in combination with MTX in DMARD−inadequate responders (-IRs), showed ACR20 response rates for the PP population at Week 24 of 58.5% (study WA17823), 63.3% (study WA17822), and 64.3% (study WA18063). The pooled ACR20 response rate for these three studies was 62.5%.

Assuming that Group B had an ACR20 response rate of 62.5%, 450 patients per treatment arm would be required to provide 90% power to demonstrate that Group A was non-inferior to Group B using a 12-percentage point non-inferiority margin and assuming that Group A was 1% worse than Group B. Based on the Phase III IV TCZ studies described above, it was estimated that approximately 25% of patients would not be eligible for the PP population. Therefore, a total sample size of 600 patients per arm was planned to be randomized into the study to ensure adequate patient numbers for the primary analysis.

In addition, a sample size of 600 patients per arm also allowed a 95% chance of observing at least 1 patient with a specific AE, if the AE had an event rate of at least 0.5%.

Randomisation

Eligible patients who fulfilled the inclusion and exclusion criteria were randomly assigned to two treatment groups at baseline for the double-blind period and subsequently re-randomized within each treatment group at Week 24 for the open-label period, utilizing an interactive voice response system (IVRS). These two sets of randomization numbers were generated by Perceptive Informatics, Inc. and were linked to a unique patient identification number through the IVRS. At baseline, randomization was by minimization and stratified by geographic region (Europe, North America, South America, rest of world) and body weight category (< 60 kg, 60 to 100 kg, ≥ 100 kg). The minimization procedure was implemented by Perceptive. This involved maintaining an updated record of treatment assignments by stratification factors and was used to determine the treatment of choice for a newly recruited patient. The minimization procedure was based on an 80:20 random element, i.e., a patient was assigned to the treatment of choice with a probability of 0.8.

Randomization at Week 24 was implemented by permuted block.

Blinding (masking)

This study was blinded during the first 24 weeks, and a “dual assessor” approach was used to evaluate first efficacy and then safety data to prevent potential unblinding because of observed efficacy or laboratory changes. The efficacy assessor was a rheumatologist or other skilled arthritis assessor but could not be the principal investigator. The efficacy assessor was responsible for assessing the joint counts and the Physician’s Global Assessment of Disease VAS components but was not allowed access to other patient data. The safety assessor was a rheumatologist or medically qualified physician with access to both the safety and efficacy data and was permitted to be the principal investigator. The study centres, Roche monitors, and study

team members were blinded to some laboratory data (i.e. TCZ, CRP, IL-6, and sIL-6R) before the primary analysis.

Blinding of the treatment received was maintained for patients, investigators, and Roche personnel until after completion of the last patient visit at Week 24 and subsequent database lock. The initial randomization for the double-blind treatment will be unblended to investigators and patients after the primary analysis result is reported.

Per regulatory requirements, study treatment was to be unblinded for all unexpected SAEs that were considered by the investigator to be related to study drug.

After the Week 24 data analysis and following specific instructions from the Sponsor, a single assessor approach (using a qualified physician to perform all efficacy and safety assessments) could be used for subsequent visits in the open-label part of the study.

Statistical methods

Non-inferiority of 162 mg SC TCZ qw (group A) compared to 8 mg/kg IV TCZ q4w (group B) with regard to ACR20 response at week 24 was to be concluded if the lower limit of the two-sided 95% confidence interval (CI) for the difference in percentage of ACR20 responders on group A minus group B was not less than −12%. The primary analysis was performed on the PP population, excluding all patients with pre-defined major protocol violations. Patients in whom week 24 ACR20 was not available, were considered non-responder in the primary analysis. In case the null-hypothesis of inferiority of group A compared to group B was rejected, the analysis was to be repeated with a non-inferiority margin of -10%.

As a sensitivity analysis, the primary analysis was repeated for the ITT population. To assess homogeneity of treatment effect, explorative analyses on the primary endpoint were performed, if appropriate, in patient subgroups defined by region, weight at baseline, or any relevant clinically meaningful characteristics at baseline. All exploratory efficacy subgroup analyses were based on the PP population.

To investigate whether treatment assignment by dynamic randomisation did affect the outcome of the study, the primary analysis was re-analysed using a re-randomization test.

For secondary endpoints treatment effects at week 24 were characterised by point estimates and the corresponding 95% CI. The analyses were carried out using the PP population. No formal tests for non-inferiority were performed given that a non-inferiority margin was only defined for the primary endpoint.

No formal statistical analyses of exploratory efficacy endpoints were performed to compare treatment arms at week 24.

Results

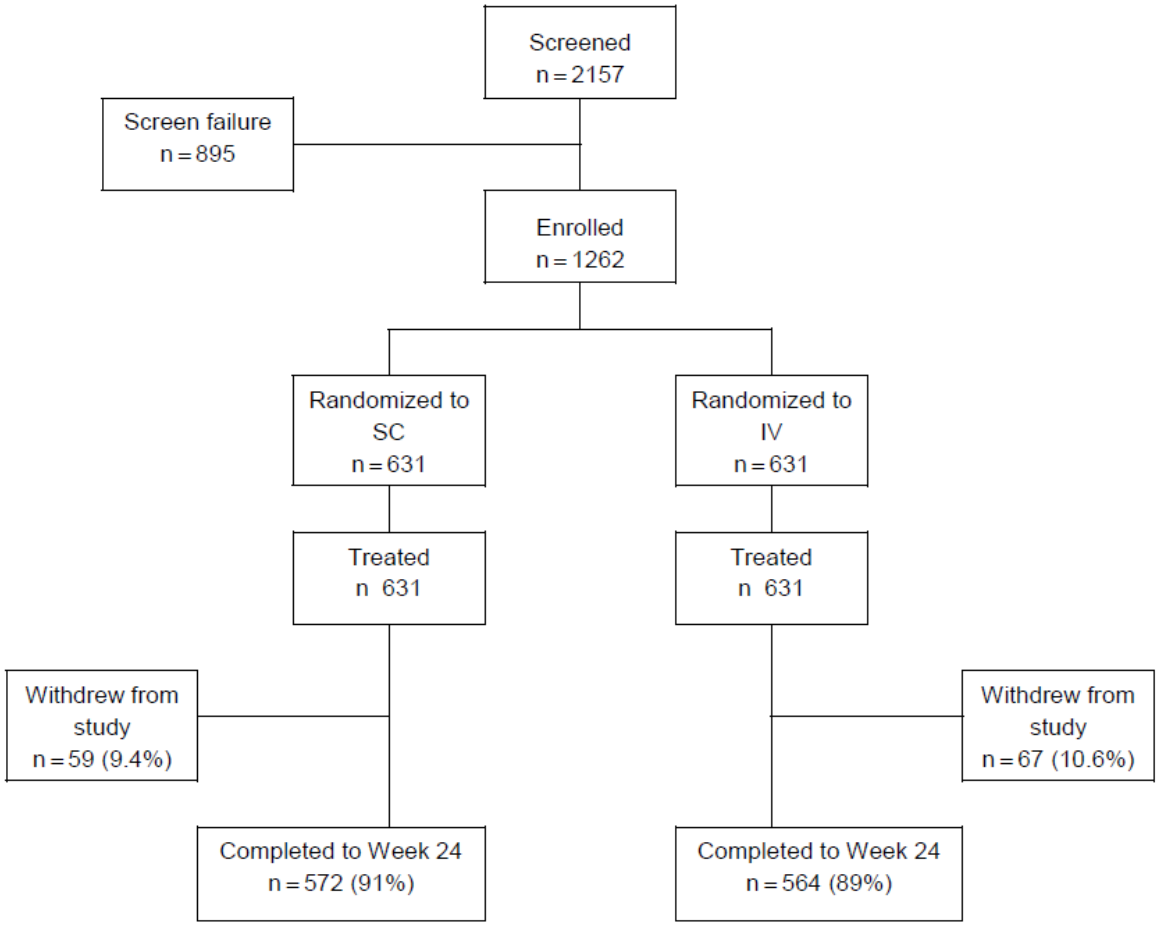
Participant flow

Of the 2157 patients screened, a total of 1262 patients were randomized into the study.

The main reason for screening failure was CRP < 10 mg/L (1 mg/dL) and ESR < 28 mm/hr prior to baseline (unvalidated data obtained from the IVRS).

Of the 1262 patients enrolled into the study, 631 patients were randomized into each of the study arms (see figure below). All patients received at least one dose of study drug.

Figure 8. Overview of Patient Disposition



Note: Percentages were based on the number of randomized patients.

Recruitment

Patients were enrolled at 209 centres in 25 countries. The highest recruiting centres were in Bulgaria, which enrolled 1.9% of the total number of patients, and Poland, Brazil, and Mexico, each of which enrolled 1.7%.

The first patient was screened on 18 August 2010, and the first patient was randomized on 1 September 2010. The last patient was randomized on 1 August 2011, and the date of the clinical cut-off for the 24-week analysis was 16 January 2012.

Conduct of the study

The protocol was amended twice: on 19 November 2010 (Amendment B) and on 2 December 2011 (Amendment C). The final protocol used for the double-blind period of the study was Amendment C.

Amendment B (19 November 2010)

- Following one case of a fatal hypersensitivity reaction in an IV TCZ-treated patient that occurred in the post-marketing setting, additional guidance was added to the protocol.
- Event-driven blood sample collection for the analysis of anti-TCZ antibodies was included in the amendment for patients who withdrew because of anaphylaxis or serious hypersensitivity

Amendment C (2 December 2011)

- Additional serum sample collection for the analysis of anti-TCZ antibodies from patients who had terminated from the study early, completed the study, or missed TCZ treatment during the study in order to adjust for the higher than expected mean TCZ trough concentration in the TCZ SC group. A longer washout period was required.

These two amendments of the protocol did no impact on the safety and efficacy analysis of the study.

There were no key changes to the analysis of the primary efficacy endpoint or key secondary endpoints after database lock.

Baseline data

Demographic Data

The study population comprised predominantly Caucasian (76%) females (83%), at a mean age of approximately 53 years (range: 18-86; see table below). The two treatment arms were balanced with respect to all baseline demographic characteristics recorded.

Geographic region and body weight category were baseline stratification factors at randomization. The majority of the patients (67%) weighed between 60 and 100 kg, with 23% weighing < 60 kg and 10% weighing ≥ 100 kg. The maximum weight was capped at 150 kg (per an exclusion criterion).

The baseline demographic characteristics of patients in the PP population were consistent with of the safety population.

Table 18. Baseline Demographic Characteristics (Safety Population)

stdm11_gen_saf General Demographic Variables at Baseline (Safety Population)
Protocol(s): WA22762 (R22762A)
Analysis: SAFETY Center: ALL CENTERS

	162mg SC qw + DMARD N = 631	8mg/kg IV q4w + DMARD N = 631
Sex		
MALE	111 (17.6%)	110 (17.4%)
FEMALE	520 (82.4%)	521 (82.6%)
n	631	631
Race		
ASIAN	41 (6.5%)	43 (6.8%)
AMERICAN INDIAN / ALASKA NATIVE, WHITE	-	1 (0.2%)
AMERICAN INDIAN / ALASKA NATIVE	24 (3.8%)	26 (4.1%)
BLACK	32 (5.1%)	27 (4.3%)
NATIVE HAWAIIAN / OTHER PACIFIC ISLANDER	2 (0.3%)	1 (0.2%)
WHITE	486 (77.0%)	479 (75.9%)
NOT AVAILABLE	46 (7.3%)	54 (8.6%)
n	631	631
Age in years		
Mean	52.7	52.8
SD	12.35	12.53
SEM	0.49	0.50
Median	54.0	54.0
Min-Max	18 - 83	18 - 86
n	631	631
Weight in kg		
Mean	74.591	74.406
SD	19.1310	19.0081
SEM	0.7616	0.7567
Median	72.300	72.000
Min-Max	38.00 - 150.00	32.40 - 149.90
n	631	631
Height in cm		
Mean	162.259	162.275
SD	9.6688	8.9760
SEM	0.3852	0.3582
Median	161.000	162.000
Min-Max	129.50 - 198.00	124.00 - 192.00
n	630	628
Baseline Weight Category (kg)		
<60	144 (22.8%)	146 (23.1%)
60-100	425 (67.4%)	422 (66.9%)
>=100	62 (9.8%)	63 (10.0%)
n	631	631
Ethnicity		
HISPANIC	186 (29.5%)	194 (30.7%)
NON-HISPANIC	440 (69.7%)	428 (67.8%)
NA	5 (0.8%)	9 (1.4%)
n	631	631
Geographic Region		
Europe	199 (31.5%)	198 (31.4%)
North America	180 (28.5%)	181 (28.7%)
Rest of World	97 (15.4%)	97 (15.4%)
South America	155 (24.6%)	155 (24.6%)
n	631	631

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
For reproductive status, NA stands for Not Applicable and Con. Prot. stands for Contraceptive Protection.
DM11 14MAY2012:15:04:04 (1 of 2)

Protocol(s): WA22762 (R22762A)
Analysis: SAFETY Center: ALL CENTERS

	162mg SC qw + DMARD N = 631	8mg/kg IV q4w + DMARD N = 631
Female reproductive status		
HYSTERECTOMY	48 (9.2%)	58 (11.1%)
HYSTERECTOMY / TUBAL LIGATION	-	3 (0.6%)
POST-MENOPAUSAL	240 (46.2%)	232 (44.5%)
POST-MENOPAUSAL / HYSTERECTOMY	15 (2.9%)	12 (2.3%)
POST-MENOPAUSAL / HYSTERECTOMY / TUBAL LIGATION	3 (0.6%)	1 (0.2%)
POST-MENOPAUSAL / TUBAL LIGATION	20 (3.8%)	22 (4.2%)
PRE-MENOPAUSAL	158 (30.4%)	155 (29.8%)
PRE-MENOPAUSAL / TUBAL LIGATION	8 (1.5%)	4 (0.8%)
TUBAL LIGATION	28 (5.4%)	34 (6.5%)
n	520	521
Smoking status		
CURRENT	106 (16.8%)	115 (18.2%)
NEVER	401 (63.5%)	392 (62.1%)
PREVIOUS	124 (19.7%)	124 (19.7%)
n	631	631
Family history of Chronic Heart Disease		
YES	105 (16.6%)	85 (13.5%)
NO	491 (77.8%)	508 (80.5%)
UNK	35 (5.5%)	38 (6.0%)
n	631	631

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
For reproductive status, NA stands for Not Applicable and Con. Prot. stands for Contraceptive Protection.
DM11 14MAY2012:15:04:04 pagination modified (2 of 2)

Baseline RA Disease Characteristics

Overall, the treatment arms were balanced with respect to RA disease characteristics. The duration of RA was 8.7 years for patients in the SC arm and 8.6 years in the IV arm (see table below).

From 6 months prior to screening to baseline, patients enrolled in the study in each arm had been treated with a mean of 1.4 of DMARDs (see table below). Approximately 55% of patients in the SC arm and 54% of patients in the IV arm were treated with oral corticosteroids at baseline for which the dose was similar (mean of 7 mg/day). The majority of patients were positive for rheumatoid factor (74% in each arm) and anti–cyclic citrullinated peptide positive at baseline (72% SC arm vs. 76% IV arm). The study population had moderate to severe RA disease, as reflected by the mean DAS28 score of 6.6 (range: 3–9) for the SC arm and 6.7 (range: 4–9) for the IV arm.

The proportion of the patients who were anti–TNF-IRs was 22.5% in the SC arm and 21.6% in the IV arm, reflecting the capping rule (the protocol stipulated the proportion of patients who failed one or more anti-TNF agents should be approximately 20%).

The baseline RA disease characteristics of the PP population were consistent with those observed in the safety population.

Table 19. Baseline RA Disease Characteristics (Safety Population)

stdm11_ra_sat RA Characteristics at Baseline (Safety Population)
Protocol(s): WA22762 (R22762A)
Analysis: SAFETY Center: ALL CENTERS

	162mg SC qw + DMARD N = 631	8mg/kg IV q4w + DMARD N = 631
Duration of RA (years)		
Mean	8.7	8.6
SD	8.26	8.05
SEM	0.33	0.32
Median	5.8	6.2
Min-Max	0 - 47	1 - 44
n	631	631
No. of previous DMARDS		
Mean	1.4	1.4
SD	0.72	0.70
SEM	0.03	0.03
Median	1.0	1.0
Min-Max	0 - 6	0 - 5
n	631	631
Baseline Oral Corticosteroid Use (y/n)		
NO	287 (45.5%)	293 (46.4%)
YES	344 (54.5%)	338 (53.6%)
n	631	631
Baseline Oral Corticosteroid Dose (mg/day)		
Mean	6.92	6.76
SD	2.607	2.548
SEM	0.141	0.139
Median	5.00	5.00
Min-Max	0.0 - 20.0	0.0 - 10.0
n	341	337
Baseline RF Positivity		
NO	164 (26.5%)	160 (25.6%)
YES	456 (73.5%)	465 (74.4%)
n	620	625
Baseline Anti-CCP Positivity		
NO	167 (27.8%)	150 (24.2%)
YES	434 (72.2%)	471 (75.8%)
n	601	621

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
Previous DMARDs included those that were ongoing at baseline).
DM11 14SEP2012:01:43:16 footnote added (1 of 2)

stdm11_ra_saf RA Characteristics at Baseline (Safety Population)
Protocol(s): WA22762 (R22762A)
Analysis: SAFETY Center: ALL CENTERS

	162mg SC qw + DMARD N = 631	8mg/kg IV q4w + DMARD N = 631
Baseline DAS28		
Mean	6.6	6.7
SD	1.00	1.02
SEM	0.04	0.04
Median	6.6	6.7
Min-Max	3 - 9	4 - 9
n	623	626
IVRS Failed Prior anti-TNF Treatment?		
N	489 (77.5%)	495 (78.4%)
Y	142 (22.5%)	136 (21.6%)
n	631	631

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
Previous DMARDs included those that were ongoing at baseline.
DM11 14SEP2012:01:43:16 footnote added (2 of 2)

Numbers analysed

Of the 1262 patients enrolled into the study (631 in each of the treatment arms), all patients received study treatment and were eligible for inclusion in the ITT and safety populations.

The PP population comprised 1095 patients (558 SC arm, 537 IV arm), with approximately 13% of the overall population being excluded from the PP population for one or more reasons (see table below).

More patients in the IV arm (15%) compared with the SC arm (12%) were excluded from the PP population. The most common reason for exclusion from the PP population in both arms was because of the background DMARD not remaining at a stable dose (38 patients in the SC arm vs. 37 patients in the IV arm).

There was an imbalance in the number of patients excluded for receiving less than two-thirds or more than four-thirds of the total allocated SC treatment of TCZ or placebo (6 patients SC arm vs. 19 patients IV arm), and this was the second most common reason for exclusion from the PP population in the IV arm. In addition, more patients in the IV arm than in the SC arm were excluded because they received less than the two-thirds or more than four-thirds of the total allocated IV TCZ or placebo (5 patients SC arm vs. 9 patients IV arm).

In the SC arm, the third most common reason for exclusion was “patients do not have at least one permitted DMARD with a stable dose for at least 8 weeks prior to baseline.”

Eight patients were excluded despite this being an inclusion criterion. A similar number of patients (7) were excluded from the IV arm for this reason.

All patients who reached Week 24 (a total of 1136 patients: 572 in the SC arm, 564 in the IV arm) were re-randomized to the 72-week open-label treatment period. Of note, 1 patient in the SC arm who completed the double-blind period died after re-randomization and did not receive any open-label drug.

Table 20. Analysis Population

stecl1_all Analysis Populations by Randomized Trial Treatment (All Patients Population)
Protocol(s): WA22762 (R22762A)
Analysis: ALL PATIENTS Center: ALL CENTERS

	162mg SC qw + DMARD	8mg/kg IV q4w + DMARD
No. of Patients Randomized	631	631
No. Included in INTENT TO TREAT	631	631
No. Excluded from INTENT TO TREAT	-	-
No. Included in SAFETY	631	631
No. Excluded from SAFETY	-	-
No. Included in PER PROTOCOL	558	537
No. Excluded from PER PROTOCOL	73	94

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More patients in the IV arm (15%) compared with the SC arm (12%) were excluded from the PP population. The most common reason for exclusion from the PP population in both arms was because of the background DMARD not remaining at a stable dose (38 patients in the SC arm vs. 37 patients in the IV arm).

Six patients (2 patients in the SC arm; 4 patients in the IV arm) were excluded from the PP population because of a treatment code break.

In 2011 an unscheduled health authority/ethics committee inspection occurred at a Lithuanian center. As a result of this inspection, critical findings related to GCP were reported. Nine of the 12 patients randomised at the site were eligible to be included in the per-protocol (PP) population, 6 in the SC arm and 3 in the IV arm. An ACR20 response at Week 24 was achieved in 2 of the 6 patients (33%) in the SC arm compared with 3 of 3 patients (100%) in the IV arm. Since removal of these patients would favor the efficacy of the SC arm, it was decided to maintain patients randomized to this site in the analysis in order to be conservative in the primary analysis, which was based on the PP population. No sensitivity analysis was performed on the data. All 12 patients were included in the intent-to-treat (ITT) population. Data from the 12 patients were also included in the safety population as a conservative approach.

Outcomes and estimation

The data presented are based on the primary analysis, which was conducted after all patients had completed the double-blind treatment period, i.e. 24 weeks of study treatment unless prematurely withdrawn.

The population used for the primary and secondary analyses was the PP population. The ITT population was used for sensitivity analysis of the primary endpoint.

Table 21. Overview of efficacy (PP population)

	162 mg SC qw + DMARD n = 558	8 mg/kg IV q4w + DMARD n = 537
Primary endpoint: percentage of ACR20 responders at Week 24		
Percentage of ACR20 responders	69.4%	73.4%
Weighted difference (95% CI)	–4.0 (–9.2, 1.2)	
Sensitivity analysis, ITT population	n = 631	n = 631
Percentage of ACR20 responders	67.7%	70.2%
Weighted difference (95% CI)	–2.7 (–7.6, 2.2)	
Secondary endpoints at Week 24		
ACR50 responders, n (%)	262 (47.0)	261 (48.6)
Weighted difference (95% CI)	–1.8 (–7.5, 4.0)	
ACR70 responders, n (%)	134 (24.0)	150 (27.9)
Weighted difference (95% CI)	–3.8 (–9.0, 1.3)	
DAS remission (< 2.6), n (%)	198 (38.4)	184 (36.9)
Weighted difference (95% CI)	0.9 (–5.0, 6.8)	
Decrease in HAQ-DI ≥ 0.3, n (%)	336 (65.2)	337 (67.4)
Weighted difference (95% CI)	–2.3 (–8.1, 3.4)	
Withdrawal due to lack of therapeutic response, n (%)	10 (1.8)	5 (0.9)
Weighted difference (95% CI)	0.9 (–0.9, 2.7)	

ACR = American College of Rheumatology; CI = confidence interval; DAS = disease activity score; DMARD = disease-modifying anti-rheumatic drug; HAQ-DI = Health Assessment Questionnaire–Disability Index; ITT = intent to treat; IV = intravenous; LOCF = last observation carried forward; PP = per protocol; SC = subcutaneous.

Ancillary analyses

Subgroup analysis

Table 22. ACR20, ACR 50 and ACR 70 response rates at week 24 by bodyweight (PP population)

ACR Response by Body Weight at Baseline	No. of Patients (%)	
	162 mg SC qw+DMARD (n=558)	8 mg/kg IV q4w+DMARD (n=537)
ACR20 response		
<60 kg	99/131 (75.6)	100/129 (77.5)
60–100 kg	260/374 (69.5)	264 358 (73.7)
≥100 kg	28/53 (52.8)	30/50 (60.0)
ACR50 response		
<60 kg	66/131 (50.4)	71/129 (55.0)
60–100 kg	176/374 (47.1)	177 358 (49.4)
≥100 kg	20/53 (37.7)	13/50 (26.0)
ACR70 response		
<60 kg	31/131 (23.7)	47/129 (36.4)
60–100 kg	96/374 (25.7)	100/358 (27.9)
≥100 kg	7/53 (13.2)	3/50 (6.0)

ACR=American College of Rheumatology; DMARD=disease-modifying anti-rheumatic drug; IV=intravenous; pp=per protocol; q4w=every 4 weeks; qw=once weekly; SC=subcutaneous.

Table 23. ACR20, ACR 50 and ACR 70 response rates at week 24 by region (PP population)

ACR Response by Region	No. of Patients (%)	
	162 mg SC qw+DMARD (n=558)	8 mg/kg IV q4w+DMARD (n=537)
ACR20 response		
Europe	135/180 (75.0)	125/170 (73.5)
Rest of world	68/84 (81.0)	68/80 (85.0)
North America	78/152 (51.3)	86/147 (58.5)
South America	106/142 (74.6)	115/140 (82.1)
ACR50 response		
Europe	86/180 (47.8)	78/170 (45.9)
Rest of world	48/84 (57.1)	54/80 (67.5)
North America	49/152 (32.2)	43/147 (29.3)
South America	79/142 (55.6)	86/140 (61.4)
ACR70 response		
Europe	37/180 (20.6)	50/170 (29.4)
Rest of world	27/84 (32.1)	25/80 (31.3)
North America	23/152 (15.1)	23/147 (15.6)
South America	47/142 (33.1)	52/140 (37.1)

ACR=American College of Rheumatology; DMARD=disease-modifying anti-rheumatic drug; IV=intravenous; pp=per protocol; q4w=every 4 weeks; qw=once weekly; SC=subcutaneous.

Source: page 555.

Study WA22762 LTE

Results

Participant flow

The first patient was screened on 18 August 2010 and the first patient was randomized on 1 September 2010. The last patient was randomized on 1 August 2011 and the date of the clinical cut-off was 16 January 2012.

From 2157 patients screened, a total of 1262 patients at 209 centers in 25 countries were randomized into the study: 631 to TCZ SC and 631 to TCZ IV. The main reason for screen failure was CRP < 10 mg/L (1 mg/dL) and ESR < 28 mm/h prior to baseline.

All of the 1262 patients received at least one dose of study medication. Of the 1262 patients, 572 patients (91%) in the TCZ SC arm and 564 (89%) in the TCZ IV arm completed the double-blind phase to Week 24; 59 patients (9%) in the SC arm and 67 patients (11%) in the IV arm withdrew from the study before reaching Week 24. One patient in the IV arm completed Week 24 but subsequently withdrew before re-randomization due to lack of therapeutic response.

At Week 24, patients from the SC arm were re-randomized in a ratio of 11:1 to SC and IV, respectively, whilst patients from the IV arm were re-randomized in a ratio of 2:1 to IV and SC, respectively. The re-randomization resulted in 48 patients in the SC arm being re-randomized to IV (SC-IV switch arm) and 524 patients continuing with SC (SC arm).

In the IV arm, the re-randomization resulted in 186 patients being re-randomized to SC (IV-SC switch arm) and 377 patients continuing with IV (IV arm).

As of the clinical cut-off date of 16 January 2012, 21/524 (4.0%) patients in the SC arm and 17/377 (4.5%) patients in the IV arm had withdrawn prematurely since re-randomization (i.e. during the open-label period). Thus, overall, including the 59 patients who were withdrawn during the double-blind period from the SC arm and the 68 patients who were withdrawn from the IV arm, a total of 80/583 (13.7%) patients in the SC arm and 85/445 (19.1%) patients in the IV arm had withdrawn prematurely from the study by the time of the clinical cut-off. In the SC-IV and IV-SC switch arms, there were 1/48 (2.1%) and 7/186 (3.8%) withdrawals, respectively, between re-randomization and the clinical cut-off date.

Baseline data

Overall, the baseline demographic characteristics were well balanced across the treatment arms. The majority of patients in each treatment arm were female (75% to 84% across arms), white (74% to 83% across arms), and of non-hispanic ethnicity (65% to 70% across arms). The mean age ranged from 52.2 to 54.7 years across arms. The majority of patients weighed between 60 and <100 kg (67% to 69% across arms), with 22% to 25% weighing < 60 kg and 6% to 10% weighing ≥ 100 kg. The maximum weight was capped at 150 kg (per the exclusion criterion). The majority of patients in all arms had never smoked (60% to 65% across arms) and had no known family history of chronic heart disease (73% to 82% across arms).

The SC and IV treatment arms were well balanced with respect to RA disease characteristics at baseline. Baseline RA disease characteristics in the smaller IV-SC and SC-IV switch arms were

comparable with those in the IV and SC arms, respectively. Some differences between arms were observed for baseline anti-CCP positivity, RF positivity, and certain ACR core set parameters.

Numbers analysed

Table 24. Overview of analysis population (all patients)

	162 mg SC qw + DMARD	8 mg/kg IV q4w + DMARD	IV-SC	SC-IV
PP population, n	473	338	161	44
ITT population, n	524	377	186	48
PK evaluable population, n	583[a]	445[a]	186	48
Safety population, n	631[b]	631[b]	186	48

a Includes patients who were withdrawn during the double-blind period.

b Safety data from patients who switched treatment at Week 25 are included in the SC and IV arms up to the point of switch but in the SC-IV and IV-SC arms, respectively, after switch.

Source: page 203.

Based on the original randomized SC and IV populations, 110/583 (18.9%) patients in the SC arm and 107/445 (24.0%) patients in the IV arm were excluded from the PP population; the most common reason for exclusion in these arms was not being re-randomized at Week 24 due to withdrawal during the double-blind period. The next most common reason was the background DMARD not remaining at a stable dose.

