Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for tocilizumab (rch)

Proprietary Product Name: Actemra

Sponsor: Roche Products Pty Ltd

First round: 17 July 2015

Second round: 17 September 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words (Information redacted), where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ACR	American College of Rheumatology
ADEC	Australian Drug Evaluation Committee
ADRs	Adverse Drug Reactions
AE	Adverse Event
AI	Autoinjector
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{0-t}	Area under the curve from time 0 to trough
AUC_{inf}	Area under the curve from time 0 to infinity
AUC_{last}	Area under the curve from time 0 to last observation
CDS	Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMI	Consumer Medicine Information
C_{max}	Maximum concentration
CrCL	Creatinine clearance
CRP	C-reactive protein
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
C_{trough}	Trough plasma concentrations
DAS28	Disease Activity Score in 28 Joints
DB	Double Blind

Abbreviation	Meaning
DMARD	Disease Modifying Anti-Rheumatic Drug
EMA	The European Agency for the Evaluation of Medicinal Products
E_{max}	Maximum effect
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HAQ-DI	Health assessment questionnaire disability index
HDL	High-density lipoprotein
IL-6	Interleukin-6
IL-6R	Interleukin-6 receptor
ITT	Intention-to-treat
IV	Intravenous
JIA	Juvenile idiopathic arthritis
k_a	Absorption rate constant
LDL	Low-density lipoprotein
LFT	Liver function test
LTE	Long term extension
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MAS	Macrophage Activation Syndrome
MI	Myocardial infarction
mIL-6R	Membrane-bound interleukin-6 receptor
MRA	Myeloma receptor antibody (tocilizumab)
mTSS	modification of the Sharp score

Abbreviation	Meaning
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
OLE	Open Label Extension
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamics
PFS	Pre-filled syringe
PhysGADA	Physician's Global Assessment of Disease Activity
PI	Product Information
pJIA	Polyarticular juvenile idiopathic arthritis
PK	Pharmacokinetics
PMS	Post-Marketing Surveillance
PP	Per protocol
PSUR	Periodic Safety Update Report
PtGADA	Patient's Global Assessment of Disease Activity
PY	Patient-years
q2w	every 2 weeks
q4w	every 4 weeks
QoL	Quality of Life
RA	Rheumatoid arthritis
RO4877533	Tocilizumab
RMP	Risk Management Plan
RR	Relative risk
SAE	Serious adverse event
SADR	Serious adverse drug reaction
SC	Subcutaneous

Abbreviation	Meaning
sIL-6R	Soluble interleukin-6 receptor
SIR	Standardised incidence rates
SJC	Swollen joint count
sJIA	Systemic onset juvenile idiopathic arthritis
SPC	Summary of Product Characteristics
TCZ	Tocilizumab
TEAE	Treatment emergent adverse event
TJC	Tender joint count
TNF	Tumour necrosis factor
T_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal
VAS	Visual analogue scale

1. Introduction

Tocilizumab (TCZ) is a recombinant humanised monoclonal antibody of the immunoglobulin IgG1, directed against the IL-6 receptor approved for use in the treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis.

Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors and has been shown to inhibit sIL-6R- and mIL-6R-mediated signalling. IL-6 has been implicated in the pathogenesis of inflammatory diseases, including rheumatoid arthritis (RA). In clinical studies with tocilizumab, rapid decreases in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and serum amyloid A were observed.

1.1. Approved indications

1.1.1. Rheumatoid arthritis

Tocilizumab (Actemra) is indicated for:

> *The treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients in combination with methotrexate (MTX) or other non-biological disease-modifying anti-rheumatic drugs (DMARDs) in case of either an inadequate response or intolerance to previous therapy with one or more DMARDs.*

Tocilizumab is also indicated for:

> *The treatment of moderate to severe active rheumatoid arthritis in adult patients with poor prognostic factors in combination with MTX in those not previously treated with MTX.*

In the two groups of patients above, tocilizumab can:

> *Be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.*

Tocilizumab has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given in combination with methotrexate.

1.1.2. Polyarticular juvenile idiopathic arthritis

Tocilizumab (Actemra) is indicated for:

> *The treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response to or intolerance to methotrexate (MTX). Tocilizumab can be given alone or in combination with MTX.*

1.1.3. Systemic juvenile idiopathic arthritis

Tocilizumab (Actemra) is indicated for:

> *The treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older. Tocilizumab can be given alone or in combination with methotrexate (MTX).*

1.2. Currently approved dosage and route of administration

The following dosage forms and strengths (see Table 1 below) were already registered and approved for the indications listed above at the time of submission to the TGA for extension of route of administration.

All approved preparations listed below are intended for intravenous infusion.