Outcomes and estimation

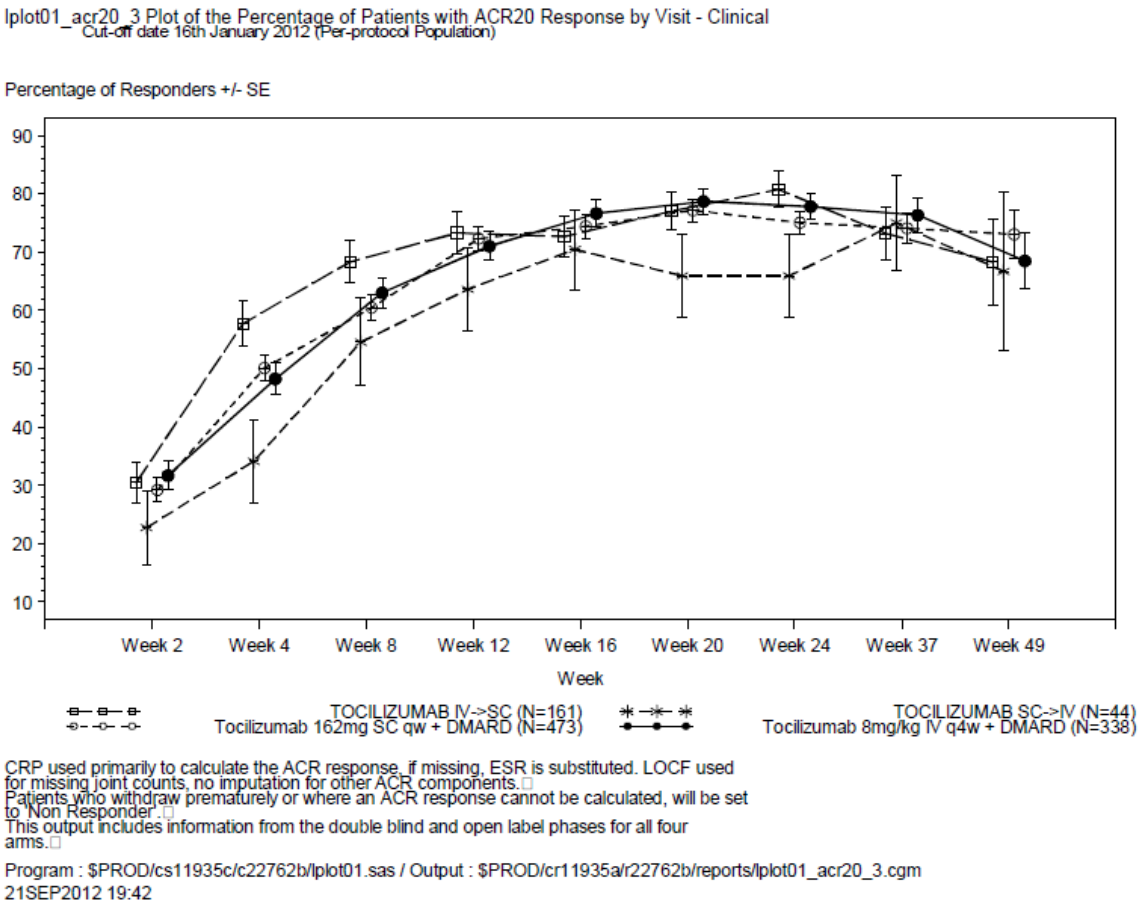
Table 25. Overview of efficacy results up to week 49 (PP population)

	No. Patients (%)			
	162 mg SC qw +DMARD n = 473	8 mg/kg IV q4w +DMARD n = 338	IV-SC n = 161	SC-IV n = 44
ACR20 response rate [Section 5.2.1]				
Week 24	355/473 (75%)	263/338 (78%)	130/161 (81%)	29/44 (66%)
Week 37	203/274 (74%)	155/203 (76%)	71/97 (73%)	21/28 (75%)
Week 49	84/115 (73%)	63/92 (69%)	28/41 (68%)	8/12 (67%)
ACR50 response rate [Section 5.2.2]				
Week 24	238/473 (50%)	176/338 (52%)	85/161 (53%)	22/44 (50%)
Week 37	146/274 (53%)	96/203 (47%)	49/97 (51%)	14/28 (50%)
Week 49	59/115 (51%)	38/92 (41%)	14/41 (34%)	5/12 (42%)
ACR70 response rate [Section 5.2.3]				
Week 24	127/473 (27%)	105/338 (31%)	45/161 (28%)	7/44 (16%)
Week 37	80/274 (29%)	60/203 (30%)	26/97 (27%)	10/28 (36%)
Week 49	39/115 (34%)	27/92 (29%)	7/41 (17%)	4/12 (33%)
Decrease in HAQ-DI ≥ 0.22 [Section 5.4]				
Week 24	343/468 (73%)	249/337 (74%)	123/161 (76%)	30/43 (70%)
Week 37	209/267 (78%)	142/196 (72%)	63/92 (69%)	18/25 (72%)
Week 49	84/107 (79%)	62/88 (71%)	29/38 (76%)	5/9 (56%)
Decrease in HAQ-DI ≥ 0.30 [Section 5.4]				
Week 24	307/468 (66%)	229/337 (68%)	107/161 (67%)	26/43 (61%)
Week 37	176/267 (66%)	129/196 (66%)	56/92 (61%)	16/25 (64%)
Week 49	76/107 (71%)	58/88 (66%)	25/38 (66%)	5/9 (56%)
DAS-ESR remission (< 2.6) [Section 5.6]				
Week 24	180/467 (39%)	122/335 (36%)	61/160 (38%)	16/43 (37%)
Week 37	110/260 (42%)	77/193 (40%)	37/90 (41%)	13/26 (50%)
Week 49	47/105 (45%)	30/87 (35%)	18/37 (49%)	8/10 (80%)
Withdrawal due to lack of therapeutic response [Section 5.7] [a]				
	3/473 (0.6%)	3/338 (0.9%)	1/161 (0.6%)	0/44 (0%)

ACR = American College of Rheumatology; DAS = disease activity score; DMARD = disease-modifying antirheumatic drug; HAQ-DI = Health Assessment Questionnaire–Disability Index; IV = intravenous; PP = per protocol; SC = subcutaneous.

a Based on data collected during the double blind and open label phases up to the clinical cut off.

Figure 9. Plot of the percentage with ACR 20 response by visit (PP population)



SC and IV Arms

Within the SC and IV treatment arms, ACR20 response rates tended to be higher in patients weighing <60 kg (78% to 85% SC vs. 82% to 87% IV) and 60 to <100 kg (75% to 76% SC vs. 71% to 78% IV) compared with patients weighing ≥ 100 kg (55% to 58% SC vs. 39% to 59% IV) from Weeks 24 to 49. The same was true for ACR50 and ACR70 response rates.

Within subgroups, ACR20 response rates in the SC and IV arms were comparable at Weeks 24 and 37 in all three body weight categories. The same was true in the <60 and 60 to <100 kg subgroups at Week 49. In the ≥ 100 kg subgroup, the response rate at Week 49 was higher in the SC arm than in the IV arm (58% vs. 39%); however, Week 49 data for the ≥ 100 kg subgroup should be interpreted with caution due to the low patient numbers (N=19 SC and 13 IV).

More variability was observed for ACR50 and ACR70 responses. Response rates in the SC arm tended to be lower than those of the IV arm in the <60 kg subgroup but comparable with or higher than those of the IV arm in the 60 to <100 kg and ≥ 100 kg subgroups.

IV-SC and SC-IV Switch Arms

Meaningful analyses of ACR20/50/70 by body weight at baseline were not possible for the switch arms due to the low numbers of patients and responses, particularly at the week 49 time point.

Pharmacodynamics

Mean sIL-6R concentrations were generally comparable in the SC and IV arms during both the double-blind and open-label extension periods, but with an overall trend for slightly higher concentrations following SC dosing.

Mean CRP concentrations in the SC arm were lower than in the IV arm at all time points between Week 4 and Week 37. At Week 49, mean concentrations were 0.11 mg/dL in the SC arm and 0.18 mg/dL in the IV arm. The trend for lower mean CRP concentrations in the SC arm compared with the IV arm is consistent with the observed trend for higher sIL-6R concentrations in the SC arm compared with the IV arm.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 26. Study NA25220

Title: A randomized, double-blind, parallel-group study of safety and the effect on clinical outcome of tocilizumab SC versus placebo SC in combination with traditional disease modifying anti-rheumatic drugs (DMARDs) in patients with moderate to severe active rheumatoid arthritis.			
Study identifier	NA 25220 / NA 25220 LTE		
Design			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks not applicable 72 weeks (open label)	
Hypothesis	Superiority		
Treatments groups	TCZ SC		TCZ 162 mg SC q2w in combination with DMARDs
	Placebo		Placebo SC q2w in combination with DMARDs
Endpoints and definitions	Primary endpoint	ACR 20	At least a 20% improvement compared with baseline in both TJC68 and SJC66, as well as in three out of five of the additional parameters
	Secondary endpoints	ACR 20/50/70 DAS 28 DAS ‹ 2,6 (DAS remission) DAS responder (EULAR) mTSS HAQ-DI	
Database lock	NA25220 (24 Week): completed NA25220LTE (72 week): 28 May 2012		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat Endpoint comparison at week 24		
Primary Analysis	Treatment group	TCZ SC	Placebo
	Number of subject	n=437	n =219
	ACR20 n (%)	266 (60.9%)	69 (31.5%)
Effect estimate per comparison	ACR20 Response	TCZ SC - Placebo	
		Weighted difference	29.5%
		95%-CI	(22.0, 37.0)
		P-value	p‹ 0.0001

Analysis description	**Secondary analyses**		
Results per parameter If not stated otherwise: TCZ: N = 437 Placebo: N = 219	Parameter	TCZ SC	Placebo
	ACR50 Response rate Weighted difference (95%-CI) p-value	39.8% 27.9 (21.5, 34.4) p < 0.0001	12.3%
	ACR70 Response rate Weighted difference (95%-CI) p-value	19.7% 14.8 (9.8, 19.9) p < 0.0001	5.0%
	DAS28 Change N Mean Weighted difference (95%-CI) p-value	344 -3.1 −1.4 (−1.7, −14.1) p < 0.0001	123 -1.7
	TJC change N mean Weighted difference (95%-CI) p-value	432 -14.2 6.4 (−8.5, −4.3) p < 0.0001	219 -7.8
	SJC change N mean weighted difference (95%-CI) p-value	432 -9.3 −3.7 (−5.1, −2.3) p < 0.0001	219 -5.5
	CRP change N mean weighted difference (95%-CI) p-value	345 -1.6 −1.2 (−1.4, −1.0) p < 0.0001	124 -0.4
	ESR change N mean	347 -35.6	124 -12.0

	weighted difference (95%-CI) p-value	−23.6 (−26.7, −20.5) p < 0.0001
	DAS LDA (≤ 3.2) N Responder weighted difference (95%-CI) p-value	 374 124 45.2% 15.3% 30.3 (22.0, 38.6) p < 0.0001
	DAS Response N Responder p-value	 374 138 41.7% 13.8% p < 0.0001
	mTSS at week 24 N Mean (SD) p-value	 391 186 0.62 (2.69) 1.23 (2.82) 0.0149
	ACR20 median time to onset Days p-value	 57 86 p < 0.0001
	Change in hemoglobin N Mean Difference (95%-CI) p-value	 344 123 8.7 0.2 8.5 (6.6, 10.3) p < 0.0001
	Patient global VAS change N Mean Difference (95%-CI) p-value	 346 123 −29.3 −19.8 −9.4 (−14.0, −4.9) p < 0.0001
	Pain VAS change N Mean Difference (95%-CI) p-value	 346 123 −24.9 −13.6 −11.2 (−15.6, −6.9) p < 0.0001
	Physician's global VAS change N Mean Difference (95%-CI) p-value	 348 124 −34.3 −28.7 −5.6 (−9.4, −1.7) p = 0.0048
	HAQ-DI change N Mean Difference (95%-CI) p-value	 348 124 −0.4 −0.3 −0.2 (−0.3, 0.0) p = 0.0054
	Decrease ≥ 0.3 in HAQ N Responder Difference (95%-CI) p-value	 348 124 58.0% 46.8% 12.1 (2.2, 22.0) p = 0.0170
	SF-36 (physical) change N Mean Difference (95%-CI) p-value	 347 123 5.3 2.9 2.4 (1.0, 3.8) p = 0.0006

	SF-36 (mental) change N Mean Difference (95%-CI) p-value	 347 6.5 2.7 (0.7, 4.6) p = 0.0068	 123 3.8
	ACR50 median time to onset Days p-value	 115 p < 0.0001	 Not reached
	ACR70 median time to onset Days p-value	 174 p < 0.0001	 Not reached

Table 27. Study WA22762

Title: A randomized, double-blind, parallel group study of the safety and effect on clinical outcome of tocilizumab SC versus tocilizumab IV, in combination with traditional disease-modifying anti-Rheumatic Drugs (DMARDs), in patients with moderate to severe active rheumatoid arthritis.			
Study identifier	WA 22762		
Design			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks not applicable 72 weeks (open label)	
Hypothesis	Non-inferiority with regard to ACR20 response at week 24 of TCZ SC treatment compared to TCZ IV		
Treatments groups	TCZ SC		TCZ 162 mg SC qw in combination with DMARDs
	TCZ IV		TCZ 8 mg/kg IV q4w in combination with DMARDs
Endpoints and definitions	Primary endpoint	ACR20 response	defined as at least a 20% improvement compared with baseline in both TJC68 and SJC66, as well as in three out of five of the additional parameters
	Secondary endpoints	ACR 50/70 DAS 28 DAS ‹ 2.6 (DAS remission) HAQ-DI Withdrawal due to lack of therapeutic response	
Database lock	WA22762 (24 Week): completed WA22762 LTE (72 week): 16 January 2012		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Intent to treat TCZ 162 mg SC q2w = 631 TCZ 8 mg/kg IV q4w = 631 Per-Protocol (PP) population (primary analysis population for non-inferiority) TCZ 162 mg SC q2w = 558 TCZ 8 mg/kg IV q4w = 537 Endpoint comparison at week 24		
Primary Analysis	Treatment group	TCZ SC	TCZ IV
	Number of subject	558	537
	ACR 20 n(%)	387 (69.4 %)	394 (73.4 %)
Effect estimate per comparison	ACR20 Response	TCZ SC – TCZ IV	
		Weighted difference	-4%
		95%-CI	(-9.2, 1.2)
Notes	As the lower limit of the 95% CI for the difference in response rates (-9.2) is above the pre-defined non-inferiority margin (-12%), non-inferiority of TCZ SC compared to TCZ IV with regard to ACR20 has been proven.		
Analysis description			
Sensitivity analysis (non-inferiority analysis based on ITT population)		TCZ SC N = 631	TCZ IV N = 631
	ACR20 Response N (%) Weighted difference (95%-CI)	427 (67.7) −2.7 (−7.6, 2.2)	443 (70.2)
Secondary analyses *If not stated otherwise secondary analyses are based on PP population*		TCZ SC N = 558	TCZ IV N = 537
	ACR50 Response N (%) Weighted difference (95%-CI)	262 (47.0) −1.8 (−7.5, 4.0)	261 (48.6)
	ACR70 Response N (%) Weighted difference (95%-CI)	134 (24.0) −3.8 (−9.0, 1.3)	150 (27.9)
	DAS Remission N (%) Weighted difference (95%-CI)	198 (38.4) 0.9 (−5.0, 6.8)	184 (36.9)
	Decrease ≥ 0.3 in HAQ N (%) Weighted difference (95%-CI)	336 (65.2) −2.3 (−8.1, 3.4)	337 (67.4)
	Withdrawal due to lack of therapeutic response N (%) Weighted difference (95%-CI)	10 (1.8) 0.9 (−0.9, 2.7)	5 (0.9)

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

A comparative analysis of the week 24 efficacy results from the pivotal SC studies NA25220 and WA22762 were provided and with the 24-week historical IV data. The analysis is based on summary data (ITT population) of:

- Study WA22762 Week 24
- Study NA25220 Week 24
- 24-week historical Pooled IV

Furthermore long-term maintenance of efficacy for patients treated up to 1 year is analysed. The analysis is based on summary data (ITT population) of:

- Study WA22762-LTE
- Study NA25220-LTE
- All Exposure Historical Pooled IV LTE

Disposition of patients

A total of 1918 patients were enrolled in the pivotal Phase III SC program: 1262 patients in study WA22762 and 656 in study NA25220. Of the 1918 patients randomized into the two pivotal studies, 1755 patients (92%) completed the 24-week period of the study.

Table 28. Disposition of the pivotal studies (all randomized patients)

Study	Treatment Arms	Ran-do-mized	With-drawn Prior to Week 24	Escap-ed Prior to Week 24	Com-pleted Week 24	Treatment Arms in LTE Period	Re-Ran-domized	Withdrawn During OL LTE up to Clinical Cut-off	Escaped During OL LTE up to Clinical Cut-off	Com-pleted OL LTE up to Clinical Cut-off
WA22762	TCZ 162 mg SC qw + DMARD (PFS)	631	59 (9.4%)	NA	572 (91%)	TCZ 162 mg SC qw (PFS)	524	21 (4.0%)	NA	503
						TCZ 8 mg/kg IV q4w	48	1 (2.1%)	NA	47
	TCZ 8 mg/kg IV q4w + DMARD (PFS)	631	67 (10.6%)	NA	564 (89%)	TCZ 8 mg/kg IV q4w	377	17 (4.5%)	NA	360
						TCZ 162 mg SC qw (PFS)	186	7 (3.8%)	NA	179
NA25220	TCZ 162 mg SC q2w + DMARD (PFS)	437 [a]	26 (5.9%)	72	410 [b] (94%)	TCZ 162 mg SC q2w (AI)	167	6 (3.6%)	2	161
						TCZ 162 mg SC q2w (PFS)	167	3 (1.8%)	3	164
	PBO SC q2w + DMARD (PFS)	219 [a]	7 (3.2%)	90	209 [b] (96%)	TCZ 162 mg SC q2w (AI)	59	0 (0.0%)	1	59
						TCZ 162 mg SC q2w (PFS)	60	2 (3.3%)	1	58
MRA229JP	TCZ 162 mg SC q2w (PFS)	174	12 [c]	NA	161					
	TCZ 8 mg/kg IV q4w	174	12 [c]	NA	161					
NP22623	TCZ 162 mg SC qw + MTX [d]	14	0 [e]	NA	14 [e]					
	TCZ 162 mg SC q2w + MTX [d]	15	1 [e]	NA	14 [e]					

TCZ = tocilizumab; DMARD = disease modifying anti-rheumatic drug; MTX – methotrexate; SC = subcutaneous; IV = intravenous; qw = once weekly; q2w / q4w = once every 2/4 weeks; OL = open label; LTE = Long-term extension; PFS = pre-filled syringe; AI = autoinjector

[a] Treated patients (received at least one dose of study medication) included 438 in the TCZ arm and 218 in the placebo arm.
[b] Includes escape patients. [c] An additional 1 patient from each arm never received treatment.
[d] Received via vial + syringe. [e] At Week 12 in this study, not Week 24.

Source: WA22762:Section 4.1, WA22762-LTE:Section 4.1, NA25220:Section 4.1, NA25220-LTE:Section 4.1, MRA229JP:Section 10.1, NP22623:Section 4.1

The historical 24-week IV data used for comparison included four Phase III studies.

Table 29. Disposition in historical 24 weeks IV studies (all patients)

	WA17822	WA17823	WA18063	WA18062
Total Randomized	**623**	**1196**	**1220**	**499**
Placebo + DMARD*	204	394	415	161
TCZ 4 mg/kg + MTX	214	401		164
TCZ 8 mg/kg + DMARD*	205	401	805	174
Received Study Medication	**622**	**1190**	**1216**	**498**
Placebo + DMARD*	204	392	414	160
TCZ 4 mg/kg + MTX	212	399		163**
TCZ 8 mg/kg + DMARD*	206	399	802	175**
Completed 24 weeks (initial therapy)				
Placebo + DMARD*	124 (91%)	215 (88%)	325 (78%)	64 (40%)
TCZ 4 mg/kg + MTX	157 (86%)	308 (93%)		108 (66%)
TCZ 8 mg/kg + DMARD*	174 (93%)	326 (91%)	732 (91%)	132 (76%)
Completed 24 weeks (escape therapy)				
Placebo + DMARD*	65 (96%)	141 (94%)	45 (100%)	63 (95%)
TCZ 4 mg/kg + MTX	28 (90%)	65 (97%)		30 (97%)
TCZ 8 mg/kg + DMARD*	18 (95%)	40 (98%)	19 (100%)	20 (100%)
Completed 24 weeks (of initial or escape therapy)				
Placebo + DMARD*	189 (93%)	356 (91%)	370 (89%)	127 (79%)
TCZ 4 mg/kg + MTX	185 (87%)	373 (93%)		138 (85%)
TCZ 8 mg/kg + DMARD*	192 (93%)	366 (92%)	751 (93%)	152 (87%)

DMARD = disease modifying anti-rheumatic drug; MTX – methotrexate; TCZ = tocilizumab.

Percentages are based on the number of patients in each randomized treatment group

* In Studies WA17822, WA17823 and WA18062 the DMARD received was MTX.

** In Study WA18062, one patient was randomized to receive TCZ 4 mg/kg + MTX, this patient actually received 6 mg/kg TCZ, and so was included in the TCZ 8 mg/kg + MTX group for all analyses.

Source: WA17822:Figure 2; WA17823:Figure 2; WA18063:Figure 2; WA18062:Figure 2

Baseline characteristics

Table 30. Key demographic parameters at baseline – Studies NA 25220 and WA22762 vs. historical pooled IV 24 week data

	Study WA22762		Study NA25220		Historical IV Data: Pooled 24-Week Phase III Studies		
	TCZ 162 mg SC qw + DMARD (N = 631)	TCZ 8 mg/kg IV q4w + DMARD (N = 631)	TCZ 162 mg SC q2w + DMARD (N = 437)	Placebo SC q2w + DMARD (N = 219)	TCZ 8 mg/kg IV q4w + DMARD (N = 1576)	TCZ 4 mg/kg IV q4w + MTX (N = 773)	Placebo IV q4w + DMARD (N = 1168)
Sex							
Male	18%	17%	14%	17%	18%	17%	18%
Female	82%	83%	86%	83%	82%	83%	82%
Race							
White	77%	76%	74%	69%	74%	75%	75%
Black	5%	4%	5%	6%	4%	4%	4%
Asian	7%	7%	4%	6%	8%	6%	8%
American Indian/ Alaska native	4%	4%	0.7%	0.5%	7%	6%	6%
Other race*	--	--	15%	17%	--	--	--
Other	0.3%	0.2%	1.4%	0.9%	6%	9%	7%
Not available **	7.3%	8.6%	--	--	--	--	--
Age (mean, years)	52.7	52.8	52.1	52.0	52.9	51.3	52.3
Weight (mean, kg)	74.6	74.4	70.3	70.0	72.8	73.0	73.5
Weight category (kg)							
< 60	22.8%	23.1%	27.2%	26.5%	23.9%	23.9%	24.4%
60 – < 100	67.4%	66.9%	66.8%	68.5%	68.1%	67.8%	66.2%
≥ 100	9.8%	10.0%	5.9%	5.0%	7.6%	7.8%	9.0%
Geographic region							
Europe	31.5%	31.4%	23.1%	22.4%	31.7%	40.6%	35.7%
North America	28.5%	28.7%	20.4%	20.5%	37.5%	29.1%	34.4%
South America	24.6%	24.6%	40.3%	40.6%	20.3%	20.4%	19.8%
Rest of World	15.4%	15.4%	16.2%	16.4%	10.5%	9.8%	10.1%

TCZ = tocilizumab; SC = subcutaneous; IV = intravenous; DMARD = disease modifying anti-rheumatic drug; MTX = methotrexate; qw = once weekly; q2w / q4w = once every 2/ 4 weeks.

* "Other race" was not a category in Study WA22762.

** "Not available" was not a category in Study NA25220.

Table 31. RA characteristics at baseline – Studies NA 25220 and WA22762 vs. historical pooled IV 24 week data (ITT population)

	Study WA22762		Study NA25220		Historical IV Data: Pooled 24-Week Phase III Studies		
	TCZ 162 mg SC qw + DMARD (N = 631)	TCZ 8 mg/kg IV q4w + DMARD (N = 631)	TCZ 162 mg SC q2w + DMARD (N = 437)	Placebo SC q2w + DMARD (N = 219)	TCZ 8 mg/kg IV q4w + DMARD (N = 1576)	TCZ 4 mg/kg IV q4w + MTX (N = 773)	Placebo IV q4w + DMARD (N = 1168)
Duration of RA (mean, years)	8.7	8.6	11.1	11.1	9.7	9.2	9.4
No. of previous DMARDs (mean)	1.4	1.4	1.3	1.4	1.8	2.1	1.9
Oral corticosteroid use	55%	54%	65%	57%	45%	37%	40%
Oral corticosteroid dose (mean, mg/day)	6.9	6.8	6.5	6.3	Not available		
RF positive	74%	74%	81%	82%	80%	78%	77%
Anti-CCP positive	72%	76%	84%	83%	Not available		
Failed prior anti-TNF treatment	23%	22%	20%	22%	10.8%	20.8%	13.5%

TCZ = tocilizumab; SC = subcutaneous; IV = intravenous; DMARD = disease modifying anti-rheumatic drug; MTX = methotrexate; qw = once weekly; q2w / q4w = once every 2/ 4 weeks; RF = rheumatoid factor; cycli citrullinated peptide; TNF = tumor necrosis factor.

Table 32. Mean ACR/DAS28 characteristics at baseline – Studies NA 25220 and WA22762 vs. historical pooled IV 24 week data (ITT population)

	Study WA22762		Study NA25220		Historical IV Data: Pooled 24-Week Phase III Studies		
	TCZ 162 mg SC qw + DMARD (N = 631)	TCZ 8 mg/kg IV q4w + DMARD (N = 631)	TCZ 162 mg SC q2w + DMARD (N = 437)	Placebo SC q2w + DMARD (N = 219)	TCZ 8 mg/kg IV q4w + DMARD (N = 1576)	TCZ 4 mg/kg IV q4w + MTX (N = 773)	Placebo IV q4w + DMARD (N = 1168)
DAS28	6.6	6.7	6.7	6.6	6.7	6.6	6.7
TJC (68 joints)	27.3	28.6	28.0	27.4	30.3	30.1	29.5
SJC (66 joints)	15.0	16.5	17.5	17.6	19.0	18.3	18.4
ESR (mm/hr)	51.7	52.0	50.8	49.4	48.2	47.9	49.1
CRP (mg/dL)	2.1	2.2	2.0	1.9	2.5	2.5	2.6
HAQ-DI score (0 – 3)	1.6	1.7	1.6	1.6	1.5	1.6	1.6
Patient global VAS (mm)	67.0	67.2	63.6	62.1	65.6	64.2	65.1
Patient pain VAS (mm)	59.7	61.5	57.8	56.8	58.6	57.4	58.0
Physician global VAS (mm)	61.3	62.5	61.1	61.8	63.7	63.5	63.9

DAS28 = disease activity score 28; TJC = tender joint count; SJC = swollen joint count; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; HAQ-DI = Health Assessment Questionnaire Disability Index; VAS = visual analoq scale; TCZ = tocilizumab; SC = subcutaneous; IV = intravenous; DMARD = disease modifying anti-rheumatic drug; MTX = methotrexate; qw = once weekly; q2w / q4w = once every 2/ 4 weeks.
Note: n's for each parameter varied from 623 to 631 in Study WA22762; from 434 to 427 for the TCZ arm and from 217 to 219 for the placebo arm of Study NA25220. See source documents for n's.

Baseline RA characteristics were balanced across the two SC pivotal studies and the historical pooled IV pooled studies, with the following exceptions:

- The mean duration of RA was longer in study NA25220 (11.1 years) than in Study WA22762 (8.6– 8.7 years) and the IV historical control studies (9.2– 9.7 years).
- The mean number of previous DMARDs was greater in the historical control studies (1.8–2.1 units) then in the two pivotal SC studies (1.3–1.4 units).
- The proportion of patients who were RF positive was also higher in study NA25220 (81 –82%) compared in study WA22762 (74%) and historical IV control (77 –80%). The proportion of patients receiving background oral corticosteroids was higher on both SC pivotal studies (54%– 55% on Study WA22762, 65%– 56% in study NA25220) compared with historical IV control (37–45%).

The proportion of patients who were anti–TNF-IRs was 20 – 23% across the four arms in the pivotal studies, reflecting the capping rule (the protocol stipulated the proportion of patients who failed one or more anti-TNF agents should be approximately 20%) but was lower in the historical pooled IV control population (10.8– 20.8% across the arms).