Table 1. Currently registered dosage forms and strengths of Actmera

AUST R	Strength	Dosage Form
149403	80 mg	Single use vial containing 80 mg of Actemra in 4 mL (20 mg/mL). Packs of 1 and 4* vials.
149404	200 mg	Single use vial containing 200 mg of Actemra in 10 mL (20 mg/mL). Packs of 1 and 4* vials.
149402	400 mg	Single use vial containing 400 mg of Actemra in 20 mL (20 mg/mL). Packs of 1 and 4* vials.

*The packs of 4 vials are not marketed.

1.3. Submission type

This is a Category 1, Type F re-submission to register a new subcutaneous (SC) formulation (as opposed to IV formulation) of Actemra for adult rheumatoid arthritis (RA) indication. This formulation was originally submitted, which was withdrawn by the sponsor in January 2014 for commercial reasons.

The submission proposes registration of the following dosage form and strength as shown in Table 2 below.

1.4. Proposed registration of new route, dosage from and strength

Table 2. Proposed registration of new route, dosage form and strength

Submission application	Strength	Dosage Form
PM-2014-04309-1-3	162 mg	Single use pre-filled syringe with needle safety device containing 162 mg of Actemra in 0.9 mL (180 mg/mL). Packs of 4 syringes.

This new formulation is intended for subcutaneous injection.

The proposed dosing regimen submitted by the sponsor for treatment of adult rheumatoid arthritis is:

- 162 mg given once every week as a subcutaneous injection
- can be used alone or in combination with MTX and/or other non-biological DMARDs
- patients transitioning from IV Actemra therapy to SC administration should administer the first SC dose at the time of the next scheduled IV dose under the supervision of a qualified healthcare professional
- Actemra SC formulation is not intended for IV administration
- in the SUMMACTA study, ACR 20, 50 and 70 response rates in the heaviest body weight category (≥ 100 kg) were lower compared to the other weight categories in both the SC and IV treatment arms.

The proposed method of administration for the subcutaneous formulation is:

- Actemra SC formulation is administered with a single-use pre-filled syringe. The first injection should be performed under the supervision of a qualified healthcare professional. The recommended injection sites (abdomen, thigh and upper arm) should be rotated and injections should never be given into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact. Administration in the thigh may result in slightly increased absorption compared to the other recommended injection sites but this is not considered clinically relevant
- After proper training in injection technique, patients may self-inject with Actemra if their treating healthcare professional determines that it is appropriate
- Assess suitability of patient for SC home use and instruct patients to inform a healthcare professional if they experience symptoms of allergic reaction before administering the next dose. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions.

1.5. Guidance

There is one specific EU guideline adopted by the TGA relevant to this submission, besides the general guidelines:

- CPMP/EWP/556/95 Rev 1: Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDS for Treatment of Rheumatoid Arthritis. Effective: 29 January 2007.

1.6. Overseas regulatory history

This subcutaneous formulation submission has been approved in the EU (4/2014), USA (10/2013), Canada (5/2014), Switzerland (9/2014), Japan (3/2013), and New Zealand (10/14). It is under evaluation in Singapore. Home use is approved in the EU, USA, Canada and New Zealand (relevant extracts from the labels reproduced below). The evaluator was unable to obtain the Swiss or Japanese tocilizumab labels to assess whether home use is approved in these countries.

FDA label

- 17. Patient counseling information

  Hypersensitivity and Serious Allergic Reactions

  Assess patient suitability for home use for SC injection. Inform patients that some patients who have been treated with Actemra have developed serious allergic reactions, including anaphylaxis. Advise patients to seek immediate medical attention if they experience any symptom of serious allergic reactions.

  Instruction on Injection Technique

  Perform the first injection under the supervision of a qualified healthcare professional. If a patient or caregiver is to administer subcutaneous Actemra, instruct him/her in injection techniques and assess his/her ability to inject subcutaneously to ensure proper administration of subcutaneous Actemra and the suitability for home use *[See Patient Instructions for Use].*

EU SPC

4.2 Posology and method of administration

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of RA. All patients treated with RoActemra should be given the Patient Alert Card.

Suitability of the patient for subcutaneous home use should be assessed and instruct patients to inform a healthcare professional if they experience symptoms of an allergic reaction before administering the next dose. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions (see section 4.4).

Canadian Product Monograph

Dosage and Administration

Patients should be assessed for suitability for SC home use and instructed to inform a healthcare professional if they experience symptoms of allergic reaction before administering the next dose. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions (see WARNINGS AND PRECAUTIONS).

Administration

Subcutaneous Actemra:

Actemra subcutaneous injection is intended for use under the guidance and supervision of a physician. After proper training in subcutaneous injection technique, a patient may self-inject Actemra if a physician determines that it is appropriate and with medical follow-up as necessary. The first injection should be performed under the supervision of a qualified healthcare professional. The recommended injection sites (abdomen, thigh and upper arm) should be rotated and injections should never be given into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.