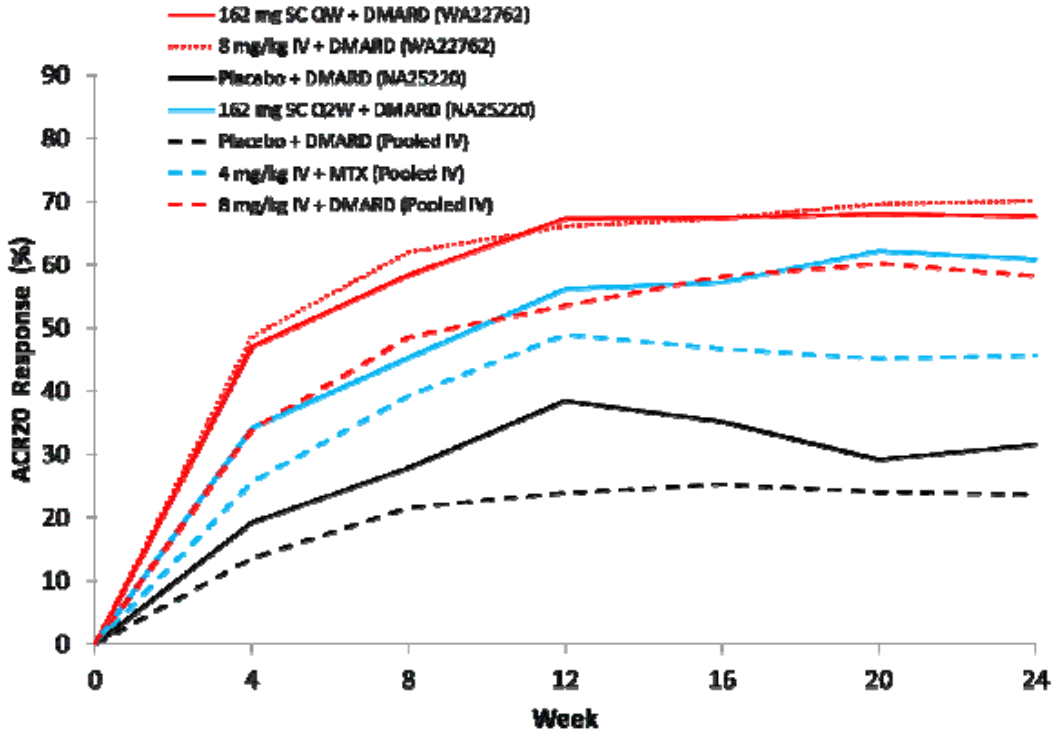
Outcomes

Table 33. Percentage with an ACR20/50/70 response at week 24 baseline – studies NA 25220 and WA22762 vs. historical pooled IV 24 week data (ITT population)

	Study WA22762		Study NA25220		Historical IV Data Pooled 24-Week Phase III Studies		
	TCZ 162 mg SC qw + DMARD (N = 631)	TCZ 8 mg/kg IV q4w + DMARD (N = 631)	TCZ 162 mg SC q2w + DMARD (N = 437)	Placebo SC q2w + DMARD (N = 219)	TCZ 8 mg/kg IV q4w + DMARD (N = 1576)	TCZ 4 mg/kg IV q4w + MTX (N = 773)	Placebo IV q4w + DMARD (N = 1168)
ACR20	67.7%	70.2%	60.9%	31.5%	58.2%	45.7%	23.7%
ACR50	45.5%	46.6%	39.8%	12.3%	36.1%	25.1%	8.8%
ACR70	23.6%	26.5%	19.7%	5.0%	17.8%	10.1%	2.2%

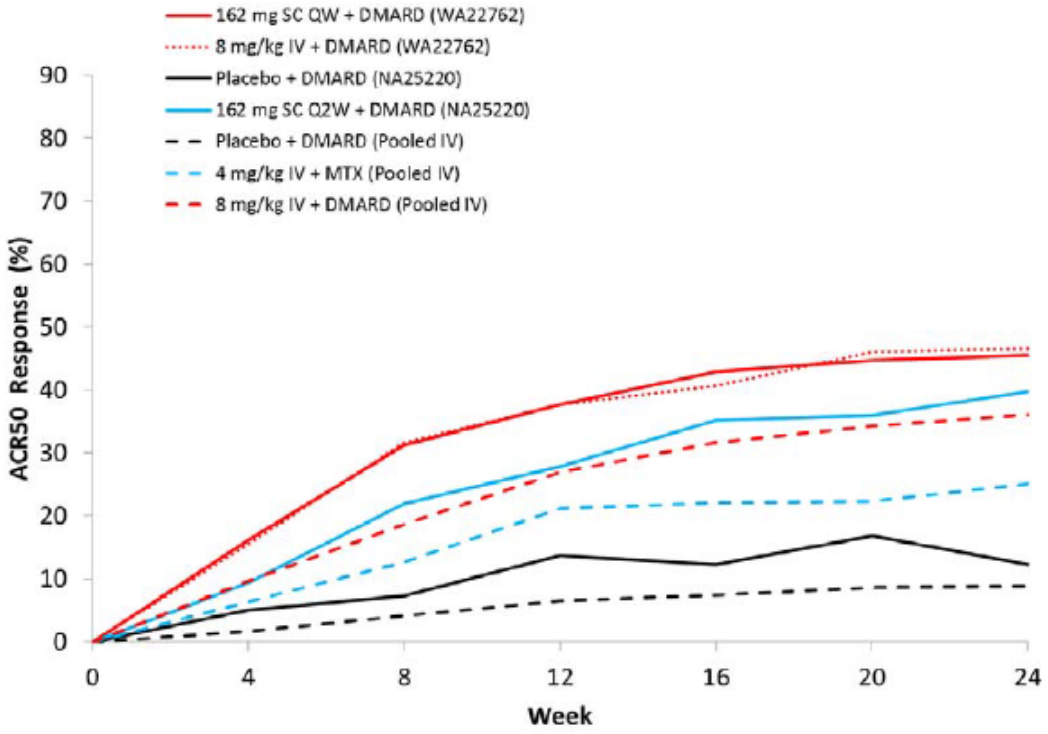
TCZ = tocilizumab; SC = subcutaneous; IV = intravenous; DMARD = disease modifying anti-rheumatic drug; qw = once weekly; q2w / q4w = once every 2/ 4 weeks.

Figure 10. ACR 20 response to week 24 (ITT population)



ACR = American College of Rheumatology; SC = subcutaneous; IV = intravenous; DMARD = disease modifying anti-rheumatic drug; MTX = methotrexate; qw = once weekly; q2w = once every 2 weeks.

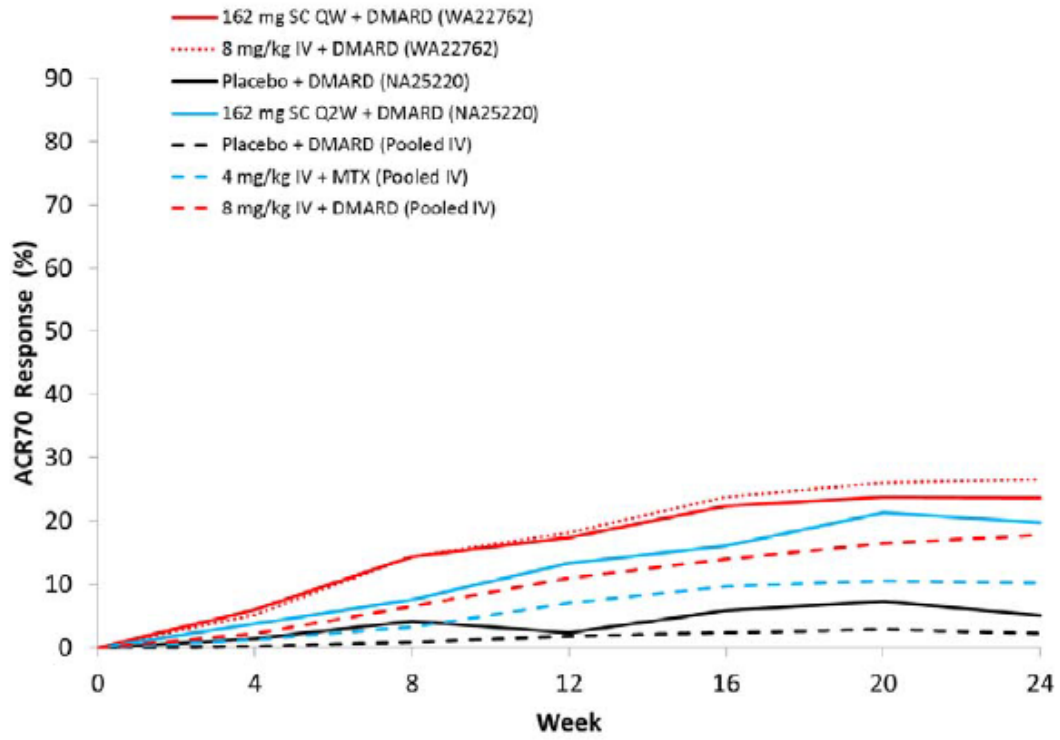
Figure 11. ACR 50 response to week 24 (ITT population)



ACR = American College of Rheumatology; SC = subcutaneous; IV = intravenous; DMARD = disease modifying anti-rheumatic drug; MTX = methotrexate; qw = once weekly; q2w = once every 2 weeks.

Source: eteprsp01_acrsp_24_1, etsum01_acr50_1, etacr205070_id003_pooli

Figure 12. ACR 70 response to week 24 (ITT population)



ACR = American College of Rheumatology; SC = subcutaneous; IV = intravenous; DMARD = disease modifying anti-rheumatic drug; MTX = methotrexate; qw = once weekly; q2w = once every 2 weeks.

Source: eteprsp01_acrsp_24_1, etsum01_acr70_1, etacr205070_id003_pooli

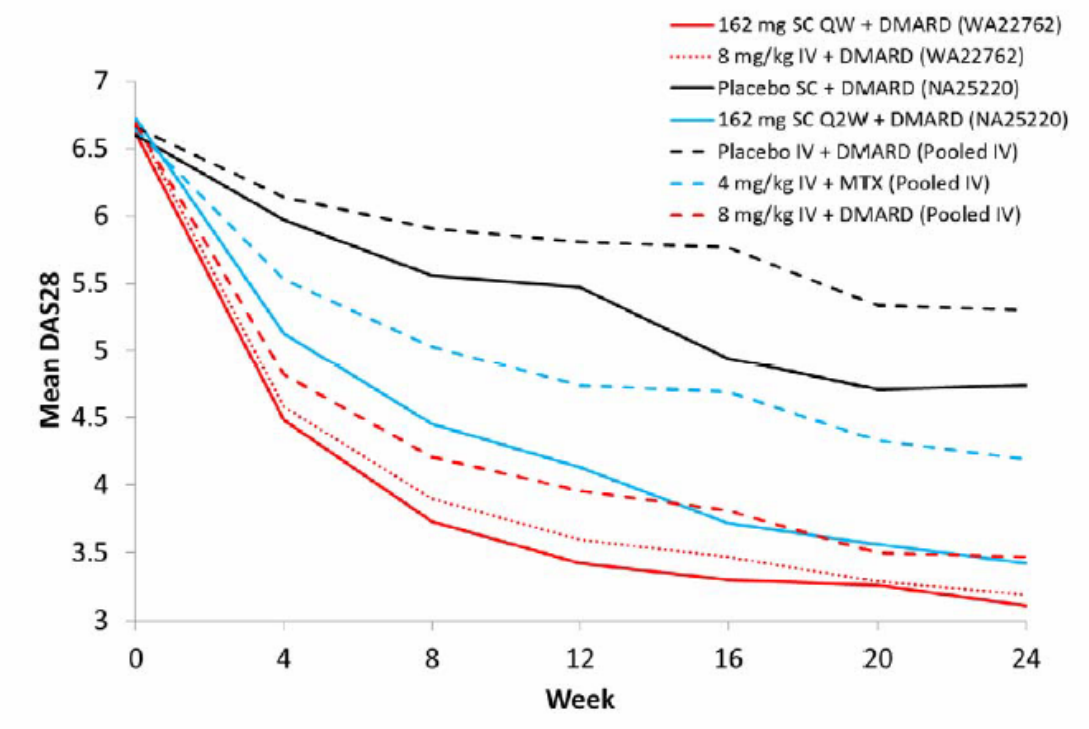
Over time, the ACR20/50/70 response profiles were similar for the SC and IV route of administration. Interestingly, at each time point, response rates for 8 mg/kg IV (WA22762) and placebo SC q2w (study NA25220) were higher on the SC pivotal studies than the historical pooled IV data.

The response profile for 162 mg SC qw in study WA22762 was comparable to 8 mg/kg IV.

Taking into account the different placebo rates for study NA25220 vs. historical pooled IV, the response rates for 162 mg SC q2w over time were lower than SC qw and more comparable to 4 mg/kg IV.

The same trend was observed for the DAS28 reduction over time up to week 24. Decreases were similar in the SC qw and IV arms of study WA22762 and greater than those in the q2w arm in study NA25220 at all time points. Compared with the historical IV data, and taking into account the different placebo rates on NA25220 vs. historical pooled IV, the mean changes with SC q2w fell between those from the 4 and 8 mg/kg historical IV groups.

Figure 13. DAS28 over time to week 24 (ITT population)



DAS28 = disease activity score; ITT = intent to treat; SC = subcutaneous; IV = intravenous; DMARD = disease modifying anti-rheumatic drug; MTX = methotrexate; qw = once weekly; q2w = once every 2 weeks.

Source: WA22762, etsum02_dascfb24_1; NA25220, etsum02_dascfb_preesc_1; Pooled Historical IV, etsumdas28vis_id003_pooli

Table 34. Percentage of ACR response at week 24 by weight - studies NA 25220 and WA22762 vs. historical pooled IV 24 week data (ITT population)

	Study WA22762		Study NA25220		Pooled IV Historical Data		
	TCZ 162 mg SC qw + DMARD (N = 631)	TCZ 8 mg/kg IV q4w + DMARD (N = 631)	TCZ 162 mg SC q2w + DMARD (N = 437)	Placebo SC q2w + DMARD (N = 219)	TCZ 8 mg/kg IV q4w + DMARD (N = 1576)	TCZ 4 mg/kg IV q4w + MTX (N = 773)	Placebo IV q4w + DMARD (N = 1168)
< 60 kg	(n = 144)	(n = 146)	(n = 119)	(n = 58)	(n = 377)	(n = 185)	(n = 286)
ACR20	74.3%	76.0%	63.0%	29.3%	63.7%	52.4%	23.4%
ACR50	50.0%	52.7%	43.7%	10.3%	37.7%	29.7%	8.7%
ACR70	23.6%	35.6%	23.5%	3.4%	19.9%	13.0%	2.1%
60–<100 kg	(n = 425)	(n = 422)	(n = 292)	(n = 150)	(n = 1073)	(n = 524)	(n = 773)
ACR20	68.0%	71.1%	62.0%	32.7%	56.9%	46.0%	24.5%
ACR50	45.6%	48.1%	40.8%	12.7%	36.0%	24.2%	8.5%
ACR70	25.2%	26.5%	19.5%	5.3%	17.4%	9.2%	1.9%
≥ 100 kg	(n = 62)	(n = 63)	(n = 26)	(n = 11)	(n = 120)	(n = 60)	(n = 105)
ACR20	50.0%	50.8%	38.5%	27.3%	53.3%	25.0%	18.1%
ACR50	33.9%	22.2%	11.5%	18.2%	33.3%	20%	10.5%
ACR70	12.9%	4.8%	3.8%	9.1%	15%	10%	4.8%

ACR = American College of Rheumatology; TCZ = tocilizumab; SC = subcutaneous; IV = intravenous; DMARD = disease modifying anti-rheumatic drug; MTX = methotrexate; qw = once weekly; q2w / q4w = once every 2/4 weeks.
Source: WA22762:eteprsp01_acrsp_wgt_24_1; NA25220:eteprsp01_acrsp_wgt_wk24_1; Pooled 24- Week IV: etsumacr20pool_id003_wk245; ACR50/70 for historical IV calculated from original filing outputs: etsumacrwgtwk24_ah338_pool_70.rp8, etsumacrwgtwk24_ah338_pool_50.rp8, etsumacrwgtwk24_ah338_062_70.rp8, etsumacrwgtwk24_ah338_062_50.rp8

Table 35. Percentage of ACR responders at week 24 by geographical region - studies NA 25220 and WA22762 vs. historical pooled IV 24 week data (ITT population)

	Study WA22762		Study NA25220		Historical IV Data Pooled 24-Week Phase III Studies		
Region Category	TCZ 162 mg SC qw + DMARD (N = 631)	TCZ 8 mg/kg IV q4w + DMARD (N = 631)	TCZ 162 mg SC q2w + DMARD (N = 437)	Placebo SC q2w + DMARD (N = 219)	TCZ 8 mg/kg IV q4w + DMARD (N = 1576)	TCZ 4 mg/kg IV q4w + MTX (N = 773)	Placebo IV q4w + DMARD (N = 1168)
North America	(n = 180) **47.8%**	(n = 181) **55.2%**	(n = 89) **38.2%**	(n = 45) **15.6%**	(n = 591) **47.5%**	(n = 225) **36.4%**	(n = 402) **20.4%**
South America	(n = 155) **74.2%**	(n = 155) **79.4%**	(n = 176) **65.3%**	(n = 89) **36.0%**	(n = 320) **69.1%**	(n = 158) **57.0%**	(n = 231) **35.9%**
Europe	(n = 199) **74.9%**	(n = 198) **70.7%**	(n = 101) **70.3%**	(n = 49) **42.9%**	(n = 500) **63.6%**	(n = 314) **46.2%**	(n = 417) **21.8%**
Rest of World	(n = 97) **79.4%**	(n = 97) **82.5%**	(n = 71) **64.8%**	(n = 36) **25.0%**	(n = 165) **58.8%**	(n = 76) **47.4%**	(n = 118) **17.8%**

ACR = American College of Rheumatology; TCZ = tocilizumab; SC = subcutaneous; IV = intravenous; DMARD = disease modifying anti-rheumatic drug; MTX = methotrexate; qw = once weekly; q2w / q4w = once every 2/4 weeks.
Source: WA22762:eteprsp01_acrsp_reg_24_1; NA25220:eteprsp01_acrsp_reg_wk24_1; Pooled 24- Week IV: etsumacr20pool_id003_wk244

Persistence of efficacy

Table 36. Percentage of ACR 20/50/70 responders by visit - studies NA 25220 and WA22762 vs. historical pooled IV 24 week data (ITT population)

	Study WA22762 (Open-Label Extension)			Study NA25220 (Open-Label Extension)		Historical IV Data
	TCZ 162 mg SC qw + DMARD (N=524)	TCZ 8 mg/kg IV q4w + DMARD (N=377)	TCZ IV → SC PFS (N=186)	TCZ 162 mg SC q2w PFS (N=167)	TCZ 162 mg SC q2w PFS → AI (N=167)	All Exposure Population Pooled (N=3368)
	n Responders	n Responders	n Responders	n Responders	n Responders	n Responders
Week 12	524	377	186	167	167	3302
ACR20	72.7%	71.4%	71.5%	65.9%	70.1%	51.2%
ACR50	40.3%	39.3%	43.5%	37.7%	31.7%	23.8%
ACR70	19.1%	21.2%	17.7%	21.0%	12.6%	9.0%
Week 24	524	377	186	167	167	3098
ACR20	74.8%	78.0%	79.6%	79.0%	77.2%	59.4%
ACR50	50.2%	52.3%	52.2%	53.9%	49.1%	33.7%
ACR70	27.1%	30.5%	28.0%	25.7%	24.6%	15.0%
Week 36/37*	309	225	113	74	77	2860
ACR20	73.8%	74.2%	76.1%	81.1%	67.5%	64.2%
ACR50	52.8%	47.1%	50.4%	51.4%	48.1%	38.8%
ACR70	30.1%	29.8%	26.5%	39.2%	28.6%	19.7%
Week 48/49**	129	96	47	19	19	2793
ACR20	69.0%	66.7%	70.2%	78.9%	73.7%	68.3%
ACR50	48.1%	40.6%	36.2%	52.6%	57.9%	43.6%
ACR70	32.6%	28.1%	19.1%	31.6%	10.5%	23.2%

ACR = American College of Rheumatology; TCZ = tocilizumab; SC = subcutaneous; IV = intravenous; DMARD = disease modifying anti-rheumatic drug; qw = once weekly; q2w / q4w = once every 2/4 weeks; PFS – pre-filled syringe; AI = autoinjector.

* Week 37 in Study WA22762.

** Week 49 in Study WA22762.

Source: WA22762-LTE: etacrsp01_acrsp_1, NA25220-LTE: etsum01_acr20_nowk24_noplc_1, etsum01_acr50_nowk24_noplc_1, etsum01_acr70_nowk24_noplc_1; All exposure pooled IV: etacr20507090_id003i

Clinical studies in special populations

In both studies NA25220 and WA22762, efficacy in various subgroups was evaluated. Notable differences in response were seen in both studies in the analysis by bodyweight. ACR 20, 50 and 70 response rates indicated a comparable response rate in the TCZ SC treatment group for all 3 parameters in the < 60 kg and in the 60 to < 100kg, whereas patients in the > 100 kg showed lower response rate for these parameters. Interestingly, for ACR 50 and 70 response in the highest body weight group was lower for the weight adjusted IV TCZ treatment than for the fixed SC TCZ dose.

Table 37. Study NA25220 LTE - ACR20, ACR 50 and ACR 70 response rates at week 36 by bodyweight (ITT population)

ACR Response by Body Weight	No. (%) of Patients: TCZ PFS q2w (N = 167) No. of Responders/n (%)	TCZ PFS q2w → TCZ AI q2w (N = 167) No. of Responders/n (%)	Placebo PFS q2w → TCZ PFS q2w (N = 60) No. of Responders/n (%)	Placebo PFS q2w → TCZ AI q2w (N = 59) No. of Responders/n (%)
ACR20 response				
<60 kg	12/15 (80.0)	15/20 (75.0)	7/8 (87.5)	5/6 (83.3)
60 to < 100 kg	46/56 (82.1)	33/50 (66.0)	10/17 (58.8)	16/21 (76.2)
≥100 kg	2/3 (66.7)	4/7 (57.1)	3/3 (100)	1/1 (100.0)
ACR50 response				
<60 kg	9/15 (60.0)	13/20 (65.0)	6/8 (75.0)	3/6 (50.0)
60 to < 100 kg	29/56 (51.8)	23/50 (46.0)	8/17 (47.1)	7/21 (33.3)
≥100 kg	0/3 (0.0)	1/7 (14.3)	2/3 (66.7)	1/1 (100.0)
ACR70 response				
<60 kg	6/15 (40.0)	9/20 (45.0)	2/8 (25.0)	2/6 (33.3)
60 to < 100 kg	23/56 (41.1)	13/50 (26.0)	4/17 (23.5)	2/21 (9.5)
≥100 kg	0/3 (0.0)	0/7 (0.0)	2/3 (66.7)	1/1 (100.0)

ACR20 = American College of Rheumatology 20% response; ACR50 = American College of Rheumatology 50% response; ACR70 = American College of Rheumatology 70% response; AI = Autoinjector; CRP = C-reactive protein; PFS = Pre filled syringe; q2w = Every 2 weeks.

Source: page 450.

Table 38. WA 22762 - ACR20, ACR 50 and ACR 70 response rates at week 24 by bodyweight (PP population)

ACR Response by Body Weight at Baseline	No. of Patients (%): 162 mg SC qw + DMARD (n = 558)	8 mg/kg IV q4w + DMARD (n = 537)
ACR20 response		
<60 kg	99/131 (75.6)	100/129 (77.5)
60–100 kg	260/374 (69.5)	264 358 (73.7)
≥100 kg	28/53 (52.8)	30/50 (60.0)
ACR50 response		
<60 kg	66/131 (50.4)	71/129 (55.0)
60–100 kg	176/374 (47.1)	177 358 (49.4)
≥100 kg	20/53 (37.7)	13/50 (26.0)
ACR70 response		
<60 kg	31/131 (23.7)	47/129 (36.4)
60–100 kg	96/374 (25.7)	100/358 (27.9)
≥100 kg	7/53 (13.2)	3/50 (6.0)

ACR = American College of Rheumatology; DMARD = disease-modifying anti-rheumatic drug; IV = intravenous; pp = per protocol; q4w = every 4 weeks; qw = once weekly; SC = subcutaneous.

Source: page 549.

Analysis of ACR response by regions revealed comparable response rates across the different regions (Europe, South America, others) but North America. Irrespective of the treatment

received, patients in North America demonstrated a lower response to therapy compared with those from other regions. This finding is consistent with the results from the historical IV data.

Supportive studies

Study MRA229JP

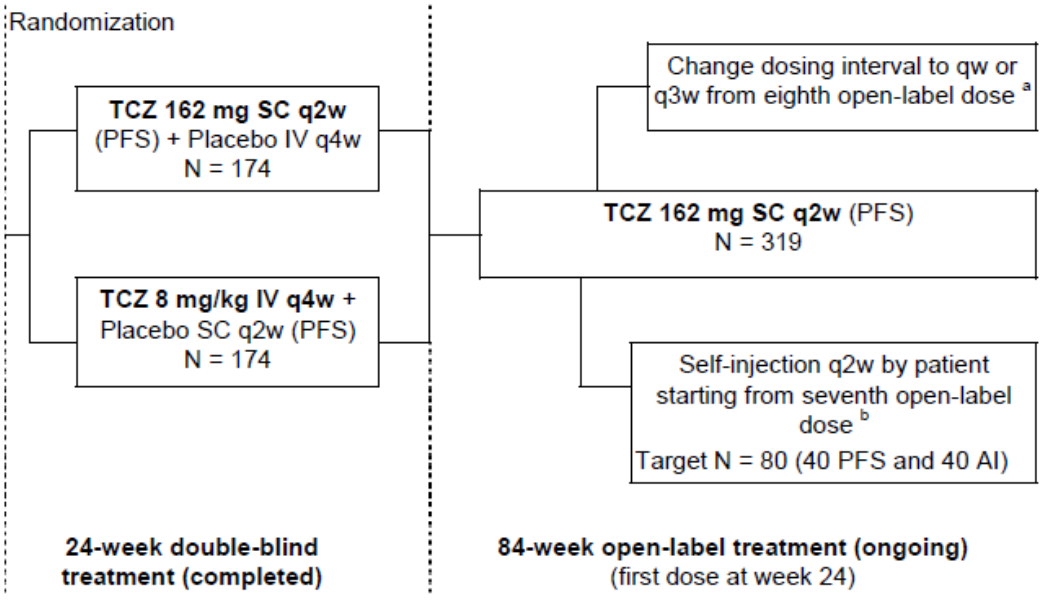
Study MRA229JP is an ongoing Phase III study comparing TCZ SC with TCZ IV as monotherapy in patients with RA.

The study objectives were to assess:

- The efficacy and safety of TCZ 162 mg SC q2w administered for 24 weeks in patients with RA.
- Efficacy and safety of long-term administration of TCZ SC (up to 108 weeks), including in patients who performed self-injections using either the PFS (same device as in studies WA22762 and NA25220) or the AI (same device as in study NA25220).

The primary endpoint was the ACR20 response rate at Week 24. Non-inferiority of TCZ SC was claimed if the lower bound of the adjusted 95% CI for the difference between the response rates, TCZ SC minus TCZ IV, was not smaller than – 18 percentage points. The non-inferiority limit was defined to ensure maintenance of at least 70% of the ACR20 response seen with TCZ 8 mg/kg IV q4w versus placebo in previous trials conducted by Chugai.

Figure 14. Design of monotherapy study MRA229JP



IV = intravenous; q2w / q3w / q4w = every 2/3/4 weeks; qw = once weekly; SC = subcutaneous; TCZ = tocilizumab; PFS = pre-filled syringe; AI = autoinjector.

[a] Starting after Week 36, at investigator discretion, the dosing interval could be increased to q3w if DAS28 < 3.2 for 24 weeks, or could be decreased to qw if a patient had less than a 20% improvement from baseline in swollen and tender joint count and CRP > 0.3 mg/dL and no notable clinically significant AEs.

[b] Starting at Week 36 in approximately 80 patients providing informed consent.

The study enrolled 348 RA patients who were randomized 1:1 to one of the two treatment arms; 12 patients in each arm were prematurely withdrawn during the double-blind period and one patient in each arm withdrew prior to administration of study drug. Withdrawals for AEs were reported in 3 and 9 patients in the TCZ SC and TCZ IV arm, respectively.

Table 39. Primary and secondary efficacy endpoints: ACR20/50/70 response rate at week 24 (PP population)

	TCZ 162 mg SC q2w N = 159	TCZ 8 mg/kg IV q4w N = 156
Primary Efficacy Parameter:		
ACR20 responders	126 (79.2%)	138 (88.5%)
Weighted difference (95% CI)	–9.4 (–17.6, –1.2)	
Secondary Efficacy Parameters:		
ACR50 responders	101 (63.5%)	105 (67.3%)
ACR70 responders	59 (37.1%)	64 (41.0%)

ACR = American College of Rheumatology; CI = confidence interval; TCZ = tocilizumab; SC = subcutaneous; IV = intravenous; q2w / q4w = once every 2/4 weeks. Analysis is adjusted for stratification factors body weight category (< 60 kg; ≥60 kg) and previous treatment with TNF antagonist (Yes, No); Last observation carried forward (LOCF) imputation was used for all ACR core set components. PP = per protocol.

Study NP22623

Study NP22623 was a Phase Ib, two-arm, randomized, open-label, parallel group, multi-centre 12-week study in patients with active RA who had an inadequate response to current MTX therapy. Patients received all SC injections into the abdominal region at the clinic by study site personnel, using a TCZ vial + syringe.

The objectives were to investigate PK, PD, efficacy and safety of in patients with active RA.

A total of 24 patients were planned (12 per group), however 29 (15 qw and 14 q2w) were randomized.

Patients in both groups showed clinical response, with 75% in the qw group and 64% in the q2w group showing an ACR20 response at Week 12, respectively, while the mean DAS28 score decreased from a value above 5.3 and 6.0 at baseline, respectively, for the qw and q2w groups to 2.9 in both treatment groups at Week 12. At least 50% of patients attained good response according to the EULAR classification at Week 12 in both groups.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical efficacy is supported by two pivotal Phase III trials (study NA25220 and study WA22762). Both of the pivotal studies were multi-centre, two-arm, randomized, double-blind, controlled trials.

The objectives of the studies were to assess the efficacy and safety of TCZ given subcutaneously.

Study WA22762 was active controlled, the comparator was TCZ IV and in study NA25220, the comparator was placebo. Both studies had 24-week double-blind periods followed by 72-week open-label extensions in which patients were re-randomized to four arms of various treatments.

In both studies, the open-label extensions are on going. The submission of the final clinical study report for study NA25220 and study WA22762 has been included as milestone in the RMP.

Patients with moderate to severe active RA who had an inadequate response to their current DMARD, which may have included one or more anti-TNF agents in up to 20% of patients, were enrolled into the study. In general the disease defining inclusion criteria applied for both studies; with the exception of SJC and TJC. Less diseased patients with regard to the number of swollen and tender joints were accepted for study WA 22762. However this had no impact on the disease characteristics; the baseline RA disease characteristics (i.e. baseline ACR and DAS characteristics) were consistent between studies. The study population was consistent with the population included in the Phase III IV TCZ program and represents the patients who receive IV TCZ. The disease duration was slightly longer in study NA25220 than in Study WA22762. Overall, the demographic characteristics and baseline criteria are well balanced between the two treatment groups as well as between the two pivotal studies.

In study NA25220, patients received TCZ 162 mg SC q2w or placebo SC q2w. Patients on escape therapy received open-label TCZ 162 mg SC PFS weekly. In study WA22762, patients received TCZ 162 mg SC qw or TCZ 8 mg/kg IV q4w. In both trials, study medication was given in combination with DMARD therapy. All patients had received at least one permitted non-biologic DMARD at a stable dose at least 8 weeks prior to baseline and throughout the study. All patients who completed to Week 24 were re-randomized for the open-label period (LTE) at Week 24. Although the applied SC TCZ dose was identical in both studies; the treatment schedule was different. The weekly schedule chosen for study WA22762 is supporting the claimed dosing regimen for this extension application. The approach to investigate in the two pivotal trials two different TCZ SC schemes namely TCZ 162 mg SC q2w and TCZ 162 mg SC qw, each tested against a different comparator is not fully comprehensible. The development program would have benefited from a head to head comparison of the TCZ SC regime which is intended to be recommended for therapeutic use i.e. TCZ SC qw with placebo, especially with regard to the safety evaluation. Furthermore a direct comparison of both TCZ SC schemes with the authorised TCZ IV 8 mg/kg q4w would have provided further meaningful results on the comparative efficacy.

For study NA25220 the primary efficacy objective was to demonstrate the superiority of TCZ SC versus placebo SC with respect to ACR20 response at Week 24. For the primary analysis, patients that received escape therapy were considered non-responders. Secondary objectives included prevention of progression of structural joint damage at Weeks 24 and 48; improvement

of physical function; long-term safety and efficacy; PK and PD of TCZ SC; and immunogenicity of TCZ SC.

The primary efficacy objective of study WA22762 was to demonstrate the non-inferiority of TCZ SC versus TCZ IV with respect to the ACR 20 response rate at Week 24. Secondary objectives included long-term efficacy; as well PK and PD of TCZ SC; immunogenicity of TCZ SC; and the effect of an IV to SC switch on the safety, efficacy, PK, and PD of TCZ. TCZ SC was considered to be non-inferior to TCZ IV if the lower limit of the 95% confidence interval (CI) for the difference in ACR20 response between the two treatment arms was not less than −12% (SC minus IV). If the primary hypothesis was rejected, the 95% CI calculated from the primary hypothesis test was to be used to test against a 10% non-inferiority limit. The MAH was requested during the evaluation to provide a clinical and statistical justification for the non-inferiority margin.

In providing the clinical rationale for the non-inferiority margin (NIM), the MAH considered that if the subcutaneous (SC) and intravenous (IV) doses to be studied in the pivotal study WA22762 were equivalent, due to natural variability, it is unlikely that the difference between the two doses in a clinical trial would be exactly equal to zero.

Therefore, assuming that the SC dose is marginally inferior to the IV dose, the MAH considered what treatment difference would be clinically acceptable. Presuming 2 or 3 out of 10 (20-30%) patients achieve an ACR20 response on methotrexate (MTX) alone, an additional 2 out of 10 patients (20%) achieving an ACR20 response provide a clinically meaningful difference between treatments. Thus, at least 20% more patients would need to achieve an ACR20 response at week 24 with tocilizumab (TCZ), compared to receiving MTX alone to provide a clinically meaningful difference.

To define the NIM, ACR20 response data from the per protocol population (PPP) of three Phase III studies of TCZ 8mg/kg IV + MTX (WA17823 - LITHE, WA17822 - OPTION and WA18063 - TOWARD) vs. placebo + MTX, were used. The populations in these three Phase III studies reflected the population in WA22762, namely patients with moderate to severe, active rheumatoid arthritis who were MTX-IR / DMARD-IR, with no more than 20% prior anti-TNF use. The TCZ 8mg/kg IV ACR20 responses at week 24 for the studies were 58.5% (WA17823), 63.3% (WA17822) and 64.3% (WA18063), and 28.1%, 29.8% & 27.6% for placebo + MTX, respectively. The pooled ACR20 response for TCZ 8mg/kg IV was 62.5%, the pooled placebo + MTX response was 28.2% resulting in a pooled treatment difference of 34.3%.

Given that the treatment differences between placebo + MTX vs. TCZ + MTX seen in the historical IV studies gave a mean treatment difference of 34.3%, a reduction by approximately one third meant a treatment difference greater than the minimum meaningful clinical difference of 20% would be maintained. Using a maximum reduction of this treatment effect of 35%, maintaining 65% of the treatment difference, would retain a treatment effect of 22.3% over MTX alone, keeping a clinically meaningful improvement in signs and symptoms. The NIM of 12% is then defined by 34.3% minus 22.3%, which equals 12.0%.

The MAH therefore believes that the 12% NIM is statistically sound and ensured clinically meaningful improvements were demonstrated in the pivotal study WA22762. The CHMP concluded that the MAH provided a satisfactory justification for the non-inferiority margin in study WA22762 although done post-hoc.

The endpoints in both studies reflect study objectives and are in line with development program proposed in the draft Guideline on clinical investigation of medicinal products other than NSAIDs for treatment rheumatoid arthritis (CPMP/EWP/556/95 Rev.2). Moreover the endpoints are consistent with the development program of the IV formulation.

Efficacy data and additional analyses

In study NA25220 the primary objective, demonstrating superiority of TCZ SC q2w over placebo SC q2w with regard to ACR 20 response rate at week 24 was met. The ACR20 response was 60.9% in the TCZ SC arm vs. 31.5% in the placebo SC arm, the weighted difference between the treatment and placebo arm of 29.5% (22.0, 37.0) was statistically significant. The sensitivity analysis of the ACR response rate in the completer population (patients with a valid efficacy assessment at week 24; escape patients are excluded) demonstrated a response rate of 76.7% in the TCZ group vs. 55.6% in the placebo arm, with a weighted difference of 22.2% and thus support the result of the main efficacy analysis. The observed difference can be considered as clinically meaningful.

This result was supported by the analysis of the secondary endpoints e.g. the harder to achieve ACR50/70 response, DAS28 remission, and decrease in HAQ-DI of ≥0.3. The mTSS results indicate a greater reduction in the progression of joint damage between baseline and week 24 for the TCZ SC group compared to placebo. The adjusted mean difference of −0.598 was associated with a p-value of 0.0149 or 0.0145 using the non-parametric van Elteren test or analysis of variance, respectively.

According the protocol patients who showed less than 20% improvement in their SJC and TJC from baseline could receive open label escape therapy (TCZ 162 mg SC qw) from week 12 onwards. Placebo patients who switched to escape therapy showed 12 and 24 weeks after initiation of the therapy an ACR 20 /50/50 response in the same range as patients in study WA22762 study (using the same treatment regimen as for escape therapy).

Furthermore, the patients who switched from TCZ SC q2w-to-qw escape therapy showed a lower response rate than the placebo patients but had still a benefit from the switch in treatment schedule. The MAH suggested that the lower response rate for patients in the TCZ SC q2w-to-qw escape group compared to placebo patients switching to escape therapy probably reflects the inclusion patients who were true TCZ non-responders. Of note, no differences in the demographics disease characteristics of the escape patients and the overall safety population were observed. However, the RA disease characteristics of the escape patients showed that the proportion of patients who were RF positive, anti-CCP positive, and who had failed one or more previous anti-TNF therapies was higher among patients who received escape therapy as compared to the overall safety population. The ACR core set and DAS28 characteristics for escape patients at the initiation of escape therapy were generally unchanged from baseline (with the exception of ESR and CRP in the prior TCZ arm) and reflected the inadequate response in these patients. The CHMP agreed that there might be a true TCZ non-responder population, however to date no robust biomarkers are available to identify these patients.

According to the study protocol the patients received concomitant DMARDs, the choice of the medication was left to the investigator. It is understood majority of patients received MTX. No analysis if the efficacy result with regard to the concomitant DMARDs is provided.

During the evaluation, the MAH clarified that both Phase III studies WA22762 and NA25220, required patients to receive background stable doses of at least one non-biologic DMARD. Permitted non-biologic DMARDs were: azathioprine, chloroquine, hydroxychloroquine, leflunomide, MTX and sulfasalazine. DMARDs could be given alone or in combination, except for the combination of MTX and leflunomide which was prohibited due to hepatotoxicity. Data from these two studies were analysed separately: the primary endpoint ACR20 at week 24, and key secondary endpoints (which represented a range of efficacy measures that had been pre-specified in the protocols and Statistical Analysis Plans), stratified by MTX use in a post hoc analysis.

In study WA22762, in the Per Protocol (PP) population at baseline, of the TCZ-SC qw group there were 453 (81.2%) patients who received MTX (alone or in combination with other DMARDs) from a total of 558; in the TCZ-IV 8mg/kg every 4 weeks group 444 (82.7%) patients received MTX (alone or in combination with other DMARDs), from a total of 537 patients.

For the primary end point, the proportion of patients achieving an ACR20 response for TCZ-SC qw+MTX were comparable to those in the overall study population who were receiving background MTX and/or other non-biologic DMARDs. ACR20 reponses were also similar for patients receiving TCZ-IV 8mg/kg every 4 weeks + MTX to those in the overall study population who were receiving background MTX and/or other non-biologic DMARDs. Additonally,responses were similar overall between TCZ-SC qw+MTX a TCZ-IV 8mg/kg 4 weekly+MTX. Analyses stratified by MTX use were also performed on the following secondary end points: ACR50 and 70, proportion of patients achieving DAS 28 remission (<2.6), and proportion of patients achieving decrease in HAQ-DI score of ≥0.3. Across all the secondary end points analysed: signs and symptoms (ACR50/70 and DAS28 remission) and physical function (HAQ-DI), efficacy responses were similar between the TCZ-SC qw and TCZ-IV 8 mg/kg groups with background MTX or the overall patient population.

In study NA25220, in the Intent to Treat (ITT) population at baseline, of the 437 patients in the TCZ-SC q2w group, 361 (82.6%) received MTX (alone or in combination with other DMARDs); of the 219 patients in the PBO group, 174 (79.5%) patients were receiving MTX (alone or in combination with other DMARDs).

For the primary end point, the proportion of patients achieving an ACR20 response for TCZ-SC q2w were comparable for patients receiving background MTX and those in the overall study population who were receiving background MTX and/or other non-biologic DMARDs. ACR20 response rates for TCZ-SC q2w were substantially higher than the rates observed with placebo, for both patients on background MTX and those in the overall study population. An analysis stratified by MTX use was also performed on the following key secondary efficacy end points at week 24: proportion of patients achieving ACR50 and 70, proportion of patients achieving DAS 28 remission(<2.6), proportion of patients achieving decrease in HAQ-DI score of ≥0.3, and mean difference in mTSS from baseline to week 24. As with the overall study population, there was a substantial efficacy advantage for TCZ-SC q2w over PBO for patients on MTX across all key secondary endpoints, including reduction in the signs and symptoms of RA (ACR20/50 and DAS28), improvement in physical function (HAQDI), and reduction in progression of joint damage (mTSS).

The post-hoc analysis provided by the MAH showed comparable efficacy with regard to the primary and key secondary efficacy endpoints in patients receiving TCZ with background MTX and the overall study population.

The clinical study report NA25220-LTE presented data up to the clinical cut-off date of 28 May 2012. The data analysis provides data up to 48 weeks. So far the data indicated that the efficacy of TCZ 162 mg SC q2w was maintained after the 24-week double-blind period of the study. Evaluation of the efficacy data in patients who switched from PFS to AI showed in general comparative efficacy. For the patients who received placebo during the double-blind phase and were then re-randomized at week 24 to receive TCZ 162 mg q2w using either the AI or PFS comparable results were obtained for the PFS vs. AI for ACR20, mean change in HAQ-DI, and decrease in HAQ-DI $\geq$ 0.3, but numerically higher responses were observed with the PFS for ACR50/70, mean DAS28, mean change in DAS28 from baseline, and DAS28 remission. However no robust conclusion can be drawn since the sample size in these arms is rather small (i.e. 60 and 59 patients per group). Of note, the MAA is limited to the use of PFS.

During the evaluation, the MAH provided further data from ongoing study NA25220-LTE at the clinical cut-off of 29 October 2012. These data indicate that the treatment response was largely maintained. Reduction in progression of joint damage (assessed by change in mTSS and APR) was also maintained through Week 48. The submission of the final clinical study report for study NA25220 has been included as a milestone in the RMP.

In study WA22762 the primary objective demonstrating the non-inferiority of TCZ SC to TCZ IV was met. In the PP population, 69.4% (95% CI: 65.5%, 73.2%) of patients in the TCZ SC arm achieved an ACR20 response at Week 24 compared with 73.4% (95% CI: 69.6%, 77.1%) in the TCZ IV arm, with a weighted difference between the arms of −4.0% (95% CI: -9.2%, 1.2%), the lower limit of the 95%-CI for the difference between arms (-9.2%) was above the pre-defined non-inferiority margin of -12%. These results were confirmed in robustness analyses on the ITT population, ACR20: −2.7% (lower boundary of the 95% CI −7.6%). Again, according the study protocol the patients received concomitant DMARDs. However the choice of the medication was left to the investigator. During the evaluation the MAH provided a post-hoc analysis on concomitant DMARDs use. For the primary end point, the proportion of patients achieving an ACR20 response for TCZ-SC qw+MTX were comparable to those in the overall study population who were receiving background MTX and/or other non-biologic DMARDs. ACR20 responses were also similar for patients receiving TCZ-IV 8mg/kg every 4 weeks + MTX to those in the overall study population who were receiving background MTX and/or other non-biologic DMARDs. Additionally, responses were similar overall between TCZ-SC qw+MTX a TCZ-IV 8mg/kg 4 weekly+MTX.

The clinical cut-off date for the extension phase study WA22762 LTE was 16 January 2012. The efficacy of TCZ 162 mg SC qw was maintained after the 24-week double-blind period of the study. The ACR response rate in the SC-IV switch arm was lower than in the other arms, at various time points, including week 24, however the sample size for is limited, thus no robust conclusion can be drawn.

During the evaluation the MAH provided further data from ongoing study WA22762-LTE at the clinical cut-off of 12 October 2012. These data indicate that the treatment response was maintained in TCZ treated patients. The submission of the final clinical study report for study WA22762 has been included as a milestone in the RMP.

In both studies efficacy in various subgroups was evaluated. Notable differences in response were seen in both studies in the analysis by bodyweight. ACR 20, 50 and 70 response rates indicated a comparable response rate in the TCZ SC treatment group for all 3 parameters in the < 60 kg and in the 60 to < 100kg, whereas patients in the > 100 kg showed lower response rate for these parameters. Interestingly, for ACR 50 and 70, response in the highest body weight group was lower for the weight adjusted IV TCZ treatment than for the fixed SC TCZ dose.

Analysis of ACR response by regions revealed comparable response rates across the different regions (Europe, South America, others) but North America. Irrespective of the treatment received, patients in North America demonstrated a lower response to therapy compared with those from other regions. This finding is consistent with the results from the historical IV data.

The applicant provided a comparative analysis of the week 24 results for the two pivotal SC studies NA25220 and WA22762 and a comparison of the results with the 24-week pooled IV historical data (TCZ application). In general the baseline demographic characteristics were well balanced across the studies. Baseline RA characteristics were also well balanced between the studies with exception of RA duration which was longer in study NA25220; the proportion of RF positive patients, which was also higher in study NA25220; the proportion of patients receiving background corticosteroids, which was higher in the SC studies and the mean number of previous DMARDS which was higher in the pivotal studies.

TCZ treated patients in the SC studies had a higher ACR 20/50/70 responses rate than the historical control, this was also seen in the placebo groups. When taking into account the difference in placebo response at Week 24, the ACR20 response rate for TCZ SC q2w fell between that of historical 4 mg/kg IV and 8 mg/kg IV data, whereas for the higher hurdles of ACR50 and ACR70, the SC q2w responses were closer to the response seen with the historical 8 mg/kg IV data.

Analysis of the escape data demonstrated that patients who initially failed to respond adequately to the TCZ SC q2w regimen may benefit from the weekly TCZ SC regimen and thus these data support the dosing regimen claimed by the MAH. However under the light of the comparative data with the historic IV data, one can argue that initiating treatment with a weekly schedule might be appropriate. In case of inadequate response the patient might switch to a weekly regimen. Based on the collected clinical evidence supporting TCZ administered SC qw, the MAH believed that 162 mg every week is the most effective dosing regimen for all patients across all body weights and patient subpopulation. According to the MAH, the most important arguments is that the PD, efficacy and safety results for TCZ SC qw are comparable with the approved IV 8mg/kg every 4 weeks regimen which provides rapid and sustained reduction in disease activity. The MAH therefore concluded that TCZ SC qw is the most appropriate dose regimen to initiate and continue therapy for patients with RA. The CHMP was in agreement with the MAH's position. The preliminary results (24 weeks) of the smaller monotherapy study in Japanese RA patients, comparing TCZ 162 mg SC q2w or TCZ 8 mg/kg IV q4w showed consistent results with the pivotal studies with regard to the ACR20/50/70 response, the primary endpoint demonstrating non-inferiority between the two arms with regard to the proportion of ACR20 responders was met.

On 20 December 2013, the MAH reported a needle clogging issue affecting the new pre-filled syringe presentation (see section 2.2.3 Finished Medicinal Product). To further strengthen the mitigation statements already included in the SmPC and PL, the MAH proposed to add some

further changes to sections 6.3 and 6.6 of the SmPC and sections 5 and 6 of the PL. The CHMP considered the proposed changes suitable to reduce the probability of a clogged syringe due to handling errors. The MAH in addition discussed what happens if a patient uses a pre-filled syringe with such defect. It was clarified that if a patient attempt to administer an injection with a pre-filled syringe that is clogged, the patient would unlikely be able to expel any drug product from the syringe. The failure mode is considered highly detectable. Assuming a replacement pre-filled syringe is at hand, the dose would not be missed. If no replacement pre-filled syringe is available, the dose would be delayed or missed. Results from studies WA22762 and NA25220 indicate that if a patient on the TCZ QW regimen has a single dose missed or delayed or a partial dose of TCZ SC there would be no impact on efficacy. The probability of receiving a partial dose from a clogged needle is extremely low as a needle clog is more likely to completely block the needle so no injection can be given. The CHMP concluded that there is no impact on clinical efficacy due to clogging incidents when using the pre-filled syringe.

With regards to the exceeded limit of the injection time with the pre-filled pen reported by the MAH on 31/01/2014, the MAH withdrew this new presentation on 11 February 2014. The MAH also confirmed their ability to ensure commercial supply of the pre-filled syringe to all rheumatoid arthritis patients once approved and to subjects enrolled in on-going clinical studies.

2.5.4. Conclusions on the clinical efficacy

TCZ IV in combination with methotrexate (MTX) is an established treatment option for adult patients with RA. In study WA22762 the non-inferiority of TCZ 162mg SC qw to TCZ 8mg/kg IV q4w in terms of efficacy was demonstrated. The primary objective demonstrating the non-inferiority of TCZ SC qw over TCZ IV q4w with regard to ACR 20 response rate at week 24 was met. These results are supported by the secondary objectives, comparable response rates were observed for e.g. ACR 50/ 70 response.

The clinical cut-off date of for the extension phase study WA22762 LTE allowing for a switch between IV and SC application was 16 January 2012. The efficacy of TCZ 162 mg SC qw was maintained after the 24-week double-blind period of the study. However the ACR response rate in the SC-IV switch arm was lower than in the other arms, at various time points, including week 24. Since the sample size is limited, long-term safety in patients in the switcher patient will be further investigated in the BSRBR registry as detailed in the RMP.

Notable difference in response was seen in the analysis by bodyweight. ACR 20, 50 and 70 response rates indicated a comparable response rate in the TCZ SC treatment group for all 3 parameters in the < 60 kg and in the 60 to < 100kg, whereas patients in the > 100 kg showed lower response rate for these parameters. Interestingly, for ACR 50 and 70 response in the highest body weight group was lower for the weight adjusted IV TCZ treatment than for the fixed SC TCZ dose. A statement has been included in section 5.1 of the SmPC regarding the impact of switching from IV to SC on exposure particularly in light and heavy body weight patients

According to the study protocol the patients received concomitant DMARDs, the choice of the medication was left to the investigator. It is understood that the majority of patients received MTX. The post hoc analysis from study NA25220 and study WA22762 comparing efficacy in patients receiving TCZ with background MTX with the overall study population showed comparable efficacy on the primary and key secondary endpoints.

Following reports of clogging of the needle with the new pre-filled syringe presentation, the MAH proposed changes to the product information in sections 6.3 and 6.6 of the SmPC as well as in the Package Leaflet. This is supported by CHMP. The CHMP concluded that there is no impact on clinical efficacy due to clogging incidents when using the pre-filled syringe device. With regards to the exceeded limit of the injection time with the pre-filled pen, the MAH withdrew this new presentation.

2.6. Clinical safety

The safety assessment of TCZ SC is based on two pivotal phase III clinical studies (studies NA25220 / LTE and WA22762 / LTE).

A safety analysis from the original Phase III clinical development program for the intravenous (IV) dosage form of TCZ in adult RA following 24 weeks of treatment (data submitted as part of initial MAA) are also summarised.

This data base is further supported by data from the safety analysis analyses on SC TCZ from a completed Phase Ib study NP22623 in RA patients and two Chugai monotherapy trials, the complete Phase I/II study MRA227JP, and the phase III study MRA229JP.

Additionally a summary of safety information from the Phase I clinical development program for SC TCZ in healthy volunteers is also included in the submission.

Table 40. Overview of clinical studies contributing to safety evaluation of TCZ SC

Protocol	Study Design	Patient Population	Dose, Route, Regimen	Number of Patients
Pivotal Phase III Studies				
WA22762	Randomized, active-controlled, parallel-group non-inferiority study of TCZ + DMARD 24-week double-blind period followed by 72-week open-label extension	Adult patients with moderate to severe active RA who had an inadequate response to current DMARD therapy that may have included one or more TNF antagonists	First 24 weeks: 162 mg SC TCZ qw (via PFS) + placebo IV q4w or Placebo SC qw (via PFS) + 8 mg/kg IV TCZ q4w Open-label extension: 162 mg SC TCZ qw (via PFS) or 8 mg/kg IV TCZ q4w	N=1262 SC TCZ qw: n=631 IV TCZ q4w: n=631 SC TCZ qw: n=524 IV TCZ q4w: n=377 IV TCZ q4w→SC qw: n=186 SC TCZ qw→IV q4w: n=48
NA25220	Randomized, placebo-controlled, parallel-group study of TCZ + DMARD 24-week, double-blind period followed by 72-week open-label extension	Adult patients with moderate to severe active RA who had an inadequate response to current DMARD therapy that may have included one or more TNF antagonists	First 24 weeks: 162 mg SC TCZ q2w (via PFS) or Placebo SC q2w (via PFS) Open-label extension: 162 mg SC TCZ q2w (PFS) or 162 mg SC TCZ q2w (AI) Escape therapy (from Week 12): 162 mg SC TCZ qw	N=656 SC TCZ q2w PFS: n=438 PI SC q2w PFS: n=218 TCZ PFS q2w: n=167 TCZ PFS q2w → AI q2w: n=167 PI PFS q2w→TCZ PFS q2w: n=60 PI PFS q2w→TCZ AI q2w: n=59 n=162 (including 90 placebo patients before week 24)

Protocol	Study Design	Patient Population	Dose, Route, Regimen	No. of Patients
Supportive Studies				
MRA229JP (Phase III)	Randomized, double-blind, parallel-group comparative study of SC TCZ monotherapy	Adult patients with RA with inadequate response to DMARDs (including TNF antagonists)	162mg SC TCZ q2w + placebo IV q4w vs 8 mg/kg IV TCZ q4w + placebo SC q2w for 24 weeks followed by open-label SC TCZ for up to 84 weeks	N=348
MRA227JP (Phase I/II)	Randomized, open-label, multiple-dose, inter-individual dose escalation study of SC TCZ monotherapy	Adult patients with RA	81 mg SC TCZ q2w for 35 weeks vs 162 mg SC TCZ q2w for 35 weeks vs 162 mg SC TCZ qw for 28 weeks	N=32
NP22623 (Phase Ib)	Open-label, randomized, parallel-group	Adult patients with RA	Part 1: 7.5-25 mg MTX (PO or IV) plus 162 mg SC TCZ qw or q2w for 12 weeks Part 2: (optional post-study phase) 8 mg/kg IV TCZ q4w for up to one year	N=29
WP18097 (Phase I)	Single-dose, single-blind, randomized, double dummy	Adult healthy volunteers	160 mg SC TCZ + IV placebo vs 160 mg IV TCZ + SC placebo	N=20
BP22065 (Phase I)	Single-dose, open-label, single-center, parallel four-group study of PK, PD, safety of SC TCZ vs IV	Adult healthy volunteers	81 or 162 mg SC TCZ, or 81 or 162 mg IV TCZ	N=48
NP25539 (Phase I)	Single-dose, randomized, open-label, parallel 2-group, 2-center relative bioavailability study (PFS vs AI)	Adult healthy volunteers	162 mg SC TCZ via PFS vs 162 mg SC TCZ via AI	N=261
BP21894 (Phase I)	Single-dose, open-label, parallel-group study of PK, PD, safety of SC TCZ	Adult healthy volunteers	single dose of 162, 324, or 648 mg with or without rHuPH20	N=48

AI=autoinjector; DMARDs=disease-modifying anti-rheumatic drugs; IV=intravenous; MTX=methotrexate; PD=pharmacodynamics; PFS=prefilled syringe; PK=pharmacokinetics; PI: Placebo; PO=orally; q2w=every two weeks; q4w=every four weeks; qw=every week; RA=rheumatoid arthritis; rHuPH20=recombinant human hyaluronidase; SC=Subcutaneous; TCZ=Tocilizumab; TNF=tumor necrosis factor

Patient exposure

The safety population included all patients who received at least one dose of TCZ (SC or IV) and had least one post-dose safety assessment.

In the pivotal studies a total of 1465 patients were exposed to TCZ SC. This includes patients treated with TCZ SC during the 24 weeks core and the LTE part of study NA25220 and study WA25220 as well as patients who switched from placebo to TSZ SC in the LTE part of study NA25220 and who switched from TCZ IV to TCZ SC in study WA25220 LTE.

Table 41. Clinical studies of TCZ SC in adult RA patients (pivotal studies)

Core Study Protocol (Number of Patients)	Extension Protocol	Number of Patients Contributing SC TCZ Safety Data
WA22672 (N=631)	IV → SC switchers (N =186)	817
NA25220 (N=438) Placebo Escaper (N=90)	Placebo → TCZ PFS (N = 61) Placebo → TCZ PFS (N = 59)	648
Total number of patients in SC TCZ All-exposure Population		**1465**

IV=intravenous; LTE=long-term extension; SC=subcutaneous; TCZ=tocilizumab

Table 42. Comparison of exposure at week 24 in SC TCZ and IV TCZ (phase III pivotal studies)

	Study WA22762		Study NA25220		Week 24 Analyses from IV TCZ Phase III Clinical Studies		
	162 mg SC TCZ qw+DMARD N = 631	8 mg/kg IV TCZ q4w+DMARD N = 631	162 mg SC TCZ q2w+DMARD N = 437	PI SC q2w +DMARD N = 218	8 mg/kg IV TCZ q4w+DMARD N = 1582	4 mg/kg IV TCZ q4w+MTX N = 774	PI+DMARD N = 1170
Duration in study [a] (PY)	289.8	288.3	182.68	81.80	753.50	344.74	507.24
Exposure to TCZ [b]							
Mean ± SD (years)	0.42 ± 0.093	0.46 ± 0.105	0.39 ± 0.100	-	0.43 ± 0.1	0.41 ± 0.1	-
Exposure (PY)	267.9	292.8	172.1	-	684.7	320.9	-
Exposure to Placebo [b]	PI IV	PI SC		PI SC			PI IV
Mean ± SD (years)	0.43 ± 0.084	0.41 ± 0.097	-	0.35 ± 0.107	-	-	0.39 ± 0.1
Exposure (PY)	271.2	260.5	-	77.2	-	-	461.8

CI=confidence interval; DMARD=disease-modifying anti-rheumatic drug; IV=intravenous; MTX=methotrexate; PI=placebo; PY=patient years; q2w= every two weeks; q4w= every four weeks; qw= every week; SC=subcutaneous; SD=standard deviation; TCZ=tocilizumab.