New Zealand Data Sheet

Dosage and Administration

Rheumatoid Arthritis in Adults (IV and SC formulation)

Subcutaneous dosing regimen

Method of administration

Subcutaneous Actemra formulation is administered with a single-use pre-filled syringe. The first injection should be performed under the supervision of a qualified healthcare professional. The recommended injection sites (abdomen, thigh and upper arm) should be rotated and injections should never be given into moles, scars, or areas where the skin is tender, bruised, red, hard or not intact.

After proper training in injection technique, patients may self-inject with Actemra if their treating healthcare professional determines that it is appropriate.

Assess suitability of patient for SC home use and instruct patients to inform a healthcare professional if they experience symptoms of allergic reaction before administering the next dose. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions (see Precautions, Hypersensitivity Reactions).

2. Clinical rationale

In the previous submission for Actemra SC, the sponsor proposed that:

- The registration of a SC formulation, in addition to the IV formulation, will have several benefits:
  - Improved patient convenience and preference (IV or SC)
  - shorter administration time
  - no requirement for intravenous access

- the option for patients to receive Actemra at home
- an alternative route of administration for patients with poor venous access
- lower resource utilisation when administered at home.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 4 Phase I studies in healthy subjects:
  - WP18097
  - BP22065
  - NP25539
  - BP21894
- 2 studies in patients with RA:
  - NP22623 (a Phase Ib study)
  - MRA227JP (a Phase I/II dose escalation study in Japanese patients)
- 3 population PK reports
- 3 Phase III studies, randomised, double-blinded in patients with RA investigating SC Actemra
  - WA22762
    - Primary report, open label extension, immunogenicity report
    - Open label extension to week 97*
  - NA25220
    - Primary report
    - Open label extension to week 96*
  - MRA229JP in Japanese patients is considered a supportive study
    - Open label extension to week 108 (synopsis only; full CSR available only in Japanese)*
  - WA18696
    - Open label extension (condition of registration from PM-2008-0256-3, not related to SC administration of TCZ)*
- Drug Safety Report*
- Research Report (Anaphylaxis based on Health Claims Data)*
- 2 Periodic Benefit-Risk Evaluation Reports (PBRERs)*
- Summary of Clinical Safety
- Literature references.

*Denotes either new data or further data was included (primarily extension of previous studies) compared with previous submission.

3.2. Good clinical practice

All the clinical studies presented in the submission are stated to have been conducted according to GCP.

In study WA18696 (submitted as a condition of registration), critical findings of non-compliance were observed at 3 sites that may have impacted patient safety and/or data integrity. The sponsor implemented corrective and preventative actions and deemed that:

> *'The validity and integrity of the analyses were not affected at any of the above 3 sites, and including all available data in the analyses is a conservative approach, as it ensures reporting of the study in its entirety*.'

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

4.1.1. Study WA22762

Longer term PK profiles of SC and IV TCZ were presented. Following re-randomisation and dose withholding at Week 24, steady state TCZ levels were reached by Week 37 and maintained until Week 97 for both routes of administration. Steady state mean TCZ concentrations in the SC then IV switch arm were generally comparable with those in the continuous IV dosing arm, while levels in the IV-SC switch arm were consistent with those in the continuous SC dosing arm. Pre-dose TCZ levels were higher in the 162mg SC weekly TCZ arms compared with the 8mg IV every 4 weeks TCZ arms.

> *Evaluator's comment: Time to reach steady state, and pre-dose TCZ concentrations for the IV and SC administration routes in the OLE study are consistent with the data from the DB phase of the study.*

4.1.2. Study NA25220

Longer term PK profiles from Week 24 to Week 96 were presented. Following re-randomisation at Week 24, mean pre dose TCZ concentrations in patients who received SC TCZ every 2 weeks up to Week 24 (TCZ pre filled syringe (PFS) and TCZ PFS to autoinjector (AI) arms) were generally maintained and comparable. Mean pre dose TCZ concentrations in patients who received placebo up to Week 24 (placebo to TCZ PFS arm and placebo to TCZ AI arm) increased with repeat dosing of TCZ via PFS or AI following re-randomisation and reached comparable levels to the continuous TCZ arms by about Week 40 to 48.

In an additional ad hoc analysis, pre-dose TCZ concentration data from Week 48 (steady state for the placebo switch arms) to Week 96 were combined for the PFS arms (TCZ PFS arm and placebo to-TCZ PFS arm) and the AI arms (TCZ PFS-to-AI arm and placebo-to-TCZ AI arm). This analysis demonstrated that mean steady state pre dose TCZ concentrations were comparable between the PFS and AI arms between Week 48 and Week 96.