Data on escape therapy is excluded.

[a] Date of last assessment - date of first dose + 1 day / 365.25; duration in study is used to calculate rates of AEs per 100 patient years.

[b] Exposure per administration = difference between the dates of a patient's injection and the subsequent injection (capped at length of dosing interval); total extent of exposure = sum of the exposure for all injections + dosing interval.

Source: stextexp_sc_2, stmeddur_2, stextexp_iv_2, stextexp_preesc_sc_2, staerate01_serious_wk24_2 in WA22762 and NA25520 24-week CSRs, and Table 12 (STmed_ext_t01), Table 17 (STrate_ae Rate) in original submission.

Out of the 1465 patients in the two pivotal studies NA25220 and WA22762 who received SC TCZ treatment; 557 patients received 162 mg q2w treatment and 908 patients received 162 mg qw treatment.

The clinical cut-off dates for the analyses in this summary represent the 24-week cut-off point 28 May 2012 for study NA25220 and 16 January 2012 for study WA22762.

Table 43. Studies NA25520 and WA22767 summary of extend of exposure to TCZ SC (SC all-exposure population)

	ALL TCZ
No. Pts Randomized	1465
No. With at Least One Dose	1465
No. Completing 12 weeks Treatment	1308
No. Completing 24 weeks Treatment	1095
No. Completing 36 weeks Treatment	650
No. Completing 40 weeks Treatment	483
No. Completing 44 weeks Treatment	357
No. Completing 48 weeks Treatment	239
No. Completing 60 weeks Treatment	82
No. Completing 72 weeks Treatment	4

Source: stex13 14NOV2012:12:45:40

Regarding the Chugai studies one study the Phase I/II study (MRA227JP) is completed. From the ongoing study MRA229JP safety data for the 24-week double-blind period (date of the last assessment was 14 April 2011) are available.

Adverse events

Table 44. Overview of all AEs at week 24 in SC TCZ and IV TCZ clinical studies (safety population)n

	Study WA22762		Study NA25220		Week 24 Analyses from IV TCZ Phase III Clinical Studies		
	162 mg SC TCZ qw+DMARD N = 631	8 mg/kg IV TCZ q4w+DMARD N = 631	162 mg SC TCZ q2w+DMARD N = 437	PI SC q2w +DMARD N = 218	8 mg/kg IV TCZ q4w +DMARD N = 1582	4 mg/kg IV TCZ q4w + MTX N = 774	PI+DMARD N = 1170
Duration in study (PY)	289.82	288.39	182.68	81.80	753.50	344.74	507.24
Patients with at least one AE	481 (76.2%)	486 (77.0%)	274 (62.7%)	126 (57.8%)	1134 (71.7%)	547 (70.7%)	733 (62.6%)
Number of AEs	1747	1697	803	283	3484	1628	1914
Rate per 100 PY (95% CI)	602.79 (574.85, 631.73)	588.44 (560.77, 617.12)	439.56 (409.68, 471.04)	345.96 (306.82, 388.71)	462.37 (447.15, 477.99)	472.24 (449.58, 495.76)	377.34 (360.62, 394.63)

AE = adverse event; CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; IV = intravenous; MTX = methotrexate; PI = placebo; PY = patient years; q2w = every two weeks; q4w = every four weeks; qw = every week; SC = subcutaneous; TCZ = tocilizumab.

Duration in study = date of last assessment - date of first dose + 1 day / 365.25.

Multiple occurrences of the same event in one individual are counted.

MedDRA versions used for analyses: version 10.0 for week 24 analyses of IV TCZ data; version 14.1 for study WA22762; version 15.0 for study NA25220.

Source: stae11, staerate01_all_wk24_2,from study WA22762 staerate01_all_wk24_2,from study NA25220 stae11, from study NA25220 Table 15, Table 17 in Safety Summary of original IV TCZ submission.

Table 45. Overview of all AERs in the pivotal studies until clinical cut-off

	WA22762		NA25220
	162 mg SC TCZ qw (PFS)+DMARD N=631	8 mg/kg IV TCZ q4w+DMARD N=631	162 mg SC TCZ q2w (PFS)+DMARD N=437
Total duration in study (PY)	454.20	401.02	222.09
Patients with AE	527 (84%)	502 (80%)	292 (66.8%)
Number of AEs	2501	2137	947
Rate per 100 PY (95% CI)	550.64 (529.27, 572.66)	532.89 (510.54, 555.98)	426.40 (399.67, 454.44)

AE = adverse event; CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; IV = intravenous; PFS = prefilled syringe; PY = patient years; q2w = every two weeks; q4w = every four weeks ; qw = every week; SC = subcutaneous; TCZ = tocilizumab.

Clinical cutoff 16 January 2012 for WA22762 and 28 May 2012 for NA25220.

SC TCZ arms: Analyses include all patients who received SC TCZ using the PFS in the double-blind period starting from their first dose. Data after switch to IV TCZ (in WA22762) or the AI (in NA25220) in the open-label extension are not included.

IV TCZ arm: Analyses include all patients who received IV TCZ in the double-blind period starting from their first dose. Data after switch to SC TCZ in the open-label extension are not included.

Multiple occurrences of the same AE in one individual are counted.

Source: stae11_b LTE CSR WA22762, staerate01_all_2 LTE CSR WA22762, stae11_s_pt_b LTE CSR NA25220.

Table 46. Overview of all AEs in pooled TCZ SZ and IV TCZ application all exposure population

	SC TCZ all-exposure N=1465	IV TCZ all-exposure N=4171
Total Exposure (PY)	893.92	16204.77
Patients with AE	1052	3941
Number of AEs	4483	47970
Rate per 100 PY (95% CI)	501.50 (486.92, 516.40)	296.02 (293.38, 298.68)

AE = adverse event; CI=confidence interval; IV=intravenous; PY=patient years; SC=subcutaneous; TCZ=tocilizumab.
Multiple occurrences of the same AE in one individual are counted.
Source: STae_rategp6_all and STae_rategp6_all (IV safety update report).

In study NA25220 the most common SOCs (≥ 10% of patients in either arm) in which AEs were reported were:

- Infections and infestations (30.0% TCZ arm vs. 28.0% placebo arm): most commonly, upper respiratory tract infections (6.4% in each treatment arm), urinary tract infections (4.1% vs. 3.2%), and nasopharyngitis (4.3% vs. 2.3%)
- Investigations (16.9% TCZ arm vs. 6.9% placebo arm): most commonly, increased ALT (13.3% vs. 5.0%, respectively) and increased AST (8.2% vs. 3.7%)
- GI Disorders (11.9% TCZ arm vs. 10.1% placebo arm): most commonly, diarrhoea (1.8% vs. 1.4%), dyspepsia (2.1% vs. 0.9%), and nausea (1.4% vs. 0.9%, respectively)
- Musculoskeletal and connective tissue disorders (8.7% TCZ arm vs. 12.4% placebo arm): most commonly, arthralgia (2.3% vs. 0.5%) and RA (1.1% vs. 1.8%).

A greater percentage of patients experienced injection site reactions (IRS) in the TCZ arm (7.1%) than in the placebo arm (4.1%). Similarly, a greater percentage of patients in the TCZ arm experienced hypersensitivity events (retrieved events occurring during or within 24 hours of an injection or infusion (excluding ISRs) and not deemed by the investigator as unrelated to treatment) compared with patients in the placebo arm, 4.3% vs. 3.7%, respectively. Musculoskeletal and Connective Tissue Disorders was the only SOC with a notably higher percentage of patients reporting events in the placebo arm (12.4%) compared with the TCZ arm (8.7%), most commonly arthralgia. The majority of AEs in both arms (95% each) were Grade 1 or 2 in intensity. The proportion of patients experiencing at least one Grade 3 event was the same in both arms (5.0% each). In the SC arm, 0.9% of patients experience at least one Grade 4 event, while no patients in placebo had such an event.

Table 47. NA25220 AEs by weight at baseline (safety population)

Body Weight at Baseline	Number of Patients (%)	
	TCZ PFS q2w (n=437)	Placebo PFS q2w (n=218)
<60 kg	74/119 (62.2)	36/58 (62.1)
60 to <100 kg	179/292 (61.3)	84/149 (56.4)
≥100 kg	21/26 (80.8)	6/11 (54.5)

PFS = pre-filled syringe; q2w = twice weekly.
Source: page 848.

Table 48. Study NA25220 LTE adverse event rates until clinical cut-off (all safety population)

staerate01_all_2 Rate of Adverse Events per 100 Patient Years - Clinical Cut-off date 28 May 2012 (Safety Population)

	TCZ PFS q2w (N=437)	TCZ PFS q2w -> TCZ AI q2w (N=168)	Placebo PFS q2w -> TCZ PFS q2w (N=61)	Placebo PFS q2w -> TCZ AI q2w (N=59)	Placebo PFS q2w (N=218)
Total Patient Years	222.09	37.20	13.82	13.75	82.12
Number of Adverse Events	947	201	56	51	277
Adverse Events per Patient Year	4.26	5.40	4.05	3.71	3.37
Adverse Events per 100 Patient Years	426.40	540.33	405.27	370.85	337.29
95% CI	[399.67;454.44]	[468.21;620.42]	[306.14;526.28]	[276.12;487.60]	[298.74;379.44]

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Multiple occurrences of the same adverse event in one individual are counted.
CI is based on events per 100 patient years.
Duration in study (years) = (date of last assessment - date of first dose + 1) / 365.25.
Escape patients are included until time of escape when they will be classed as withdrawn.

Program : $PROD/cs11935c/c25220a/staerate01.sas / Output : $PROD/cr11935a/r25220b/reports/staerate01_all_2.out
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In study NA25220 LTE patients were re-randomised at Week 24. Adverse event data in the TCZ PFS Arm included all patient data for patients who received TCZ PFS up to Week 24, data for patients who received TCZ PFS up to the time of escape therapy, and data for patients who continued to use the PFS during the open label treatment period up to the date of the clinical data cut. In the TCZ PFS Arm a total of 292 patients experienced 947 AEs. The most common SOCs (≥ 10.0%) in which AEs were reported were as follows:

- Infections and infestations (34.1%): most commonly upper respiratory tract infections (8.2%), nasopharyngitis (5.3%), urinary tract infection (4.3%), and sinusitis (2.5%).
- Investigations (16.2%): most commonly increased ALT (12.8%) and increased AST (8.5%).
- GI Disorders (14.2%): most commonly diarrhea (3.0%) and dyspepsia (2.3%)
- General Disorders and Administration Site Conditions (10.8%): most commonly injection-site erythema (2.5%), injection site pain (2.5%), and injection site haematoma (0.7%).

Among the 168 patients in study NA25220 LTE who switched from TCZ PFS to TCZ AI at Week 24, 74 patients had 201 AEs. Most (51/54) of these AEs were Grade 1 or Grade 2 in intensity and resolved within 7 days, on average. The most common SOCs (≥ 10.0%) in which AEs were reported were as follows:

- Infections and infestations (22.6%): most commonly upper respiratory tract infections (4.2%), nasopharyngitis (3.0%), urinary tract infection (2.4%), and sinusitis (2.4%).

- Investigations (11.3% AI): most commonly increased ALT (8.3%, respectively) and increased AST (4.2%).

Sixty one patients switched from Placebo to TCZ PFS. Twenty-seven of these patients had 56 AEs. The most common AEs (SOC) reported after the switch from Placebo to TCZ PFS was infections and infestations (24.6%). The incidence for all other SOCs was ≤ 10.0%. Individual AEs (preferred terms) reported in ≥ 5.0% of patients were ALT increased (5 patients; 8.2%), AST increased (4 patients; 6.6%), dyslipidemia (4 patients; 6.6%), and upper respiratory tract infection (4 patients; 6.6%).

Among the 59 patients who switched from Placebo to TCZ AI, 25 patients had 51 AEs. The most common AEs (SOC) in this treatment arm were investigations (11.9%) and gastrointestinal disorders (10.2%). The incidence for all other SOCs were ALT increased (5 patients; 8.5%), AST increased (4 patients; 6.8%), and hypertriglyceridemia (4 patients; 6.8%).

In the Escape Patients (study NA25220 LTE) the most common AEs (SOC) were infections and infestations (29.2% and 34.4%, respectively]). The next most common AEs were gastrointestinal disorders (16.7% and 17.8%), investigations (11.1% and 21.1%), musculoskeletal and connective tissue disorders (12.5% and 11.1%), blood and lymphatic system disorders (8.3% and 12.2%), and general disorders and administration site conditions (12.5% and 4.4%). The incidence for all other SOCs was ≤ 10.0%.

In study WA22762 the proportion of patients who experienced at least one AE during the 24 weeks was 631 patients (76.2%) in the SC arm vs. 486 of 631 patients (77.0%) in the IV arm.

Table 49. Study WA22762 rate of adverse events per 100 Patient-Years (safety population)

staerate01_all_wk24_2 Rate of Adverse Events per 100 Patient Years (Safety Population)

	162mg SC qw + DMARD (N=631)	8mg/kg IV q4w + DMARD (N=631)
Total Patient Years	289.82	288.39
Number of Adverse Events	1747	1697
Adverse Events per Patient Year	6.03	5.88
Adverse Events per 100 Patient Years	602.79	588.44
95% CI	[574.85;631.73]	[560.77;617.12]

Investigator text for adverse events encoded using MedDRA Version 14.1
Multiple occurrences of the same adverse event in one individual are counted.
CI is based on events per 100 patient years.
Duration in study (years) = (date of last assessment - date of first dose + 1) / 365.25.

Program : $PROD/cs11935c/c22762a/staerate01.sas / Output :
$PROD/cr11935a/r22762a/reports/staerate01_all_wk24_2.out
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In study WA22762 the most common SOCs (≥ 10% in either arm) in which AEs were reported were:

- Infections and infestations (36.0% SC arm vs. 39.1% IV arm): most commonly, upper respiratory tract infections (7.3% vs. 11.6%, respectively), nasopharyngitis (5.7% in each arm), and urinary tract infections (4.1% vs. 5.1%)

- Investigations (23.3% SC arm vs. 21.2% IV arm): most commonly, increased ALT (18.7% vs. 16.5%, respectively) and increased AST (13.5% vs. 10.5%)
- GI Disorders (19.2% SC arm vs. 18.5% IV arm): most commonly, nausea (4.0% vs. 4.6%, respectively) and diarrhea (4.3% vs. 4.1%)
- Musculoskeletal and connective tissue disorders (15.4% in each arm): most commonly, arthralgia (1.4% vs. 2.5%, respectively) and back pain (1.3% vs. 2.4%)
- Skin and subcutaneous tissue disorders (11.6% SC arm vs. 13.0% IV arm): most commonly, rash (2.9% vs. 2.7%, respectively), and pruritus (2.4% vs. 1.7%)
- General disorders and administration-site conditions (14.9% SC arm vs. 7.0% IV arm): most commonly, injection-site erythema (4.4% vs. 0.8%, respectively), and peripheral edema (1.7% vs. 1.4%, respectively)
- Nervous system disorders (9.4% SC arm vs. 11.6% IV arm): most commonly, headache (4.4% vs. 5.2%, respectively) and dizziness (2.1% vs. 2.4%).

The majority of AEs in both arms (1436 of 1515 events (94.8%) in the SC arm vs. 1387 of 1479 events (93.8%) in the IV arm) were Grade 1 or 2 in intensity. The proportion of patients experiencing at least one Grade 3 event was comparable for the SC and IV arms (9.4% vs. 10.0%, respectively), as was the proportion of patients experiencing at least one Grade 4 event (1.0% vs.0.8%, respectively). The most common SOCs in which Grade ≥ 3 AEs were reported were infections and infestations, with no single event being predominant, and investigations (i.e. increased ALT and AST liver enzymes).

In study WA22762 LTE the data based on the safety population, this includes data from the double-blind and open-label periods in the SC and IV arms but only from the open-label period (i.e. after switching) in the IV-SC and SC-IV switch arms.

Table 50. Study WA22762 LTE rate of adverse events per 100 patient years (safety population)

staerate01_all_2 Rate of Adverse Events per 100 Patient Years - Clinical Cut-off date 16th January 2012 (Safety Population)

	Tocilizumab 162mg SC qw + IMARD (N=631)	Tocilizumab 8mg/kg IV q4w + IMARD (N=631)	TOCILIZUMAB SC->IV (N=48)	TOCILIZUMAB IV->SC (N=186)
Total Patient Years	454.20	401.02	12.98	58.37
Number of Adverse Events	2501	2137	39	370
Adverse Events per Patient Year	5.51	5.33	3.01	6.34
Adverse Events per 100 Patient Years	550.64	532.89	300.52	633.88
95% CI	[529.27;572.66]	[510.54;555.98]	[213.70;410.82]	[570.93;701.87]

Investigator text for adverse events encoded using MedDRA Version 14.1
Multiple occurrences of the same adverse event in one individual are counted.
CI is based on events per 100 patient years.
Duration in study (years) = (date of last assessment - date of first dose + 1) / 365.25.
Tocilizumab SC -> IV' and 'Tocilizumab IV -> SC' arms include information from the open label phase only.
Patients in the switcher columns are re-baselined to the visit of their first open label dose.

Program : $PROD/cs11935c/c22762b/staerate01.sas / Output : $PROD/cr11935a/r22762b/reports/staerate01_all_2.out
01JUN2012 16:49

In study WA22762 LTE the incidence of AEs was also similar in both arms; 527/631 (83.5%) patients in the SC arm and 502/631 (79.6%) patients in the IV arm. The most common SOCs (≥ 10.0% in either arm) in which AEs were reported were:

- Infections and infestations (49.4% SC vs. 45.2% IV): most commonly upper respiratory tract infections (11.4% vs. 15.1%, respectively), nasopharyngitis (10.0% vs. 7.9%), and urinary tract infections (7.1% vs. 5.7%).
- Investigations (27.3% SC vs. 23.3% IV): most commonly increased ALT (21.4% vs. 18.4%, respectively) and increased AST (14.7% vs. 12.0%).
- GI Disorders (24.1% SC vs. 21.7% IV): most commonly diarrhea (6.2% vs. 4.8%, respectively) and nausea (4.1% vs. 5.2%).
- Musculoskeletal and connective tissue Disorders (21.9% SC vs. 18.5% IV): most commonly RA in the SC arm (3.0% vs. 2.1%) and back pain in the IV arm (2.4% vs. 3.6%).
- General disorders and administration site conditions (17.1% SC vs. 7.9% IV): most commonly injection site erythema (5.4% vs. 0.8%, respectively), injection site pruritus (2.7% vs. 0.0%), and injection site pain (2.4% vs. 0.8%).
- Skin and subcutaneous tissue disorders (14.7% SC vs. 14.3% IV): most commonly rash (4.3% vs. 3.3%, respectively) and pruritus (2.9% vs. 1.7%).
- Nervous system disorders (12.4% SC vs. 13.5% IV): most commonly headache (5.5% vs. 5.9%, respectively) and dizziness (2.2% vs. 2.9%).
- Injury, poisoning and procedural complications (12.0% SC vs. 9.4% IV): most commonly contusion (2.7% vs. 1.3%, respectively) and fall (1.7% vs. 1.9%).
- Metabolism and Nutrition Disorders (10.1% SC vs. 9.8% IV): most commonly hypertriglyceridaemia (2.1% vs. 2.4%, respectively), dyslipidemia (2.5% vs. 1.4%), and hypercholesterolemia (1.4% vs. 2.1%).
- Respiratory, thoracic, and mediastinal disorders (8.6% SC vs. 10.6% IV): most commonly cough (2.9% vs. 2.1%, respectively).
- Vascular Disorders (8.7% SC vs. 10.0% IV): most commonly hypertension (5.4% vs. 7.6%, respectively).

35% of AEs in both the SC and IV arms were reported by the investigator as being related to treatment; 748 of 2128 events [35.2%] vs. 662 of 1863 events [35.5%], respectively. The most common related AEs in both treatment arms were 'infections and infestations' and 'investigations' SOCs (mainly increased liver enzymes).

In study WA22762 LTE 186 patients switched after the 24 weeks period form IV TCZ to TCZ SC. In this IV-SC Switch Arm the rate of AEs was 633.88 (95% CI: 570.93; 701.87) events per 100 PY. The most common AEs (SOC) were infections and infestations (50/186 patients (26.9%)). The next most common AEs were musculoskeletal and connective tissue disorders (27/186 (14.5%)). The incidence for all other SOCs was ≤ 8.0%. Individual AEs (preferred terms) with an incidence ≥ 5.0% (≥ 10/186 patients) were nasopharyngitis (14/186 (8%)) and upper respiratory tract infection (11/186 (6%)). The proportion of patients with a related AE was 48/186 (25.8%). The most common related AEs were infections.

In the SC-IV Switch Arm the rate of AEs was 300.52 [95% CI: 213.70; 410.82] events per 100 PY. The most common AEs (SOC) were infections and infestations (10/48 patients (20.8%). The

incidence for all other SOCs was ≤ 10.0%. Individual AEs (preferred terms) with an incidence ≥ 5.0% (≥ 3/48 patients) were nasopharyngitis (4/48 (8.3%)) and upper respiratory tract infection (3/48 (6.3%)). A total of 9/48 (18.8%) patients experienced an AE that was reported by the investigator as being related to treatment.

Table 51. Study WA22762 LTE summary of adverse events by intensity (safety population)

	No. of patients (%)			
	162 mg SC qw +DMARD n=631	8 mg/kg IV q4w +DMARD n=631	SC-IV n=48	IV-SC n=186
All grades	527 (83.5)	502 (79.6)	18 (37.5)	88 (47.3)
Grade 1	431 (68.3)	379 (60.1)	14 (29.2)	69 (37.1)
Grade 2	299 (47.4)	297 (47.1)	10 (20.8)	33 (17.7)
Grade 3	84 (13.3)	81 (12.8)	0 (0.0)	11 (5.9)
Grade 4	12 (1.9)	5 (0.8)	0 (0.0)	2 (1.1)
Grade 5	1 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)

Note: SC-IV and IV-SC switch arms include data from the open label phase only.

Source: page 501.

For study WA22762 LTE the incidence of AEs was analysed by body weight at baseline. In both the SC and IV treatment arms, a higher proportion of heavier patients (≥ 100 kg) experienced at least one AE compared with patients in the lighter subgroups.

Table 52. Adverse events by body weight at baseline (safety population)

	No. of patients (%)			
	162 mg SC qw +DMARD	8 mg/kg IV q4w +DMARD	SC-IV	IV-SC
<60 kg	n=144 117 (81.3)	n=146 108 (74.0)	n=12 3 (25.0)	n=46 24 (52.2)
60 to <100 kg	n=425 352 (82.8)	n=422 339 (80.3)	n=33 14 (42.4)	n=125 56 (44.8)
≥ 100 kg	n=62 58 (93.5)	n=63 55 (87.3)	n=3 1 (33.3)	n=15 8 (53.3)

Note: SC-IV and IV-SC switch arms include data from the open label phase only.

Source: page 392 .

In study NP22623, 73 treatment-emergent AEs were reported in 22/29 patients (76%) during the randomized SC treatment phase. The SOC with the highest frequency of AEs were gastrointestinal disorders (most commonly nausea), infections and infestations (most commonly upper respiratory tract infection) and musculoskeletal and connective tissue disorders SOC (most commonly RA).

Two AEs (both injection site erythema) in 2 patients were considered as probably related to trial treatment and 19 AEs in 9 patients were considered as possibly related by the investigator. The remaining 52 AEs were classified as either remotely related or unrelated.

In the ongoing supportive monotherapy Study MRA229JP AEs were reported for 154 patients (89.0%) in the SC TCZ group (q2w) and for 157 patients (90.8%) in the IV TCZ group. The most common SOCs in which AEs were reported were:

- Investigations: 93 patients (53.8%) and 89 patients (51.4%) (most commonly blood cholesterol increased (19.1% vs. 17.9%), low density lipoprotein (LDL] increased (17.3% vs. 13.9%), blood triglycerides increased (0.4% in both groups), and ALT increased (10.4% vs. 9.8%)
- Infections and infestations: 72 patients (41.6%) and 78 patients (45.1%) (most commonly nasopharyngitis (20.8% vs. 17.9%) and upper respiratory tract infection (9.2% vs. 7.5%)
- Skin and subcutaneous tissue disorders: 39 patients (22.5%) and 42 patients (24.3%)
- Gastrointestinal disorders: 34 patients (19.7%) and 43 patients (24.9%)
- General disorders and administration site Conditions: 33 patients (19.1%) and 13 patients (7.5%)
- Metabolism and nutrition Disorders: 9 patients (5.2%) and 20 patients (11.6%) Nervous System Disorders: 18 patients (10.4%) and 5 patients (2.9%).

Injection site reactions (mostly injection site erythema) at the site of subcutaneous administration (of active substance or placebo) were more frequent in the SC TCZ group with an incidence of 12.1% than in the IV TCZ group (5.2%).

In the dose escalation study MRA227JP (monotherapy) all of the 32 patients experienced AEs By SOC, the most frequently reported AEs included: investigations (with most commonly increased blood triglycerides, followed by low density lipoprotein, and increased ALT); infections and infestations (most commonly nasopharyngitis) and gastrointestinal disorders.

Serious adverse event / deaths / other significant events

Table 53. Overview of SAEs at week 24 in SC TCZ and IV TCZ clinical studies (safety population)

	Study WA22762		Study NA25220		Week 24 Analyses from IV TCZ Phase III Clinical Studies		
	162 mg SC TCZ qw+DMARD N = 631	8 mg/kg IV TCZ q4w+DMARD N = 631	162 mg SC TCZ q2w+DMARD N = 437	PI SC q2w+DMARD N = 218	8 mg/kg IV TCZ q4w+DMARD N = 1582	4 mg/kg IV TCZ q4w+MTX N = 774	PI+DMARD N = 1170
Duration in study (PY)	289.82	288.39	182.68	81.80	753.50	344.74	507.24
Patients with SAE	29 (4.6%)	33 (5.2%)	20 (4.6%)	8 (3.7%)	95 (6.0%)	46 (5.9%)	62 (5.3%)
Number of SAEs	34	43	25	12	115	51	75
Rate per 100 PY (95% CI)	11.73 (8.12, 16.39)	14.91 (10.79, 20.08)	13.68 (8.86, 20.20)	14.67 (7.58, 25.62)	15.26 (12.60, 18.32)	14.79 (11.02, 19.45)	14.79 (11.63, 18.53)

CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; IV = intravenous; PI = placebo; PY = patient years; q2w = every two weeks; q4w = every four weeks; qw = every week; SAE = serious adverse event; SC = subcutaneous; TCZ = tocilizumab.

Duration in study = date of last assessment - date of first dose + 1 day / 365.25.

Multiple occurrences of the same event in one individual are counted.

Source: staerate01_serious_wk24_2, stae11_s, and Table 23 and Table 24 in Safety Summary of original IV TCZ submission.

In study NA25220 the percentage of patients who experienced at least one SAE during the study was similar in both arms 4.6% of patients in the TCZ arm vs. 3.7% in the placebo arm. The most common SOC in which SAEs were reported was infections/infestations (TCZ 2.1%) and placebo 1.8%. These cases were all rated as treatment related. Three patients were reported with malignancies (one classified as non-serious AE) during the study, all in the TCZ arm. The events were considered unrelated by the investigator. One SAE of bleeding was reported, an event of haemorrhage in the TCZ arm.

In study WA22762 core the proportion of patients who experienced at least one SAE during the study was similar in both arms (4.6% of patients in the SC arm vs. 5.2% in the IV arm), with the total number of SAEs higher in the IV arm (33 SC arm vs. 41, IV arm). The most common SOC in which SAEs were reported was infections and infestations, which occurred at a similar frequency in both arms (1.4% each), with no specific type of event being predominant. Musculoskeletal and connective tissue disorders were the next most commonly reported SAEs (3 patients in the SC arm vs. 6 patients in the IV arm), followed by nervous system disorders (2 patients SC arm vs. 6 patients IV arm), with higher numbers of SAEs in the IV arm. Two events of haemorrhage (haemorrhoidal haemorrhage and rectal haemorrhage were reported. The two cases were not associated with Grade 2 or 3 decreased platelet count. The proportion of SAEs considered by the investigator to be related to treatment was balanced across the two arms at 27% (9 of 33 events) in the SC arm and 29% (12 of 41 events) in the IV arm. The most frequent treatment-related SAEs were from the infections and infestations SOC (5 of 33 events in SC arm vs. 7 of 41 events IV arm).

Table 54. Overview of SAEs in studies WA22762 and NA25220 until clinical cut-off (safety population)

	WA22762		NA25220
	162 mg SC TCZ qw (PFS)+DMARD N=631	8 mg/kg IV TCZ q4w+DMARD N=631	162 mg SC TCZ q2w (PFS)+DMARD N=437
Total duration in study (PY)	454.20	401.02	222.09
Patients with SAE	50 (7.9%)	47 (7%)	23 (5.3%)
Number of SAEs	66	61	29
Rate per 100 PY (95% CI)	14.53 (11.24, 18.49)	15.21 (11.64, 19.54)	13.06 (8.74, 18.75)

CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; IV = intravenous; PFS = prefilled syringe; PY = patient years; q4w = every four weeks ; q2w = every two weeks; qw = every week; SAE = serious adverse event; SC = subcutaneous; TCZ = tocilizumab.

Clinical cutoff 16 January 2012 for WA22762 and 28 May 2012 for NA25220.

SC TCZ arms: Analyses include all patients who received SC TCZ using the PFS in the double-blind period starting from their first dose. Data after switch to IV TCZ (in WA22762) or the AI (in NA25220) in the open-label extension are not included.

IV TCZ arm: Analyses include all patients who received IV TCZ in the double-blind period starting from their first dose. Data after switch to SC TCZ in the open-label extension are not included.

Multiple occurrences of the same AE in one individual are counted.

Source: stae17_s_b LTE CSR WA22762, staerate01_serious_2 LTE CSR WA22762, staerate01_serious_2 LTE CSR NA25220, stae11_s_pt_b LTE CSR NA25220.

In the supportive monotherapy study MRA229JP SAEs were recorded for 13 of 173 patients (7.5%) in the SC TCZ group and for 10 of 173 patients (5.8%) in the IV TCZ group. Events classified in the SOC of infections and infestations were reported for 2 patients (1.2%) in the SC TCZ group and for 5 patients (2.9%) in the IV TCZ group. The only types of events reported for more than one patient in a given treatment group were 2 patients each with herpes zoster or pneumonia in the IV TCZ group.

One SAE was reported in the supportive phase I/II study MRA227JP, a causal relationship between TCZ and the pyelonephritis could not be excluded.

There were no SAEs during the randomized SC treatment phase of the phase Ib study NP22623. In the post-study provisional care program, 1 out of 13 patients) was diagnosed with lung adenocarcinoma. The SAE was considered unrelated to the study drug.

Table 55. Overview of death in pooled SC TCZ and IV TCZ (all exposure population)

	SC TCZ All-exposure N=1465	IV TCZ All-exposure N=4171
Total Exposure (PY)	893.92	16204.77
Deaths	5	94
Rate per 100 PY (95% CI)	0.56 (0.18, 1.31)	0.58 (0.47, 0.71)

CI=confidence interval; IV=intravenous; PY=patient years; SC=subcutaneous; TCZ=tocilizumab.

Source: STrate_dd, and STrate_dd in IV safety update report.

Table 56. Overview of death in studies WA22762 and NA252220 until clinical cut-off (safety population)

	WA22762		NA25220
	162 mg SC TCZ qw (PFS) + DMARD N=631	8 mg/kg IV TCZ q4w + DMARD N=631	162 mg SC TCZ q2w (PFS) + DMARD N=437
Total duration in study (PY)	454.20	401.02	182. 68
Patients who died	1	2	4
Rate per 100 PY (95% CI)	0.22 (0.01, 1.23)	0.50 (0.06, 1.80)	1.35 (0.28, 3.95)

CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; IV = intravenous; PFS = prefilled syringe; PY = patient years; q2w = every two weeks; q4w = every four weeks; qw = every week; SC = subcutaneous; TCZ = tocilizumab.

Clinical cutoff 16 January 2012 for WA22762 and 28 May 2012 for NA25220.

SC TCZ arms: Analyses include all patients who received SC TCZ using the PFS in the double-blind period starting from their first dose. Data after switch to IV TCZ (in WA22762) or the AI (in NA25220) in the open-label extension are not included.

IV TCZ arm: Analyses include all patients who received IV TCZ in the double-blind period starting from their first dose. Data after switch to SC TCZ in the open-label extension are not included.

Source: staerate01_death_2 LTE CSR WA22762, staerate01_death_2 LTE CSR NA25220.

Three deaths were reported in study NA25220 during 24 weeks period in the TCZ arm, two as a result of a sepsis and one death as result of a lower respiratory tract infection. One additional death due to angina pectoris was reported in study NA25220 LTE.

In study WA22762 one death due to sepsis, secondary to bacterial arthritis of the right tarsus, was reported in the TCZ IV group during the 24 weeks treatment period. Two more deaths were reported in in study WA22762 LTE, one in the SC arm and one in the IV arm. The patient in the SC arm died of shock (unknown cause) associated with pelvic pain 11 days after her last dose of TCZ. The investigator considered the death as well as the pelvic pain and shock SAEs to be related to study treatment. The patient in the IV arm died approximately 6 months after her last dose of TCZ due to hyperkalaemia and hypocalcaemia AEs. The investigator considered the death

to be unrelated to study treatment. At the time of the data cut, the cause of death was unknown; however, the death has since been attributed to idiopathic pulmonary fibrosis.

There were no deaths in any of the supporting studies, including the monotherapy study MRA229JP.

Immunological events

Table 57. Patients who developed confirmatory or neutralising ant-TCZ antibodies during 24 week period (safety population)

	WA22762		NA25220	
Assay	162 mg SC TCZ qw+DMARD (N=631)	8 mg/kg TCZ IV q4w+DMARD (N=631)	162 mg SC TCZ q2w (N=437)	Placebo SC q2w (N=219)
N (%)				
Tested by screening assay at any time point	625 (99.0)	627 (99.4)	434 (99.3)	217 (99.5)
Patients with positive assay post-baseline				
Confirmation assay +	5 (0.8)	5 (0.8)	7 (1.6)	3 (1.4)
Confirmation assay + and Neutralizing assay +	5 (0.8)	5 (0.8)	6 (1.4)	1 (0.5)

IV = intravenous; q2w = every two weeks; q4w = every four weeks; qw = every week; SC = subcutaneous; TCZ = tocilizumab.

Source: Table 105 in NA25220 CSR and Table 8 in WA22762 Immunogenicity Report

Table 58. Study NA22520 LTE patients with anti-TCZ results or positive anti-TCZ neutralising assay results (safety population)

Assay	TCZ PFS q2w (N=437)	TCZ PFS q2w → TCZ AI q2w (N=168)	Placebo PFS q2w → TCZ PFS q2w (N=61)	Placebo PFS q2w → TCZ AI q2w (N=59)
N (%)				
Tested by screening assay at any time point	434 (99.3)	167 (99.4)	60 (98.4)	59 (100)
Patients with positive assay post-baseline				
Confirmed assay	7 (1.6)	1 (0.6) [a]	1 (1.6)	1 (1.7)
Neutralizing assay + and Confirmation assay + [b]	6 (1.4)	1 (0.6)	0	1 (1.7)

IV = intravenous; q2w = every two weeks; SC = subcutaneous; TCZ = tocilizumab.

[a] Patient counted in both TCZ PFS and TCZ PFS to TCZ AI group

[b] At any timepoint

Table 59. Study WA22762 LTE patients with anti-TCZ results or positive anti-TCZ neutralising assay results (safety population)

Assay	162 mg SC TCZ (N = 631)	8 mg IV TCZ (N = 631)	SC-to-IV Switch (N=48)	IV-to-SC Switch (N=186)
N (%)				
Tested by screening assay at any time point	625 (99.0)	627 (99.4)	48 (100)	185 (99.5)
Patients with positive assay post-baseline				
Confirmed assay	6 (1.0) [a]	6 (1.0) [b]	1 (2.1)	1 (0.5)
Neutralizing assay + and Confirmation assay +	6 (1.0) [a]	6 (1.0) [b]	1(2.1)	1 (0.5)

IV = intravenous; SC = subcutaneous; TCZ = tocilizumab.

[a] Data are cumulative (from baseline to LTE data cutoff) and include results for patients in the SC-to-IV crossover group.

[b] Data are cumulative (from baseline to LTE data cutoff) and include results for patients in the IV-to-SC crossover group.

Source: Sections 3.3 and 3.4.2 in WA22762 Immunogenicity Report

In patients receiving TCZ SC who developed neutralizing anti-TCZ antibodies post-baseline, there appeared to be no impact on efficacy. None of these patients withdrew for lack of efficacy or loss of efficacy (defined as achieving an ACR50 or DAS28-EULAR good response prior to withdrawal for insufficient therapeutic response).

Of patients treated with TCZ SC who experienced a serious or clinically significant hypersensitivity reaction, none were positive for anti-TCZ antibodies. Only one patient who experienced an ISR had a positive ADA result.

Adverse events of special interest

The types of AEs were predefined based on findings from nonclinical and clinical studies with TCZ, safety concerns for the RA population (e.g. cardiovascular risk, malignancies), as well as the safety profile of other monoclonal antibodies used in RA. These AEs of special interest (AESIs) were defined using published standardized MedDRA queries (SMQs), SOCs, high-level terms (HLT), or AE group terms (AEGTs) defined by Roche Drug Safety. No new unexpected AEs occurred in the SC TCZ clinical studies.

Table 60. Rates of AEs of special interest per 100 Patient Years in pooled SC TCZ and IV TCZ all exposure population

AE of Special Interest	SC TCZ All-exposure N = 1465	IV TCZ All-exposure N = 4171
Infections (All grades)	1023	15026
Rate per 100 PY (95% CI)	114.44 (107.53, 121.67)	92.73 (91.25, 94.22)
Serious infections	39	717
Rate per 100 PY (95% CI)	4.36 (3.10, 5.96)	4.42 (4.11, 4.76)
Malignancies	13	249
Rate per 100 PY (95% CI)	1.45 (0.77, 2.49)	1.54 (1.35, 1.74)
Serious malignancies	8	156
Rate per 100 PY (95% CI)	0.89 (0.39, 1.76)	0.96 (0.82, 1.13)
Anaphylactic reactions	0	8
Rate per 100 PY (95% CI)	-	0.05 (0.02, 0.10)
Serious hypersensitivity[a]	4	44
Rate per 100 PY (95% CI)	0.45 (0.12, 1.15)	0.27 (0.20, 0.36)
Hypersensitivity leading to withdrawal	10	61
Rate per 100 PY (95% CI)	1.12 (0.54, 2.06)	0.38 (0.29, 0.48)
Injection site reactions (SC treatment)	126	N/A
Rate per 100 PY (95% CI)	64.55 (59.39, 70.04)	
Serious hepatic AEs	0	7
Rate per 100 PY (95% CI)	0	0.04 (0.02, 0.09)
Serious ischemic and hemorrhagic cerebrovascular conditions	4	52
Rate per 100 PY (95% CI)	0.45 (0.12, 1.15)	0.32 (0.24, 0.42)
Serious myocardial Infarction	3	44
Rate per 100 PY (95% CI)	0.34 (0.07, 0.98)	0.27 (0.20,0.36)
Medically confirmed GI perforation	0	33
Rate per 100 PY (95% CI)	0	0.20 (0.14,0.29)
Spontaneous or serious bleeding	5	68
Rate per 100 PY (95% CI)	0.56 (0.18, 1.31)	0.42 (0.33, 0.53)
Serious demyelinating disorders	0	3
Rate per 100 PY (95% CI)	0	0.02 (0.00, 0.05)

CI = confidence interval; IV = intravenous; PY = patient years; SC = subcutaneous; TCZ = tocilizumab.

[a] Events reported during or within 24 hours of the injection or infusion (excluding injection site reactions), and that were not deemed by the investigator as unrelated to treatment

Infections

Table 61. Overview of infections at week 24 in SC TCZ and IV TCZ clinical studies (safety population)

	Study WA22762		Study NA25220		Week 24 Analyses from IV TCZ Phase III Clinical Studies		
	162 mg SC TCZ qw + DMARD N = 631	8 mg/kg IV TCZ q4w + DMARD N = 631	162 mg SC TCZ q2w + DMARD N = 437	Pl SC q2w + DMARD N = 218	8 mg/kg IV TCZ q4w + DMARD N = 1582	4 mg/kg IV TCZ q4w + MTX N = 774	Pl + DMARD N = 1170
Duration in study (PY)	269.62	266.39	182.66	81.60	753.50	344.74	507.24
Patients with infections	227 (36.0%)	247 (39.1%)	131 (30.0%)	61 (28.0%)	592 (37.4%)	270 (34.9%)	374 (32.0%)
Number of events	348	360	176	82	888	419	525
Rate per 100 PY (95% CI)	120.07 (107.79, 133.38)	124.83 (112.27, 138.42)	96.34 (82.63, 111.67)	100.24 (79.73, 124.43)	117.85 (110.22, 125.86)	121.54 (110.18, 133.76)	103.5 (94.84, 112.75)
Patients with serious infections	9 (1.4%)	9 (1.4%)	9 (2.1%)	4 (1.8%)	38 (2.4%)	13 (1.7%)	17 (1.5%)
Number of events	9	10	12	5	39	15	19
Rate per 100 PY (95% CI)	3.11 (1.42, 5.89)	3.47 (1.66, 6.38)	6.57 (3.39, 11.47)	6.11 (1.98, 14.26)	5.18 (3.68, 7.08)	4.35 (2.44, 7.18)	3.75 (2.26, 5.85)
Deaths from infections	0	1 (0.2%)	3 (0.7%)	0	1 (0.1%)	0	1 (0.1%)
Withdrawal for infections	7 (1.1%)	8 (1.3%)	3 (0.7%)	2 (0.9%)	8 (0.5%)	5 (0.6%)	7 (0.6%)

DMARD = disease-modifying anti-rheumatic drug; IV = intravenous; Pl = placebo; PY = patient years; q2w = every two weeks; q4w = every four weeks; qw = every week; SAE = serious adverse event; SC = subcutaneous; TCZ = tocilizumab.

Duration in study = date of last assessment - date of first dose + 1 day / 365.25. Multiple occurrences of the same event in one individual are counted.

Analysis of SC TCZ data based on MedDRA version 15.0 SOC "Infections and Infestations".

Analysis of IV TCZ data based on MedDRA version 10.0 SOC "Infections and Infestations".

Source: stae11_inf , stae11_sinf, staerate01_inf_wk24_2, staerate01_serinf_wk24_2, sldd02, and stae11_inf, staerate01_inf_wk24_2, staerate01_serinf_wk24_2, sldd02; STrate_ae_inf, STrate_ae_inf_s in Safety Summary of original IV TCZ submission

Table 62. Overview of infections in studies NA25220 and WA 22762 until clinical cut-off (safety population)

	WA22762		NA25220
	162 mg SC TCZ qw (PFS) + DMARD N = 631	8 mg/kg IV TCZ q4w + DMARD N = 631	162 mg SC TCZ q2w (PFS) + DMARD N = 437
Total duration in study (PY)	454.20	401.02	222.09
Patients with infections	311 (49.3%)	284 (45.0%)	149 (34.1%)
Number of events	575	487	218
Rate per 100 PY (95% CI)	126.60 (116.46, 137.38)	121.44 (110.89, 132.72)	98.16 (85.56, 112.09)
Patients with serious infections	16 (2.5%)	11 (1.7%)	9 (2.1%)
Number of events	16	12	12
Rate per 100 PY (95% CI)	3.52 (2.01, 5.72]	2.99 (1.55, 5.23)	5.40 (2.79, 9.44)
Deaths from infections	0	1	3 (0.7%)
Rate per 100 PY (95% CI)	0 (0, 0.81)	0.25 (0.006, 1.39)	1.35 (0.28, 3.95)

CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; PFS = prefilled syringe; IV = intravenous; PY = patient years; q2w = every two weeks; q4w = every four weeks; qw = every week; SC = subcutaneous; TCZ = tocilizumab.

Clinical cutoff 16 January 2012 for WA22762 and 28 May 2012 for NA25220.

SC TCZ arms: Analyses include all patients who received SC TCZ using the PFS in the double-blind period starting from their first dose. Data after switch to IV TCZ (in WA22762) or the AI (in NA25220) in the open-label extension are not included.

IV TCZ arm: Analyses include all patients who received IV TCZ in the double-blind period starting from their first dose. Data after switch to SC TCZ in the open-label extension are not included.

Multiple occurrences of the same AE in one individual are counted

In study NA25220 the rates of infections and serious infections through week 24 were similar in the SC TCZ and the placebo arm. Nine patients in the TCZ arm (2.1%) and four patients in the placebo arm (1.8%) experienced at least one serious infection. Sepsis and lower respiratory tract infection were observed in 2 patients in the TCZ arm, and pneumonia was observed in 2 patients in the placebo arm. None of the serious infections was associated with Grade 3 or 4 neutropenia. One SAE of pulmonary tuberculosis was reported in the SC TCZ arm.

Three deaths were reported as a result of infections, all in the SC TCZ arm (see above).

During the long term follow up in study NA25220 LTE the rates of infections and serious infections in the TCZ PFS Arm up to the clinical cut-off were consistent with the rates at week 24. No additional serious infections were reported in patients in the TCZ PFS arm after re-randomization.

The rate of infections was higher in the patients who switched from TCZ PFS to TCZ AI (142.48 [95% CI: 106.72, 186.36] per 100 PY) compared to the rate observed in the TCZ PFS Arm up to week 24 (96.34 [95% CI: 82.63, 111.67]). One patient in the TCZ PFS-to-TCZ AI arm experienced Grade 4 bacterial arthritis, considered by the investigator to be related to study treatment. No additional serious infections were reported.

The rate of infection and infestation AEs in patients who switched from Placebo-to-TCZ PFS (144.74 per 100 PY) was higher than the rate in patients who switched from placebo to TCZ AI (43.63 per 100 PY) or the rate in the placebo arm in the 24-week double-blind treatment period (97.41 per 100 PY).

No events of opportunistic infection were reported in patients treated with TCZ up to the clinical cut-off. There were no cases of tuberculosis reported during the LTE at the clinical cut-off.

The rate of infections in Escape Patients was similar in the prior TCZ arm (108.23 [95% CI: 75.80, 149.84] per 100 PY) and the prior placebo arm (114.2 [95% CI: 83.30, 152.81] per 100 PY). The rate of serious infections following escape therapy was 9.02 (95% CI: 1.86, 26.36) per 100 PY in the prior TCZ arm and 7.61 (95% CI: 1.57, 22.25) per 100 PY in the prior placebo arm. Three patients each in the prior TCZ arm (4.2%) and prior placebo arm (3.3%) experienced serious infections. One event of new onset pulmonary tuberculosis (an SAE) occurred in a patient who was on TCZ Escape treatment, and led to discontinuation of treatment.

The rates for all infections and serious infections observed in the first 24 weeks of study WA22762 were similar between the SC and IV treatment arms. Of a total of 19 serious infections were reported. None of the serious infections were associated with Grade 3 or 4 neutropenia. During the long term extension study WA22762 LTE again, the overall rates of infections and serious infections were similar between SC and IV treatment arms and similar to the rates observed in the initial 24 weeks of the study.

There were no cases of tuberculosis reported at the clinical cut-off.

In the monotherapy study MRA229JP AEs classified under the SOC of infections and infestations occurred in 72 patients (41.6%) and 78 patients (45.1%) in the 162 mg SC TCZ q2w and the 8 mg/kg IV TCZ q4w groups, respectively. Serious infections were experienced by 2 patients (1.2%) and 5 patients (2.9%) in the SC and IV TCZ groups, respectively.

In study MRA2227JP AEs classified under the SOC of infections and infestations occurred in 17 patients (53.1%) in the three treatment groups combined. Although the sample size was small,

the incidence of Infections and Infestations tended to increase with dose. One infection (pyelonephritis in the 81 mg q2w group) was assessed as severe in intensity; this event was also reported as a SAE. A causal relationship to TCZ could not be excluded for the event. All other infections were mild in intensity

Malignancies

The rate of malignancies per 100 PY of exposure was comparable between the SC and IV all-exposure. The review of the events did not identify any clear pattern of event types.

No malignancies were reported in studies MRA229JP or MRA227JP.

Anaphylaxis

No events of anaphylaxis related to SC TCZ administration have occurred in the pivotal studies or study MRA229JP.

Two anaphylactic reactions were reported in the TCZ IV arm in study WA22762 LTE. Both anaphylaxis AEs occurred more than 24 hours after TCZ IV infusion.

In study MRA227JP, one AE of anaphylactoid reaction was reported in 1 of 12 patients (8.3%) in the 162 mg q2w group in Period III.

Hypersensitivity

Table 63. Overview of hypersensitivity in the pivotal studies until clinical cut-off (safety population)

	WA22762		NA25220
	162 mg SC TCZ qw (PFS) + DMARD N = 631	8 mg/kg IV TCZ q4w + DMARD N = 631	162 mg SC TCZ q2w (PFS) + DMARD N = 437
Total duration in study (PY)	454.20	401.02	222.09
All Hypersensitivity Reactions [a]			
Patients with event	57 (9.0%)	75 (11.9%)	21 (4.8%)
Number of events	87	125	27
Rate per 100 PY (95% CI)	19.15 (15.34, 23.63)	31.17 (25.95,37.14)	12.16 (8.01, 17.69)
Clinically Significant Hypersensitivity Reactions [b]			
Patients with event	7 (1.1%)	12 (1.9%)	3 (0.7%)
Number of events	7	13	3
Rate per 100 PY (95% CI)	1.54 (0.61, 3.18)	3.24 (1.73, 5.54)	1.35 (0.28, 3.95)
Serious Hypersensitivity Reactions			
Patients with event	4 (0.6%)	3 (0.5%)	0
Number of events	4	3	0
Rate per 100 PY (95% CI)	0.88 (0.24, 2.25)	0.75 (0.15, 2.19)	-
Serious Clinically Significant Hypersensitivity Reactions [b]			
Patients with event	2 (3.2%)	1 (0.2%)	0
Number of events	2	1	0
Rate per 100 PY (95% CI)	0.44 (0.05, 1.59)	0.25 (0.01, 1.39)	-

CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; IV = intravenous; PY = patient years; SC = subcutaneous; TCZ = tocilizumab.

Clinical cutoff 16 January 2012 for WA22762 and 28 May 2012 for NA25220.

SC TCZ arms: Analyses include all patients who received SC TCZ using the PFS in the double-blind period starting from their first dose. Data after switch to IV TCZ (in WA22762) or the AI (in NA25220) in the open-label extension are not included.

IV TCZ arm: Analyses include all patients who received IV TCZ in the double-blind period starting from their first dose. Data after switch to SC TCZ in the open-label extension are not included.

Multiple occurrences of the same AE in one individual are counted.

Table 64. Study WA22762 LTE rate of hypersensitivity events per 100 patient years (safety population)

	162 mg SC qw +DMARD	8 mg/kg IV q4w +DMARD	SC-IV	IV-SC
PY Exposure	454.20	401.02	12.98	58.37
All Hypersensitivity Events [a]				
Rate per 100 PY [95% CI]	19.15 [15.34; 23.63]	31.17 [25.95;37.14]	0.00	15.42 [7.05;29.27]
No. patients	57	75	0	9
No. events	87	125	0	9
Clinically Significant Hypersensitivity Events (leading to withdrawal) [b]				
Rate per 100 PY [95% CI]	1.54 [0.62; 3.18]	3.24 [1.73;5.54]	0.00	0.00
No. patients	7	12	0	0
No. events	7	13	0	0
Serious Hypersensitivity Events (reported as an SAE) [c]				
Rate per 100 PY [95% CI]	0.88 [0.24;2.25]	0.75 [0.15;2.19]	0.00	0.00
No. patients	4	3	0	0
No. events	4	3	0	0
Serious Clinically Significant Hypersensitivity Events (SAE leading to withdrawal) [d]				
Rate per 100 PY [95% CI]	0.44 [0.05; 1.59]	0.25 [0.01;1.39]	0.00	0.00
No. patients	2	1	0	0
No. events	2	1	0	0

Note: SC-IV and IV-SC switch arms include data from the open label phase only.

a Hypersensitivity event defined as any AE (excluding ISRs) that occurred during or within 24 hours of a TCZ/placebo infusion or injection and not deemed 'unrelated' to trial treatment. Includes all types of AE except ISRs that occurred within 24 hours of study drug administration, regardless of whether or not they were clinically consistent with hypersensitivity.

b Hypersensitivity event that led to withdrawal from treatment.

c Hypersensitivity event reported as an SAE.

d Hypersensitivity event reported as an SAE and leading to withdrawal.

Source: page 787, page 789, page 791; page 793; page 779.

Injection site rections

Table 65. Overview of injection site reactions in the pivotal studies until clinical cut-off (safety population)

	Study WA22762 [a]		Study NA25220	
	162 mg SC TCZ qw + DMARD N = 631	8 mg/kg IV TCZ q4w + DMARD N = 631	162 mg SC TCZ q2w + DMARD N = 437	PI SC q2w + DMARD N = 218
Duration in study (PY)	289.82	288.39	182.68	81.80
Patients with event	64 (10.1%)	15 (2.4%)	31 (7.1%)	9 (4.1%)
Number of events	168	94	57	10
Rate per 100 PY (95% CI)	57.97 (49.53, 67.43)	32.59 (26.34, 39.89)	31.20 (23.63, 40.43)	12.22 (5.86, 22.48)

CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; IV = intravenous; PI = placebo; PY = patient years; q2w = every two weeks; q4w = every four weeks; qw = every week; SC = subcutaneous; TCZ = tocilizumab.

Duration in study = (date of last assessment - date of first dose + 1 day) / 365.25.

Multiple occurrences of the same event in one individual are counted.

[a] Events in the IV TCZ arm refer to ISRs to SC injections of placebo

Source: stae11_isr, and taerate01_isreact_wk24_2.

In study MRA227JP and Study MRA229JP, 3.1% and 12.1% of patients, respectively, who received SC TCZ experienced injection site reactions, as did 5.2% of patients in the IV arm of study MRA229JP.

Laboratory findings

Neutropenia and abnormal neutrophil count

Table 66. Incidence of neutropenia by CTC Grade at week 24 (safety population)

Neutropenia Grade	No. of Patients (%)						
	WA22762 (TCZ qw)		NA25220 (TCZ q2w)		Pooled Historical IV TCZ Data		
	TCZ 162 mg SC qw N = 631	TCZ 8 mg/kg IV q4w N = 631	TCZ 162 mg SC q2w N = 437	Placebo SC q2w N = 218	Placebo IV q4w N = 1170	TCZ 4 mg/kg IV q4w N = 774	TCZ 8 mg/kg IV q4w N = 1582
n	631	631	417	196	1170	774	1582
Normal	406 (64.3%)	464 (73.5%)	334 (80.1%)	191 (97.4%)	1122 (95.9%)	614 (79.3%)	1047 (66.2%)
Grade 1	126 (20.0%)	86 (13.6%)	45 (10.8%)	5 (2.6%)	30 (2.6%)	88 (11.4%)	298 (18.8%)
Grade 2	81 (12.8%)	61 (9.7%)	22 (5.3%)	0 (0%)	10 (<1%)	53 (6.8%)	179 (11.3%)
Grade 3	17 (2.7%)	20 (3.2%)	15 (3.6%)	0 (0%)	0 (0%)	9 (1.2%)	48 (3.0%)
Grade 4	1 (<1%)	0 (0.0%)	1 (0.2%)	0 (0%)	1 (<1%)	5 (<1%)	6 (<1%)

IV = intravenous; q2w = every two weeks; q4w = every four weeks; qw = every week; SC = subcutaneous; TCZ = tocilizumab.

CTC Grade 1: <LLN - 1500/mm^3; CTC Grade 2: <1500 - 1000/mm^3 ; CTC Grade 3: <1000 - 500/mm^3; CTC Grade 4: <500/mm^3

Source: ST1b_gradtt in WA22762 and NA25520 24-week CSRs, and and ST1b+gradtt in Safety Summary of original IV TCZ submission

Study NA25220

Table 67. Neutropenia by worst NCI CTCAE grade (safety population)

Baseline Body Weight	No. of Patients (%)	
	TCZ PFS q2w (n=437)	Placebo PFS q2w (n=218)
All body weights	n=429	n=218
Grade 1	49 (11)	6 (3)
Grade 2	20 (5)	0
Grade 3	13 (3)	0
Grade 4	1 (< 1)	0
< 60 kg	n=112	n=58
Grade 1	16 (14)	2 (3)
Grade 2	7 (6)	0
Grade 3	1 (< 1)	0
Grade 4	0	0
60 to < 100 kg	n=292	n=149
Grade 1	32 (11)	4 (3)
Grade 2	13 (4)	0
Grade 3	9 (3)	0
Grade 4	0	0
≥ 100 kg	n=25	n=11
Grade 1	1 (4)	0
Grade 2	0	0
Grade 3	3 (12)	0
Grade 4	1 (< 1)	0

Table 68. Number and percentage of patients with neutropenia (worst neutrophil value from baseline normal value), by observed week 24 C_{trough} Quartiles (PK-ITT population)

	Q1	Q2	Q3	Q4
Group A (162 mg SC q2w via PFS)	n=81	n=80	n=80	n=80
Grade 1 (%)	5 (6)	3 (4)	12 (15)	18 (23)
Grade 2 (%)	0 (0)	4 (5)	5 (6)	9 (11)
Grade 3 (%)	1 (1)	2 (3)	4 (5)	1 (1)

PFS = pre-filled syringe; q2w = every 2 weeks; SC = subcutaneous.
Note: Quartiles were defined for patients whose values fell within 0 to ≤25%, >25 to ≤50%, >50% to ≤75%, >75 to 100% of exposures.
Source: page 792.

Neutropenia (including "decreased neutrophil count") was reported as an AE for 5% patients in the TCZ arm. One patient was withdrawn because of the event. For an additional 8 patients (2%) of the 437 patients in the TCZ arm, the neutropenia led to dose modification or interruption. Of the 16 patients with NCI CTCAE Grade 3 or 4 non-serious neutropenia, 2 patients in the TCZ arm experienced a non-serious infection with onset after the episode neutropenia.

Platelet count

In the TCZ arm, mean and median platelet counts decreased within the normal range after the first study drug dose and remained lower for the remainder of the 24-week treatment period

Markedly low platelet counts ($< 100 \times 10^9$/L and a $\geq$ 30% change from baseline) were reported in less than 1% of TCZ treated patients. In one patient this resulted in a dose modification.

During the long term extension in study NA25220 LTE the results on platelet counts were consistent with the week 24 data.

Table 69. Study WA22762 newly occurring neutropenia, by worst NCI CTCAE grade and baseline body weight (safety population)

Baseline Body Weight	No. of Patients (%)	
	162 mg SC qw + DMARD (n = 631)	8 mg/kg IV q4w + DMARD (n = 631)
All body weights	n = 628	n = 628
Grade 1	124 (19)	86 (14)
Grade 2	80 (13)	60 (10)
Grade 3	17 (3)	20 (3)
Grade 4	1 (< 1)	0 (0)
< 60 kg	n = 142	n = 144
Grade 1	29 (20)	18 (12)
Grade 2	28 (20)	16 (11)
Grade 3	5 (4)	6 (4)
Grade 4	1 (< 1)	0 (0)
60–100 kg	n = 425	n = 421
Grade 1	85 (20)	61 (14)
Grade 2	50 (12)	41 (10)
Grade 3	10 (2)	12 (3)
Grade 4	0 (0)	0 (0)
≥ 100 kg	n = 61	n = 63
Grade 1	10 (16)	7 (11)
Grade 2	2 (3)	3 (5)
Grade 3	2 (3)	2 (3)
Grade 4	0 (0)	0 (0)

AE = adverse events; DMARD = disease-modifying anti-rheumatic drug; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; q4w = every 4 weeks; qw = once weekly; SC = subcutaneous.

Table 70. Study WA22762 LTE newly occurring neutropenia by worst NCI CTCAE Grade (ITT population)

	No. of Patients (%)			
	162 mg SC qw +DMARD (N=524)	8 mg/kg IV q4w +DMARD (N=377)	IV-SC (N=186)	SC-IV (N=48)
Grade 1	107 (20.4)	58 (15.4)	30 (16.1)	16 (33.3)
Grade 2	68 (13.0)	35 (9.3)	25 (13.4)	7 (14.6)
Grade 3	19 (3.6)	15 (4.0)	5 (2.7)	0 (0.0)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

DMARD = disease-modifying antirheumatic drug; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; q4w = every 4 weeks; qw = once weekly; SC = subcutaneous.

Includes data from the double blind and open label phases for all four arms.

Source: page 864.

Table 71. Study WA22762 LTE neutropenia adverse events (safety population)

	No. of Patients (%)			
	162 mg SC qw +DMARD (N=631)	8 mg/kg IV q4w +DMARD (N=631)	IV-SC (N=186)	SC-IV (N=48)
Neutropenia				
AE	31 (4.9)	26 (4.1)	2 (1.1)	0 (0.0)
Withdrawal	2 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)
Dose modification	14 (2.2)	14 (2.2)	1 (0.5)	0 (0.0)
Decreased neutrophil count				
AE	8 (1.3)	2 (0.3)	0 (0.0)	0 (0.0)
Withdrawal	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Dose modification	3 (0.5)	2 (0.3)	0 (0.0)	0 (0.0)
Total				
AE	39 (6.2)	28 (4.4)	2 (1.1)	0 (0.0)
Withdrawal	3 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)
Dose modification	17 (2.7)	16 (2.5)	1 (0.5)	0 (0.0)

AE = adverse event; DMARD = disease-modifying antirheumatic drug; IV = intravenous; q4w = every 4 weeks; qw = once weekly; SC = subcutaneous.

Includes data from the double blind and open label phases for the SC and IV arms but only from the open-label phase for the IV-SC and SC-IV switch arms.

Source: page 282 , page 644 , and page 652.

In study MRA229JP, mean neutrophil count decreased by approximately 30% from baseline values by 24 weeks. Decreases in neutrophil count were comparable between the SC TCZ and IV

TCZ groups. In both groups, Grade 3 or 4 decreases in neutrophil count occurred in 5 patients. Among these patients, non-serious infections were recorded for 2 patients in the SC TCZ group and 3 patients in the IV TCZ group; all infections were mild.

In study MRA227JP, mean neutrophil count decreased by Week 35, in each of the three treatment groups. A reduction in neutrophil count of two or more grades occurred in 1 patient in the 81 mg q2w and in 3 patients in the 162 mg q2w group. Among these patients, non-serious infections of pharyngitis and nasopharyngitis (all mild) and one event of pyelonephritis (severe) were recorded.

Platelet count

Table 72. Incidence of thrombocytopenia by CTC Grade at week 24 (safety population)

Thrombocyopenia Grade	No. of Patients (%)						
	WA22762 (TCZ qw)		NA25220 (TCZ q2w)		Pooled Historical IV TCZ Data		
	TCZ 162 mg SC qw N = 631	TCZ 8 mg/kg IV q4w N = 631	TCZ 162 mg SC q2w N = 437	Placebo SC q2w N = 218	Placebo IV q4w N = 1170	TCZ 4 mg/kg IV q4w N = 774	TCZ 8 mg/kg IV q4w N = 1582
n	630	630	427	218	1170	774	1582
Normal	575 (91.3%)	568 (90.2%)	396 (92.7%)	215 (100.0%)	1144 (97.8%)	721 (93.2%)	1434 (90.6%)
Grade 1	54 (8.6%)	59 (9.4%)	29 (6.8%)	0 (0%)	15 (1.3%)	42 (5.4%)	136 (8.6%)
Grade 2	1 (0.2%)	2 (0.3%)	2 (0.5%)	0 (0%)	1 (<1%)	3 (<1%)	4 (<1%)
Grade 3	0 (0%)	1 (0.2%)	0 (0%)	0 (0%)	1 (<1%)	-	3 (<1%)
Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	3 (<1%)	2 (<1%)

IV = intravenous; q2w = every two weeks; q4w = every four weeks; qw = every week; SC = subcutaneous; TCZ = tocilizumab.
Platelets: CTC grade 1 <LLN - 75,000/mm3; CTC grade 2: <75,000 - 50,000/mm3; CTC grade 3: <50,000 - 25,000/mm3; CTC grade 4: <25,000/mm3[1]
Source: ST1b_gradtt in WA22672 and NA25520 Week 24 CSRs and ST1b+gradtt in Safety Summary of original IV TCZ submission

The data in the long term extension in study NA25220 LTE and study WA22762 LTE were consistent with the 24 weeks data. In study WA22762 LTE one new Grade 3 decreased platelet count was observed in the IV-SC Switch Arm. All other newly observed cases in both studies were Grade 1 or 2.

No association between decreases in platelet counts and serious bleeding events were reported. There was no relationship between body weight and the incidence of thrombocytopenia

In study MRA229JP, mean platelet counts decreased by approximately 25% from baseline values after 4 weeks, and these levels were sustained through 24 weeks. Decreases in platelet count were similar between the SC TCZ and IV TCZ groups. There were no Grade 3 or 4 decreases in platelet count in either treatment group. No serious bleeding events were associated with decreased platelet count.

In study MRA227JP, mean platelet count decreased by Week 35; the reduction in platelet count occurred in each of the three treatment groups. A reduction in platelet count of two or more grades occurred in 1 patient in the 162 mg q2w group.

Liver enzymes

The liver profile consisted of AST, ALT, total bilirubin, and alkaline phosphatase. Direct and indirect bilirubin levels were tested only if total bilirubin was greater than the ULN.

Table 73. Study NA25220 shifts in ALT and AST from normal at baseline to worst post-baseline value above the ULN (safety population)

	Liver Enzyme	No. of Patients (%)			
		TCZ PFS q2w (N = 167)	TCZ PFS q2w → TCZ AI q2w (N = 167)	Placebo PFS q2w → TCZ PFS q2w (N = 60)	Placebo PFS q2w → TCZ AI q2w (N = 59)
Normal value at BL	AST	162 (97.0)	159 (95.2)	57 (95.0)	58 (98.3)
	ALT	157 (94.0)	157 (94.0)	54 (90.0)	57 (96.6)
Normal value at BL and post-BL	AST	113 (67.7)	111 (66.5)	45 (75)	43 (72.9)
	ALT	87 (52.1)	80 (47.9)	40 (66.7)	32 (54.2)
Normal at BL to > ULN-3 × ULN post-BL [a]	AST	47 (28.1)	45 (26.9)	12 (20)	14 (23.7)
	ALT	66 (39.5)	72 (43.1)	12 (20.0)	21 (35.6)
Normal at BL to > 3 × ULN – 5 × ULN post-BL [a]	AST	2 (1.2)	2 (1.2)	0	1 (1.7)
	ALT	3 (1.8)	4 (2.4)	2 (3.3)	4 (6.8)
normal at BL to > 5 × ULN post-BL [a]	AST	0	1 (0.6)	0	0
	ALT	1 (0.6)	1 (0.6)	0	0
Marked shift post-BL [b]	AST	2 (1.2)	3 (1.8)	0	1 (1.7)
	ALT	5 (3.0)	6 (3.6)	2 (3.3)	4 (6.8)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL = baseline; PFS = prefilled syringe; q2w = every 2 weeks; AI = autoinjector; TCZ = tocilizumab; ULN = upper limit of normal.

a Excludes patients with missing values.

b Shift from normal to > 3 – 5 × ULN, from normal to > 5 × ULN, plus from > ULN - 3 × ULN to > 5 × ULN).

N used as denominator to calculate percentage.

Source: page 892.

In escape patients a similar proportion of patients in the prior TCZ and placebo arms experienced markedly high AST levels following escape therapy. The incidence of markedly high ALT levels was higher in the prior placebo arm as compared to the prior TCZ arm (8/90 (9%) vs 3/72 (4%)). None of the elevations in transaminases were associated with simultaneous elevations in total bilirubin of >2 ULN. Following the initiation of escape therapy, the incidence of AEs associated with elevated ALT and AST was higher in the patients who previously received placebo.

In study NA25220 no notable differences in total bilirubin or alkaline phosphatase levels were observed between the TCZ and placebo treatment arms. A greater percentage of patients within the 60 to < 100 kg body weight category in both treatment arms showed an increase in ALT or

AST as compared with the < 60 kg and ≥ 100 kg categories. There were no patients who met the laboratory criteria for Hy's law, i.e. no patients in this study were identified as having a > 3 × the ULN elevation in AST or ALT and 2 × ULN in total bilirubin.

During the long term extension in study NA25220 LTE the results the results were consistent with the 24 weeks data.

Table 74. Study WA 22762 shifts in ALT and AST from normal at baseline to worst post-baseline value above the ULN (ITT population)

		162 mg SC qw + DMARD (n = 524)	8 mg/kg IV q4w + DMARD (n = 377)	IV-SC (n=186)	SC-IV (n=48)
No. (%) patients with a normal value at BL	ALT	484 (92.4)	343 (91.0)	169 (93.9)	43 (90.0)
	AST	497 (94.8)	353 (93.6)	175 (94.1)	45 (93.8)
No. (%) patients with a normal value at BL and post-BL	ALT	197 (37.6)	160 (42.4)	80 (43.0)	19 (39.6)
	AST	281 (53.6)	197 (52.3)	108 (58.1)	23 (47.9)
No. (%) patients with an increase from normal at BL to > ULN to 3 × the ULN [a]	ALT	264 (50.4)	166 (44.0)	76 (40.9)	20 (41.7)
	AST	214 (40.8)	152 (40.3)	64 (34.4)	22 (45.8)
No. (%) patients with an increase from normal at BL to > 3 to 5 × the ULN [a]	ALT	20 (3.8)	14 (3.7)	10 (5.4)	3 (6.3)
	AST	1 (0.2)	4 (1.1)	3 (1.6)	0 (0.0)
No. (%) patients with an increase from normal at BL to > 5 × the ULN [a]	ALT	3 (0.6)	3 (0.8)	3 (1.6)	1 (2.1)
	AST	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
No. (%) of patients with a marked shift [b]	ALT	23 (4.4)	17 (4.5)	13 (7.0)	4 (8.3)
	AST	2 (0.4)	4 (1.1)	3 (1.6)	0 (0.0)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL = baseline; IV = intravenous; DMARD = disease-modifying antirheumatic drug; q4w = every 4 weeks; qw = once weekly; SC = subcutaneous; TCZ = tocilizumab; ULN = upper limit of normal.

a Excludes patients with missing values.

b Shift from normal to > 3 - 5×ULN, from normal to > 5× ULN, plus from > ULN - 3× ULN to > 5× ULN).

Includes data from the double blind and open label phases for all four arms.

The majority of elevations in both arms occurred at a single time point only: 19 patients (3.6%) in the SC arm and 15 patients (4.0%) in the IV arm. Non-consecutive elevations were experienced by 8 (1.5%) and 6 patients (1.6%) in the SC and IV arms, respectively. One patient in the SC arm experienced a sustained consecutive elevation (i.e. from time of first elevation to the last record). Among patients with an increased ALT and/or AST level, the majority experienced a Grade 1 elevation at worst; Grade 1 elevations were reported for a slightly higher proportion of patients in the SC arm compared with the IV arm for ALT (48% vs. 42%), whereas no notable difference between arms was seen for AST (38% vs. 37%). No notable differences between arms were observed for Grade 2, 3, or 4 elevations. Grade 3 or 4 elevations in ALT and AST occurred in ~1% of patients.

Increased ALT and increased AST were reported as AEs for 9 (4.8%) and 7 (3.8%) patients in the IV-SC arm, respectively. One patient was withdrawn due to increased ALT and AST AEs. There were no hepatic AEs in the IV-SC Switch Arm.

Table 75. Study WA22762 patients with an increase in AST and Alt from < 3x ULN at baseline to worst value > 3x ULN by weight at baseline (ITT population)

	162 mg SC qw +DMARD N=524	8 mg/kg IV q4w +DMARD N=377	IV-SC N=186	SC-IV N=48
ALT				
< 60 kg	3/120 (2.5)	3/84 (3.6)	3/46 (6.5)	0/12 (0.0)
60 to <100 kg	22/355 (6.2)	18/254 (7.1)	10/125 (8.0)	5/33 (15.2)
≥ 100 kg	4/49 (8.1)	6/39 (15.4)	2/15 (13.3)	0/3 (0.0)
AST				
< 60 kg	1/120 (0.8)	1/84 (1.2)	0/46 (0.0)	0/12 (0.0)
60 to <100 kg	2/355 (0.6)	4/254 (1.6)	3/125 (2.4)	0/33 (0.0)
≥ 100 kg	1/49 (2.0)	1/39 (2.6)	0/15 (0.0)	0/3 (0.0)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; DMARD = disease-modifying antirheumatic drug; IV = intravenous; q4w = every 4 weeks; qw = once weekly; SC = subcutaneous.
Includes data from the double blind and open label phases for all four arms.
Source: page 900.

In both treatment arms of Study WA22762 mean and median total bilirubin levels increased within the normal range following initiation of TCZ treatment and remained stable at the higher levels for the duration of treatment. No notable differences were observed between the SC and IV treatment arms. Markedly high bilirubin levels (>2 × ULN) were rare, occurring in 2% of patients in each treatment arm, and were all elevations of indirect bilirubin. There were no occurrences of markedly high direct bilirubin. The results in the long term extension study WA22762 LTE were consistent with the week 24 data.

In study MRA229JP, the time courses of ALT, AST and ALP levels were similar in the two treatment groups. Grade 3 or 4 increases were recorded in the SC TCZ and IV TCZ groups for ALT (1 and 3 subjects, respectively) and AST (1 and 0 patients, respectively). One patient in the IV TCZ group experienced a SAE of hepatic function abnormal.

In study MRA227JP, some fluctuation was noted in the mean values of the liver function-related test variables, but mean values remained within the normal range for all the liver function parameters. For ALT, the CTC Grade worsened by at least two grades for 1 patient in each of the 81 mg q2w and 162 mg q2w groups, and for 2 patients in the 162 mg qw group. For AST, the CTC Grade worsened by at least two grades for two patients in the 162 mg qw group. Two patients experienced an AE of hepatic function abnormal.

Lipid parameters

Changes in each lipid profile (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein [HDL] cholesterol, and triglycerides) at Week 24 were similar for TCZ SC and TCZ IV in both frequency and grade across SC (qw and q2w) and TCZ IV populations.

At Week 24, the proportion of patients who experienced a sustained elevation in total cholesterol of ≥6.2 mmol/L (240 mg/dL), or in LDL of ≥4.1 mmol/L (160 mg/dL), was comparable between both TCZ SC dosing regimens (qw and q2w) and TCZ IV populations.

Following an initial increase after the first administration of TCZ SC, the mean values for lipid profile parameters remained stable throughout the remainder of the studies. There was no trend for an increased risk of cholesterol increases over time, which is a known risk in patients receiving TCZ IV. Changes in the lipid profiles for the SC and IV all-exposure populations were comparable.

Safety in special populations

Bodyweight

Table 76. Pivotal studies: Key Safety Parameters by body weight category (24 weeks data)

	< 60 kg		60-100 kg		≥100 kg	
	TCZ qw	TCZ q2w	TCZ qw	TCZ q2w	TCZ qw	TCZ q2w
Number of patients	N=144	N=119	N=425	N=292	N=62	N=26
AEs	105 (73%)	74 (62.2%)	322 (76%)	179 (61.3%)	54 (87%)	21 (80.8%)
Infections	49 (34%)	41 (34.5%)	151 (36%)	79 (27.1%)	27 (44%)	11 (42.3%)
Serious AE	10 (6.9%)	8 (6.7%)	17 (4.0%)	9 (3.1%)	2 (3.2%)	3 (11.5%)
Serious infections	5 (3.5%)	5 (4.2%)	4 (0.9%)	3 (1.0%)	0	1 (3.8%)
Neutropenia						
Grade 1	29 (20%)	17 (11.8%)	85 (20%)	32 (7.5%)	10 (16.1%)	1 (1.6%)
Grade 2	28 (19.4%)	9 (6.3%)	51 (12%)	13 (3.1%)	2 (3.2%)	0
Grade 3	5 (3.5%)	1 (0.7%)	10 (2.4%)	11 (2.6%)	2 (3.2%)	3 (4.8%)
Grade 4	1 (0.7%)	0	0	0	0	1 (1.6%)

AE: AE; qw weekly; q2w every two weeks; TCZ: tocilizumab.

Source: Sections 7.3, 7.6, 7.9.1 and 7.11.1.1 in the WA22762 24-week CSR, and Sections 7.3, 7.6, and 7.11.1.1 in the NA25520 24-week CSR.

In the long-term extension phases of study NA25520 and study WA22672, subgroup analyses of selected AE parameters by body weight category at baseline (< 60 kg, 60 to < 100 kg, and ≥100 kg) indicated a trend for higher incidences of all AEs and SAEs among patients weighing ≥ 100 kg at baseline compared with patients weighing < 100 kg.

In subgroup analyses of laboratory parameters, the incidence of newly occurring Grade 1 and 2 neutropenia showed a trend for increase with decreasing body weight. However, this effect was not observed with Grade 3 or 4 events.

Discontinuation due to adverse events

Table 77. Overview of AEs leading to withdrawal at week 24 in SC TCZ and IV TCZ clinical studies (safety population)

	Study WA22762		Study NA25220		Week 24 Analyses from IV TCZ Phase III Clinical Studies		
	162 mg SC TCZ qw+DMARD N = 631	8 mg/kg IV TCZ q4w+DMARD N = 631	162 mg SC TCZ q2w+DMARD N = 437	PI SC q2w+DMARD N = 218	8 mg/kg IV TCZ q4w+DMARD N = 1582	4 mg/kg IV TCZ q4w+MTX N = 774	PI+DMARD N = 1170
Duration in study (PY)	289.82	288.39	182.68	81.80	753.50	344.74	507.24
Patients withdrawn for AE	30 (4.8%)	41 (6.5%)	9 (2.1%)	3 (1.4%)	11 (3.8%)	38 (4.9%)	26 (2.4%)
Number of AEs	41	54	9	3	11	38	28
Rate per 100 PY (95% CI)	14.15 (10.15, 19.19)	18.72 (14.07, 24.43)	4.93 (2.25, 9.35)	3.67 (0.76, 10.72)	1.46 (0.73, 2.61)	11.02 (7.80, 15.30)	5.70 (3.83, 8.21)

AE = adverse event; CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; IV = intravenous; PI = placebo; PY = patient years; q2w = every two weeks; q4w = every four weeks; qw = every week; SC = subcutaneous; TCZ = tocilizumab.
Duration in study = (date of last assessment - date of first dose + 1 day) / 365.25.
Multiple occurrences of the same event in one individual are counted.
Source: stae11_wd, staerate01_withd_wk24_2, stae11_wd. stae11_wd in Safety Summary of original IV TCZ submission.

Table 78. Overview of AEs leading to withdrawal in pooled SC TCZ and IV TCZ (all exposure population)

	SC TCZ All-exposure N = 1465	IV TCZ All-exposure N = 4171
Total Exposure (PY)	893.92	16204.77
Patients withdrawn for AE	58	788
Number of AEs	77	793
Rate per 100 PY (95% CI)	8.61 (6.80, 10.77)	4.89 (4.56, 5.25)

AE = adverse event; CI = confidence interval; IV = intravenous; PY = patient years; SC = subcutaneous; TCZ = tocilizumab.
Multiple occurrences of the same AE in one individual are counted.
Source: STae_rategp6_wd and STae_rategp6_wd in IV LTE safety update report.

During the 24 weeks treatment period in study NA252209 most common reasons for treatment discontinuation were attributed to infections and infestations (individual events in each arm, with the exception of two cases of lower respiratory tract infection in the TCZ arm) and investigations SOCs (individual events of elevated ALT and increased body weight). Other SOCs included 1 patient withdrawal each because of blood and lymphatic system disorders (neutropenia); hepatobiliary disorders (hepatic steatosis); neoplasms benign, malignant and unspecified (including Cysts and Polyps; adenocarcinoma pancreas); and respiratory, thoracic and mediastinal disorders (pulmonary fibrosis).

In study WA22762 the most common reasons for treatment discontinuation during the 24 weeks period were infections and infestations (individual events in each arm, with the exception of two cases of bacterial arthritis in the IV arm) and investigations SOCs (due to elevated liver enzymes). Other SOCs occurring at an incidence of 1% in either arm were immune system disorders (hypersensitivity reactions) and skin and subcutaneous tissue disorders (including urticaria, rash, and erythema). Two patients in the SOC respiratory, thoracic, and mediastinal disorders with interstitial lung disease and pulmonary fibrosis had pre-existing conditions.

In the randomized SC treatment phase of study NP22623, no patients withdrew due to an AE.

In study MRA229JP AEs leading to withdrawal of the investigational product were recorded for 3 patients (1.7%) in the SC TCZ group and 9 patients (5.2%) in the IV TCZ group. The events include subileus and hyponatraemia in the TCZ SC group and herpes zoster, hepatic function abnormal, colitis ischemic, large intestine perforation, spinal column stenosis, Meniere's disease, spinal compression fracture and anaphylactic reaction in the TCZ IV group.

On patient withdrew from study MRA227JP due to decreases in neutrophils and in white blood cells (two events). A causal relationship to TCZ could not be excluded for either event.

Table 79. Overview of AEs leading to dose modifications at week 24 in the SC TCZ and IV TCZ clinical studies (safety population)

	Study WA22762		Study NA25220		Week 24 Analyses from IV TCZ Phase III Clinical Studies		
	162 mg SC TCZ qw + DMARD N = 631	8 mg/kg IV TCZ q4w + DMARD N = 631	162 mg SC TCZ q2w + DMARD N = 437	PI SC q2w + DMARD N = 218	8 mg/kg IV TCZ q4w + DMARD N = 1582	4 mg/kg IV TCZ q4w + MTX N = 774	PI + DMARD N = 1170
Duration in study (PY)	289.82	288.39	182.68	81.80	753.50	344.74	507.24
Patients with at least one AE leading to dose modification	172 (27.3%)	170 (26.9%)	59 (13.5%)	18 (8.3%)	194 (12.3%)	103 (13.3%)	84 (7.2%)
Number of AEs leading to dose modification	288	240	80	28	235	136	95
AEs per 100 PY (95% CI)	104.55 (93.11, 117.01)	87.38 (76.93, 98.86)	44.34 (35.21, 55.11)	34.23 (22.75, 49.47)	NA	NA	NA

AE = adverse event; CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; IV = intravenous; PI = placebo; PY = patient years; q2w = every two weeks; q4w = every four weeks; qw = every week; SAE = serious adverse event; SC = subcutaneous; TCZ = tocilizumab.

Duration in study = date of last assessment - date of first dose + 1 day / 365.25.

Multiple occurrences of the same event in one individual are counted.

Source: from WA22762 Week 24 CSR stae11_dm_2 ,from NA25220 Week 24_2 CSR, stae11_dmod in Safety Summary of original IV TCZ submission.

In the SC all-exposure population, the most common events leading to dose modification were reported in the investigations (mainly elevation in hepatic transaminase) and Blood and lymphatic system (neutropenia, leucopaenia and thrombocytopaenia) SOCs. In the IV all-exposure population, the most common AEs leading to dose modifications were in the Infections (most commonly URTI, bronchitis, nasopharyngitis, and sinusitis) and Investigations SOCs (mainly elevation in hepatic transaminase).

In the randomized SC treatment phase of study NP22623, 3 patients, all in the q2w group, experienced AEs (tracheitis, bronchitis, and diarrhea, respectively) that led to dose modification.

AEs leading to modification of the dosing interval or temporary suspension of treatment occurred in 25 patients (14.5%) in the SC TCZ group and in 22 patients (12.7%) in the IV TCZ group of Study MRA229JP. There were no events with a marked difference in incidence between the two groups.

AEs resulting in modification of the dosing interval occurred in 5 patients (15.6%) in study MRA227JP. By treatment group, the incidence was 1 patient (12.5%) in the 81 mg q2w group, 1 patient (8.3%) in the 162 mg q2w group and 3 patients (25.0%) in the 162 mg qw group.

2.6.1. Discussion on clinical safety

The safety assessment of TCZ SC is based on the two pivotal phase III clinical studies (studies NA25220 and WA22762). This database is further supported by the data from the safety analysis analyses on SC TCZ from a completed Phase Ib study NP22623 in RA patients and two Chugai monotherapy trials, the complete Phase I/II study MRA227JP, and the Phase III study MRA229JP.

Safety data from the original Phase III clinical development program for the intravenous (IV) dosage form of TCZ in adult RA following 24 weeks of treatment (data submitted as part of initial MAA) are also summarised.

In the pivotal studies a total of 1465 patients were exposed to TCZ SC. This includes patients treated with TCZ SC during the 24 weeks core and the LTE part of study NA25220 and study WA25220 as well as patients who switched from placebo to TSZ SC in the LTE part of study NA25220 and who switched from TCZ IV to TCZ SC in study WA25220 LTE. So far 1095 of these patients completed 24 weeks of treatment, 483 patients completed 40 weeks of treatment, and 239 patients have completed 48 weeks of treatment with TCZ SC. This gives a robust database to assess the safety TCZ SC. However the data on the long term safety of TCZ SC are limited, the submission of the final clinical study report for study NA25220 and study WA22762 has been included as milestone in the RMP.

The design of the pivotal study WA22762 further allows a head to head comparison of the safety of the requested dosage scheme for TCZ SC and the authorised TCZ IV scheme. In both treatment groups patients had comparable exposure to the respective treatment. Further, in a smaller population, the preliminary data on the safety of the switch IV-SC and vice versa were provided. Nevertheless the patient population who switched from IV to SC or vice versa is still small. The safety in “switchers” directly after the switch needs to be further evaluated, especially with regard to hypersensitivity. Long-term safety in patients in the switcher patient population will be further investigated in the BSRBR registry as detailed in the RMP. A statement has also been included in section 4.2 of the SmPC.

In the pivotal studies the overall AE rate until clinical cut-off was comparable in the SC TCZ and TCZ IV groups, and the AE profile of TCZ SC was consistent with the established safety profile of IV TCZ profile with exception of the higher of injection site reaction in the TCZ arm. However the AE rate in Study WA22762 was higher in both groups, TCZ SC and TCZ IV, than in the historical control.

The MAH attributed the higher overall adverse events rates in study WA22762 compared to historical control to partly design issues e.g. open design and thus the knowledge of treatment might have introduced a bias as well as increased interaction between patient and study site due to weekly study drug applications. The second argument presented by the MAH during the evaluation was not considered acceptable by the CHMP since self-administration of TCZ SC was foreseen if feasible.

The main difference between reported AEs in WA22762 and the historical TCZ IV studies was in the Investigation SOC i.e. ALT increase. Of note, the 24-week analyses of laboratory parameters

from study WA22672 showed that the shifts in ALT (and similarly AST) were comparable between TCZ SC and TCZ IV treatment arms in study WA22762 and the TCZ IV historical studies. This was considered reassuring by the CHMP.

Another contributing factor to the numerically higher frequency of AEs in study WA22762 versus historical control may be due to AEs in the SOC General Disorders and Administration Site Conditions. A higher incidence of these AEs can be expected due to the SC application.

Beyond week 24, at the time of the clinical cut-off of 16 January 2012, the types and overall pattern of AEs occurring after SC TCZ treatment were similar to those for IV TCZ treatment (except for injection site reactions [ISRs]), with no new safety signals identified.

The overall AE rate was higher in the SC TCZ arm of study WA22762 (qw dosing) than in the SC TCZ arm of study NA25220 (q2w dosing). This might be due the higher exposure. Of note, the AE rate in the TCZ SC group in study WA22762 was comparable to the rate in TCZ IV patients. However, comparing all-exposure TCZ SC and all-exposure TCZ IV data a higher incidence of AEs in the TCZ SC patients is observed.

A significant higher AE rate (633.88 (95% CI: 570.93; 701.87) events per 100 PY) was observed in the IV-SC Switch Arm as compared to the SC-IV Switch Arm (300.52 [95% CI: 213.70; 410.82] events per 100 PY). The sample size however, is still small, thus to data a robust conclusion cannot on the clinical significance cannot be drawn.

However, comparing all-exposure TCZ SC and all-exposure TCZ IV data a higher incidence of AEs in the TCZ SC patients is observed.

The most common body system and organ classes in which AEs were reported were: infections and infestations, gastrointestinal disorders and investigations.

The rate of AEs decreases with prolonged treatment duration for both the SC TCZ and the IV TCZ all-exposure populations, however the number of patients completing beyond 36 weeks TCZ SC treatment is still low. The submission of the final clinical study report for study NA25220 and study WA22762 has been included as milestone in the RMP.

According to the study protocol the patients received concomitant DMARDs. However the choice of the medication was left to the investigator. It is understood that the majority of patients received MTX. The MAH was requested during the evaluation to provide an analysis of the safety results regarding concomitant use of DMARDs. The MAH provided post hoc analyses from study NA25220 and from study WA22672 comparing safety data of patients taking TCZ with MTX against the overall study population. The safety profile was consistent among patients receiving TCZ with background MTX and the overall study population.

Following 24 weeks of treatment, the incidence of SAEs and the rates of SAEs per 100 PY were very similar between SC TCZ and IV TCZ as well as between the different dose groups (162 mg SC TCZ qw or q2w, IV TCZ doses of 4 or 8 mg/kg q4w) in the pivotal studies and the historical controls.

The most common SOC in which SAEs were reported was infections and infestations. In both pivotal studies, SAEs in this SOC occurred at similar frequencies in both the SC TCZ and control arms and within the Week 24 analysis and in the long-term extension, with no specific type of event being predominant. However the long term SC exposure is still low, the submission of the

final clinical study report for study NA25220 and study WA22762 has been included as a milestone in the RMP.

The death rate per 100 PY in the SC TCZ pooled population was 0.56 (95% CI: 0.18, 1.31). This death rate is comparable with the rate observed in the historical IV TCZ all-exposure population of 0.58 (95% CI: 0.41, 0.71).

No patients died during the course of the study MRA227JP, study MRA229JP and study NP22623.

Consistent with TCZ IV, SC administration of TCZ induced a dose dependent decrease in neutrophil counts, with the most notable change being observed within the first 4 weeks of treatment.

Infections, malignancies, anaphylaxis, hypersensitivity, ISRs, serious myocardial infarction events, and serious haemorrhagic and ischemic stroke, were defined as adverse events of special interest. Most of the events occurred with comparable rates in the TCZ SC and TCZ IV group with a few exceptions. The rate of infections was higher under TCZ SC treatment; however the rate for serious infections was comparable. Although the rate of hypersensitivity reactions was low, the rate of serious clinically significant reactions was higher in the TCZ SC group. However no anaphylactic relations occurred under TCZ SC treatment. As expected the in the TCZ SC groups a high rate of injection site reactions were reported.

In both pivotal studies analysis of the key safety parameters by body weight revealed no obvious differences between the treatment arms in the two lower weight categories, however a numerically higher rate of AEs and infections is patients with higher bodyweight of (≥100kg) was observed in the TCZ SC and IV arms of WA22762 study as well as the historical TCZ IV treatment arm.

Analysis of the baseline and disease characteristics indicated that a higher proportion of patients in the high body weight category have been found to have a history of previous TNF failures, as well as baseline COPD and diabetes contributing to poorer healthy status than in the other weight groups. The CHMP concluded that there is no established exposure-safety relationship between high body weight patients and the occurrence of AEs and SAEs.

Considering the above the analysis suggests that the numerically higher incidence of AEs and infections is patients with higher bodyweight are triggered rather by comorbidity than by TCZ exposure.

The overall AE rate was higher in the SC TCZ arm of study WA22762 (qw dosing) than in the SC TCZ arm of study NA25220 (q2w dosing) suggesting an exposure related rate of AEs. The MAH was requested during the evaluation to present the AE rates by $C_{through}$ Quartiles. There was no association between TCZ exposure and AE rates looking at AE rates by $C_{through}$ Quartiles.

Further events were defined as events of special interest such as gastrointestinal perforation, demyelinating disorders, serious hepatic events, serious haemorrhagic cerebrovascular events, serious ischaemic cerebrovascular events, and serious bleeding that either did not occur or occurred at a low frequency with TCZ SC.

On 20 December 2013, the MAH reported a needle clogging issue affecting the new pre-filled syringe presentation (see section 2.2.3 Finished Medicinal Product). To further strengthen the mitigation statements already included in the SmPC and PL, the MAH proposed to add some further changes to sections 6.3 and 6.6 of the SmPC and sections 5 and 6 of the PL. The CHMP

considered the proposed changes suitable to reduce the probability of a clogged syringe due to handling errors. The MAH in addition discussed what happens if a patient uses a pre-filled syringe with such an injection force defect. It was clarified that if a patient attempt to administer an injection with a pre-filled syringe that is clogged, the patient would unlikely be able to expel any drug product from the syringe. The failure mode is considered highly detectable. Assuming a replacement pre-filled syringe is at hand, the dose would not be missed. If no replacement pre-filled syringe is available, the dose would be delayed or missed. Results from studies WA22762 and NA25220 indicate that if a patient on the TCZ QW regimen has a single dose missed or delayed or a partial dose of TCZ SC safety would not be affected. The probability of receiving a partial dose from a clogged needle is extremely low as a needle clog is more likely to completely block the needle so no injection can be given. The CHMP concluded that there is no impact on clinical safety due to clogging incidents when using the pre-filled syringe.

With regards to the exceeded limit of the injection time with the pre-filled pen reported by the MAH on 31/01/2014, the MAH withdrew this new presentation on 11 February 2014. The MAH also confirmed their ability to ensure commercial supply of the pre-filled syringe to all rheumatoid arthritis patients once approved and to subjects enrolled in on-going clinical studies.

2.6.2. Conclusions on the clinical safety

The safety profile of TCZ SC is comparable with the safety profile of the TCZ IV preparation. No new safety signals were identified.

Comparing the two TCZ SC dosage schemes, SC TCZ q2w and SC TCZ qw, the two weekly scheme has a slightly favourable safety profile with regard to adverse events, however the rates of adverse events for the SC TCZ qw scheme are still comparable with the rates for the IV TCZ scheme. No such differences were seen with regard to SAEs.

The data on the long term safety of TCZ SC are limited since only a small patient number continued treatment beyond week 36. The submission of the final clinical study report for study NA25220 and study WA22762 has therefore been included as milestone in the RMP.

The data suggest that for patients switching from TCZ IV to TCZ SC, subcutaneous administration is safe and well-tolerated with the pattern of AEs observed being consistent with the known safety profile of TCZ. However, as the patient population who switched from IV to SC or vice versa is still small, the safety in “switchers” directly after the switch needs to be further evaluated, especially with regard to hypersensitivity. IgE data following TCZ SC treatment and long-term safety in patients in the switcher patient population will be further investigated in the final CSR for studies NA25220 and WA22762, and in the BSRBR registry respectively as detailed in the RMP.

Following reports of clogging of the needle with the new pre-filled syringe presentation, the MAH proposed changes to the product information in sections 6.3 and 6.6 of the SmPC as well as in the Package Leaflet. This is supported by CHMP. The CHMP concluded that there is no impact on clinical safety due to clogging incidents when using the pre-filled syringe device. With regards to the exceeded limit of the injection time with the pre-filled pen, the MAH withdrew this new presentation.

2.7. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 14.2, the PRAC considers by consensus that the risk management system for tocilizumab (RoActemra) in the proposed indication:

RoActemra, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (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, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.
RoActemra 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.

could be acceptable provided an updated risk management plan and satisfactory responses to the questions detailed in this section are submitted.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

The MAH identifies the following safety concerns.

Table 80. Summary of Ongoing Safety Concerns in Adults

Category	Safety Concern
Important Identified Risks	Serious infection
	Complications of diverticulitis
	Serious hypersensitivity reactions
	Neutropenia
Important Potential Risks	Thrombocytopenia and the potential risk of bleeding
	Liver enzyme elevations and bilirubin elevations and the potential risk of hepatotoxicity
	Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events
	Neutropenia and the potential risk of infections
	Malignancies
	Demyelinating disorders
	Immunogenicity
Important missing information	Elderly
	Paediatric patients
	Effects during pregnancy
	Hepatic impairment
	Renal impairment
	Combination with biologics
	Safety in patients <60 kg in switcher population
	Long-term safety in patients in the switcher patient population
	IgE data following TCZ SC treatment
Identified and potential interactions including food-drug and drug-drug interactions	CYP450 enzyme normalization

Table 81. Summary of Ongoing Safety Concerns in Paediatric Patients

Category	Safety Concern
Important Identified Risks	Serious Infection
	Serious hypersensitivity reactions
	Neutropenia
Important Potential Risks	Skeletal development
	Immunogenicity
	Malignancies
	CYP450 enzyme normalisation

Following the recommendations from the last assessment, the MAH implemented the following measures:

- The MAH addressed the clinical relevance of tocilizumab-specific IgE antibody development following SC administration of tocilizumab as missing information.
- The long-term safety in "switchers" is included as missing information.
- "Neutropenia" is classified as an identified risk for all indications.
- The MAH does commit to provide the final Clinical Study Report (CSR) for study WA22762 in Q2 2014 and for study NA25220 Q3 2014 and has amended the RMP, Part III, Section 10.

The heading "Important Missing information" must be replaced by "Missing information".

- **Pharmacovigilance plans**

The following changes of safety concerns were performed:

Table 82. Safety concerns and overview of planned pharmacovigilance actions for All Patients

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Objective of Proposed Action(s)
Neutropenia	• Study WA29049: a pharmacodynamics study to evaluate neutrophil kinetics and function following tocilizumab treatment in healthy volunteers. • Routine pharmaco-vigilance • Guided questionnaire (post-marketing reports) for events of special interest will collect neutrophil data in cases	**Study** • To investigate the mechanism whereby the peripheral neutrophil count is reduced **Pharmacovigilance** • To collect information in a standardized manner and monitor the frequency and nature of neutropenia and the potential risk of serious infection emerging during clinical trials and post-marketing use: • To assess risk compared

	of serious infection. • Ongoing clinical trial programme • Epidemiology data: o US claims database • EU registries (BSRBR, ARTIS, RABBIT)	with the established safety profile and other conventional and biological DMARDs • To characterize the nature and frequency of the events potentially associated with neutropenia • To assess the effectiveness of risk minimization measures
Safety of TCZ SC in patients < 60 kg in the switcher population	• Routine pharmacovigilance • Epidemiology data: EU registry (BSRBR)	To monitor the safety of TCZ SC in patients < 60 kg
Long-term safety in switcher patient population	• Routine pharmacovigilance • Epidemiology data: EU registry (BSRBR)	To monitor long-term safety in switcher patient population
IgE data following TCZ SC treatment	• Routine pharmacovigilance • Studies WA22762 and NA25220 • Epidemiology data: EU registry (BSRBR)	To monitor the longer-term immunogenicity following TCZ SC treatment

- **Risk minimisation measures**

The changes of the updated RMP version in this section are as follows (see table below):

Table 83. Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Neutropenia	Identically equal to the potential risk: "Neutropenia and the potential risk of Infection"	
Immunogenicity	SPC SPC section 4 .8. Undesirable effects Immunogenicity A total of 2,876 patients have been tested for anti- tocilizumab antibodies in the 6-month controlled clinical trials. Of the 46 patients (1.6%) who developed anti-tocilizumab antibodies, 6 had an associated medically significant hypersensitivity reaction, of which 5 led to permanent discontinuation of treatment. Thirty patients (1.1%) developed neutralising antibodies. In SC-I, a total of 625 patients treated with tocilizumab 162 mg weekly were tested for anti-tocilizumab antibodies in the 6-month controlled period. Five patients (0.8%) developed positive anti-tocilizumab antibodies; of these, all developed neutralizing anti-tocilizumab antibodies. One patient was tested positive for	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	IgE isotype (0.2%). In SC-II, a total of 434 patients treated with tocilizumab 162mg every other weekly were tested for anti-tocilizumab antibodies in the 6-month controlled period. Seven patients (1.6%) developed positive anti-tocilizumab antibodies; of these, six (1.4%) developed neutralizing anti-tocilizumab antibodies. Four patients were tested positive for IgE isotype (0.9%). No correlation of antibody development to clinical response or adverse events was observed. IV RoActemra SPC only Immunogenicity sJIA: All 112 patients were tested for anti-tocilizumab antibodies at IV RoActemra SPC only baseline. Two patients developed positive anti-tocilizumab antibodies with one of these patients having a hypersensitivity reaction leading to withdrawal. The incidence of anti-tocilizumab antibody formation might be underestimated because of interference of tocilizumab with the assay and higher drug concentration observed in children compared to adults. pJIA: One patient in the 10 mg/kg < 30kg group developed positive anti-tocilizumab antibodies without developing a hypersensitivity reaction and subsequently withdrew from the study.	
Safety in patients <60 kg in switcher population Long-term safety in the switcher patient population	SPC SPC section 5.1 Pharmacodynamic properties <u>Subcutaneous Use</u> <u>Clinical efficacy</u> Switching from 8 mg/kg intravenous once every 4 weeks to 162 mg subcutaneous once every week, will alter exposure in the patient. The extent varies with the patient's body weight (increased in light body weight patients and decreased in heavy body weight patients) but clinical outcome is consistent with that observed in intravenous treated patients.	Not applicable

Following consideration of the RMP by the PRAC, the MAH provided an updated RMP (version 14.3) to address the issues that had been identified during the PRAC assessment of the RMP.

This included the following updated tables with the summary of safety concerns and the proposed risk minimisation measures.

- **Safety concerns**

Table 84. Summary of Ongoing Safety Concerns in Adults

Category	Safety Concern
Important Identified Risks	Serious infection
	Complications of diverticulitis
	Serious hypersensitivity reactions
	Neutropenia
Important Potential Risks	Thrombocytopenia and the potential risk of bleeding
	Liver enzyme elevations and bilirubin elevations and the potential risk of hepatotoxicity
	Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events
	Neutropenia and the potential risk of infections
	Malignancies
	Demyelinating disorders
	Immunogenicity
Missing information	Elderly
	Paediatric patients
	Effects during pregnancy
	Hepatic impairment
	Renal impairment
	Combination with biologics
	Safety in patients <60 kg in switcher population
	Long-term safety in patients in the switcher patient population
	IgE data following TCZ SC treatment
Identified and potential interactions including food-drug and drug-drug interactions	CYP450 enzyme normalization

- **Pharmacovigilance plan**

Table 85. On-Going and Planned Studies in the Post-Authorisation Pharmacovigilance Development Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
WA22479 (British Society of Rheumatology Biologics Register [BSRBR])	Prospective observational cohort studies for safety data collection.	General safety profile of TCZ; Safety of TCZ SC in patients < 60 kg in the switcher population Long-term safety in switcher patient population	Ongoing	Annual updates to be provided in PSUR
WA22480 (ARTIS) registry study	To provide long term safety data from the use of TCZ in Sweden for RA patients			
GA28719 (RABBIT)	The long-term observation of treatment with biologics in RA (RABBIT) in German biologics registry			
Pregnancy registry (GA28720 [OTIS])	To evaluate pregnancy outcomes for women exposed to TCZ during pregnancy			
Paediatric Registry (name to be confirmed)	To be finalized	Safety in pediatric patients	Protocol of registry to be available by 12 March 2014	Implementation date to be confirmed June 2013
WA18696 extension	Long term extension study of safety during treatment with TCZ in patients completing treatment in core studies	General safety profile of TCZ	Ongoing	Final CSR Q3 2013

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
WA18221 (sJIA)	Part I: to evaluate the efficacy and safety of TCZ in patients with active systemic juvenile idiopathic arthritis (sJIA); Part II: to examine the effect (in completers of Part I) of long term use of TCZ on: • Safety (including immunogenicity) ; • Efficacy (including assessment of joint counts and objective measurements including hsCRP, fever, hemoglobin); • ability to reduce corticosteroid dosage to clinically significant levels; • Resumption of growth (as determined by growth velocity)	General safety profile of TCZ	Ongoing	Final CSR Q4 2014
WA19977 (pJIA)	To evaluate the efficacy and safety of TCZ in patients with active polyarticular juvenile rheumatoid arthritis	General safety profile of TCZ	Ongoing	Final CSR Q3 2013
NP22775	To investigate the effect of TCZ on the pharmacokinetics and pharmacodynamics of an oral contraceptive in female patients with active rheumatoid arthritis	CYP450 enzyme normalisation	Completed	Final CSR August 2012

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
WA28029	To evaluate decreased dose frequency in patients with sJIA who experience laboratory abnormalities during treatment with TCZ	Safety in pediatric patients	Ongoing	Projected first patient first visit June 2013 Final CSR 2016
NP25737	A pharmacokinetic and safety study of TCZ in patients less than 2 years old with active sJIA	Safety profile in pediatric patients less than 2 years old	Ongoing	Data available Q3 2013
MA21488 RA	Evaluation of three treatment strategies based on TCZ and/or methotrexate in patients with active RA who have inadequately responded to prior DMARD treatment.	Immunogenicity	Ongoing	Data available Q4 2013
WA29049	Pharmacodynamics study to evaluate neutrophil kinetics and function following tocilizumab treatment in healthy volumteers	Neutropenia and the potential risk of infection	Study in set up phase	October 2014

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
WA22762	To assess: • The efficacy of treatment with 162 mg tocilizumab (TCZ) given subcutaneously (SC) weekly versus 8 mg/kg TCZ given intravenously (IV) every 4 weeks with regard to non-inferiority of the proportion of patients who achieve ACR20 at Week 24. • The safety of treatment with 162 mg TCZ given SC weekly versus 8 mg/kg TCZ given IV every 4 weeks, with regard to AEs and laboratoryassessments. <u>Secondary Objectives:</u> • Long-term safety and efficacy • Pharmacokinetics (PK) and pharmacodynamics (PD) of TCZ following SC administration • Immunogenicity of TCZ following SC administration • Effect of IV to SC switch on the safety, efficacy, PK and PD of TCZ	Safety will be assessed using reporting of AEs, clinical laboratory results (hematology, chemistry, lipid profiles, liver function, immunogenicity [including IgE data], etc.), physical examination and vital signs.	Ongoing	Q2 2014

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
NA25220	To assess: • Efficacy of treatment with tocilizumab (TCZ) 162 mg SC versus placebo given every other week (q2w), in combination with DMARDs, at Week 24 using ACR20. • Safety of treatment with TCZ 162 mg SC versus placebo given every other week (q2w), in combination with DMARDs, with regard to adverse events (AEs) and laboratory assessments. SECONDARY • Prevention of progression of structural joint damage at Week 24 and Week 48 • Improvement of physical function • Long-term safety and efficacy • Pharmacokinetics (PK) and pharmacodynamics (PD) of TCZ following SC administration • Immunogenicity of TCZ following SC administration.	Safety will be assessed using reporting of AEs, clinical laboratory results (hematology, chemistry, lipid profiles, liver function, immunogenicity [including IgE data], etc.), physical examination and vital signs.	Ongoing	Q3 2014

The other issues raised in the PRAC assessment of the RMP were also adequately addressed in the updated RMP (version 14.4) provided by the MAH including the removal of new pre-filled pen presentation.

The CHMP endorsed this advice without changes.

The CHMP, having considered the data submitted, was of the opinion that Pharmacovigilance activities in addition to the use of routine Pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Submission of the final clinical study report for study NA25220	30 September 2014
Submission of the final clinical study report for study WA22762	30 June 2014
Submission of a revised protocol for the EU BSRBR registry (study WA22479) study)	30 June 2014

2.9. 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.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

TCZ IV in combination with methotrexate (MTX) is an established treatment option for adult patients with RA. In study WA22762 the non-inferiority of TCZ 162mg SC qw to TCZ 8mg/kg IV q4w in terms of efficacy was demonstrated. The primary objective demonstrating the non-inferiority of TCZ SC qw over TCZ IV q4w with regard to ACR 20 response rate at week 24 was met (study NA25220). These results are supported by the secondary objectives, comparable response rates were observed for e.g. ACR 50/ 70 response.

Uncertainty in the knowledge about the beneficial effects

The clinical cut-off date of for the extension phase study WA22762 LTE allowing for a switch between IV and SC application was 16 January 2012. The efficacy of TCZ 162 mg SC qw was maintained after the 24-week double-blind period of the study. However the ACR response rate in the SC-IV switch arm was lower than in the other arms, at various time points, including week 24. Since the sample size is limited, no robust conclusion could be drawn. Long-term safety in patients in the switcher patient population will be further investigated in the BSRBR registry as detailed in the RMP.

Notable difference in response was seen in the analysis by bodyweight. ACR 20, 50 and 70 response rates indicated a comparable response rate in the TCZ SC treatment group for all 3 parameters in the < 60 kg and in the 60 to < 100kg, whereas patients in the > 100 kg showed lower response rate for these parameters. Interestingly, for ACR 50 and 70 response in the highest body weight group was lower for the weight adjusted IV TCZ treatment than for the fixed SC TCZ dose. A statement has been included in section 5.1 of the SmPC regarding the impact of switching from IV to SC on exposure particularly in light and heavy body weight patients.

On 20 December 2013, the MAH reported a needle clogging issue affecting the new pre-filled syringe presentation (see section 2.2.3 Finished Medicinal Product). To further strengthen the mitigation statements already included in the SmPC and PL, the MAH proposed changes to the product information in sections 6.3 and 6.6 of the SmPC as well as in the Package Leaflet in sections 5 and 6 (Instructions for Use Steps 2 and 5). This is supported by CHMP.

Overall it was concluded that the data indicate that clogging incidents, including clogging incidents prior to cap removal, are very rare events. Furthermore, the risk assessment provided by the MAH indicated that if in the very rare event a patient were to attempt to perform an injection using a pre-filled syringe or pre-filled pen with a clogged needle, it is highly unlikely there would be any impact on clinical efficacy or safety.

The CHMP concluded that there is no impact on clinical efficacy due to clogging incidents when using the pre-filled syringe device.

With regards to the exceeded limit of the injection time with the pre-filled pen reported by the MAH on 31/01/2014, the MAH withdrew this new presentation on 11 February 2014. The MAH also confirmed their ability to ensure commercial supply of the pre-filled syringe to all rheumatoid arthritis patients once approved and to subjects enrolled in on-going clinical studies.

Risks

Unfavourable effects

The unfavourable effects of TCZ are established and include infection, gastro-intestinal disorders, infusion reactions, skin disorders, neutropenia, elevation in hepatic enzymes and lipid parameters.

No new safety signals were identified with the new route of administration. The AE profiles of TCZ 162 mg SC qw and q2w are consistent with the known safety profile of TCZ IV with a few exceptions.

The rate of infections was higher under TCZ SC treatment; however the rate for serious infections was comparable. Although the rate of hypersensitivity reactions was low, the rate of serious clinically significant reactions was higher in the TCZ SC group; however no anaphylactic relations occurred under TCZ SC treatment. As expected high rate of injection site reactions were reported in the TCZ SC groups. A numerically higher incidence of Grade 1 and 2 neutropenia (not Grade 3 or 4) and ALT elevations to below 3× ULN were found with the TCZ SC 162 mg qw dosing regimen compared with the TCZ SC 162 mg q2w regimen. However, the rates of these laboratory abnormalities with the qw regimen were comparable to those seen in the pooled TCZ 8 mg/kg IV pivotal data (as well as the 8 mg/kg IV arm of study WA22762).

Injection site reactions (ISRs) were only described in the TCZ SC groups. The incidence of ISRs was also comparable between the TCZ SC qw (10.1%) and q2w (7.1%) regimens and within the range reported for other biologics.

Further events characterising the safety profile of TCZ e.g. gastrointestinal perforation, demyelinating disorders, serious hepatic events, serious haemorrhagic cerebrovascular events, serious ischaemic cerebrovascular events, and serious bleeding that either did not occur or occurred at a low frequency with TCZ SC.

Uncertainty in the knowledge about the unfavourable effects

The long term safety of TCZ SC is limited. Especially safety regarding potential or identified risks such as gastrointestinal perforation, demyelinating disorders, serious hepatic events, serious haemorrhagic cerebrovascular events, serious ischaemic cerebrovascular events, and serious bleeding should be further established (as mentioned in the RMP).

The data suggest that for patients switching from TCZ IV to TCZ SC, subcutaneous administration is safe and well-tolerated with the pattern of AEs observed being consistent with the known safety profile of TCZ. However the patient population who switched from IV to SC or vice versa is still small, the safety in “switchers” directly after the switch needs to be further evaluated, especially with regard to hypersensitivity. Long-term safety in patients in the switcher patient population will be further investigated in the BSRBR registry as detailed in the RMP. A statement has also been included in section 4.2 of the SmPC.

A numerically higher rate of AEs and infections is patients with higher bodyweight of (≥100kg) was observed in the TCZ SC and IV arms of WA22762 study as well as the historical TCZ IV

treatment arm. Higher rates for AEs and infections were observed in heavier patients (≥ 100 kg), consistent for TCZ SC and TCZ IV, however, the number of patients in the highest weight category was small.

On 20 December 2013, the MAH reported a needle clogging issue affecting the new pre-filled syringe presentation (see section 2.2.3 Finished Medicinal Product). To further strengthen the mitigation statements already included in the SmPC and PL, the MAH proposed changes to the product information in sections 6.3 and 6.6 of the SmPC as well as in the Package Leaflet in sections 5 and 6 (Instructions for Use Steps 2 and 5). This is supported by CHMP.

Overall it was concluded that the data indicate that clogging incidents, including clogging incidents prior to cap removal, are very rare events. Furthermore, the risk assessment provided by the MAH indicated that if in the very rare event a patient were to attempt to perform an injection using a pre-filled syringe or pre-filled pen with a clogged needle, it is highly unlikely there would be any impact on clinical efficacy or safety.

The CHMP concluded that there is no impact on clinical safety due to clogging incidents when using the pre-filled syringe device.

With regards to the exceeded limit of the injection time with the pre-filled pen reported by the MAH on 31/01/2014, the MAH withdrew this new presentation on 11 February 2014. The MAH also confirmed their ability to ensure commercial supply of the pre-filled syringe to all rheumatoid arthritis patients once approved and to subjects enrolled in on-going clinical studies.

Benefit-risk balance

Importance of favourable and unfavourable effects

Rheumatoid arthritis is a chronic inflammatory and potentially disabling chronic systemic inflammatory disease, characterised by inflammation of the synovium leading to irreversible destruction of the joints and disability. An established treatment option for patients with adult RA is TCZ IV in combination with MTX. However IV infusion requires administration by a healthcare professional (HCP) in a clinical setting, which affects the quality of life of the patient.

The SC formulation will be a valid option for patients. From the medical point of view, one benefit of the SC route of administration is that it does not require an IV access, which is especially important for patients with poor venous access. The shorter administration time and the option to receive the treatment independent for a HCP are additional advantages of the SC route compared to the IV route.

The unfavourable effects of TCZ are established and include infection, gastro-intestinal disorders, infusion reactions, skin disorders, neutropenia, elevation in hepatic enzymes and lipid parameters.

Following reports of clogging of the needle with the new pre-filled syringe presentation, the MAH proposed changes to the product information in sections 6.3 and 6.6 of the SmPC as well as in the Package Leaflet in sections 5 and 6 (Instructions for Use Steps 2 and 5). This is supported by CHMP. The CHMP concluded that there is no impact on clinical efficacy or safety due to clogging

incidents when using the pre-filled syringe device. With regards to the exceeded limit of the injection time with the pre-filled pen, the MAH withdrew this new presentation.

Benefit-risk balance

Discussion on the benefit-risk balance

TCZ IV in combination with methotrexate (MTX) is an established treatment option for adult patients with RA. For the proposed dose regimen of TCZ via the SC route, non-inferiority to the established TCZ IV regimen was demonstrated with a comparable safety profile. The risks are well addressed in the SmPC and appropriate additional Pharmacovigilance and risk minimisation activities are included in the RMP.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of RoActemra 162 mg solution for injection in a pre-filled syringe (subcutaneous injection) in the treatment of:

RoActemra, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (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, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

RoActemra 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.

is favourable and therefore recommends the granting of the marketing authorisation.

Conditions or restrictions regarding supply and use

Medicinal products on “restricted” medical prescription, reserved for use in certain specialised areas (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

The 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.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall provide an educational pack covering the therapeutic indications of RA, targeting all physicians who are expected to prescribe/use RoActemra containing the following:

- Physician Information Pack
- Nurse Information Pack
- Patient Information Pack.

The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority prior to distribution of the educational material.

The Physician Information pack should contain the following key elements:

- The Summary of Product Characteristics
- Risk of serious infections
- The product must not be given to patients with active or suspected infection
- The product may lessen signs and symptoms of acute infection delaying the diagnosis
- Serious injection/infusion reaction and their management
- Serious hypersensitivity reactions and their management
- Risk of gastrointestinal perforations especially in patients with history of diverticulitis or intestinal ulcerations
- Reporting of serious adverse reactions
- The Patient Information Packs (to be given to patients by healthcare professionals).

The Nurse Information Pack should contain the following key elements:

- Prevention of medical errors and injection/infusion reactions
- Preparation of injection/infusion

- Monitoring of the patient for injection/infusion reactions and hypersensitivity reactions
- Reporting of serious adverse reactions.

The Patient Information Pack should contain the following key elements:

Package leaflet with instructions for use (with instructions for use for SC)

- Patient alert card

- to address the risk of getting infections which can become serious if not treated. In addition, some previous infections may reappear.

- to address the risk that patients using RoActemra may develop complications of diverticulitis which can become serious if not treated.

- to address the risk of allergic reactions.

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

Not applicable.