> *Evaluator's comment: In the ad hoc analysis which showed similar mean and median pre dose TCZ concentrations for the PFS an AI arms, higher maximum concentrations were reached by some patients in the AI arm based on the range presented. For example at Week 48 the range for the combined PFS arm was 0.0 to 45.0 while for the AI arm it was 0.0 to 204.0. While later weeks were not as extreme, the maximum concentrations were 28%-83% higher on the AI arm at Weeks 72, 84, and 96. It is not clear whether this might have clinical implications, however as the Sponsor is not proposing to register this presentation clarification of the potential implications is not required.*

4.2. Summary of pharmacokinetics

The following is a summary of the PK from the previous evaluation:

- Absolute bioavailability from SC route was 77% (clearance changing with concentration). (Protocol: WP18097)
- Absorption was slower by the SC route with a median t_{max} of 48 hours compared to 2 hours by IV route. Absorption half-life was about 4 days.
- Both SC presentations (pre-filled syringe and autoinjector) had similar plasma concentration profiles but with high inter-subject variability. Bioequivalence between them was seen for AUC_{inf} but was slightly bioinequivalent for AUC_{last} (0.90-1.27) and C_{max} (0.94-1.27).
- Weight had a significant effect on clearance and volume of distribution. In simulations from the population PK analysis, clearance was decreased by 25% in a 40kg person and increased by 43% in a 140kg person.
- Thigh administration increased bioavailability by 10%.

4.3. Evaluator's overall conclusions on pharmacokinetics

PK from the WA22762 OLE study is consistent with the DB phase of the study with higher pre-dose TCZ plasma concentrations following 162mg SC weekly administration compared with 8mg IV every 4 weeks administration.

PK from the NA25220 OLE is consistent with the DB phase of the study, with both the PFS and AI SC presentations resulting in similar pre-dose TCZ concentrations.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

5.1.1. **Study WA22762**

Longer term PD profiles (mean sIL-6R, CRP, and ESR) were presented. Following re-randomisation and dose withholding at Week 24, mean sIL-6R levels in the ITT-PK population reached stable levels at Week 37 (consistent with levels during the DB phase of the study) and maintained this level through Week 97 in all 4 treatment arms (SC, IV, SC IV switch, IV SC switch). Levels tended to be slightly higher in the SC arms.

Mean CRP and ESR concentrations in the ITT population rapidly decreased after the first dose of TCZ in the DB phase of the study for both the SC and IV arms, and remained at stable levels through Week 97 for all 4 treatment arms.

5.1.2. **Study NA25220**

Longer term PD profiles (mean sIL-6R, CRP, and ESR) were presented. Mean sIL-6R increased rapidly in placebo patients switched to TCZ, and was generally comparable with the continuous TCZ patients by Week 36. Levels were generally similar in the PFS and AI arms.

Mean CRP and ESR levels decreased rapidly in placebo patients switched to TCZ, and were generally comparable with the continuous TCZ patients by Week 32. Levels were generally similar in the PFS and AI arms.

5.2. Summary of pharmacodynamics

The following is a summary of the PD from the previous evaluation:

- Pharmacodynamic outcomes were similar from SC and IV routes
- A dose-finding study indicated similar effects on ACR20, 50 and 70 responses and CRP from once weekly and once fortnightly dosing but a better DAS28 response for once weekly although this was not statistically significant.

5.3. Evaluator's overall conclusions on pharmacodynamics

PD from the WA22762 OLE Study is consistent with the PD from the DB phase of the study:

- Mean sIL-6R levels were maintained and comparable in the SC & IV arms
- Mean CRP levels were maintained in the normal range for the SC & IV arms
- Mean ESR levels remained low for the SC & IV arms.

PD from the NA25220 OLE Study is consistent with the PD from the DB phase of the study:

- Mean sIL-6R, CRP and ESR levels were maintained longer term
- Mean sIL-6R, CRP and ESR levels were comparable in the PFS and AI SC arms.

6. Dosage selection for the pivotal studies

SC dose selection for the pivotal studies was based on four clinical pharmacology studies investigating PK and PD in healthy subjects and PK, PD, efficacy and safety of TCZ following SC administration in RA patients. The PD profiles (CRP, ESR, and sIL-6R) of the SC TCZ 162 mg weekly regimen were determined to be most comparable to the TCZ IV 8 mg/kg dosing regimen. The 162 mg SC every 2 weeks dose regimen produced a slower and less pronounced PD response. In the current submission, the sponsor stated that

> *Study NA25220 has been established as a suitable lower dosing regimen, as part of dose modification for laboratory abnormalities*.

7. Clinical efficacy

7.1. Subcutaneous route and formulation

7.1.1. Study WA22762 (Pivotal efficacy study)

The following is a summary of clinical efficacy from the previous evaluation/overview of Study WA22762:

- Study WA22762 was a multicentre, multinational, randomised, double blind, double dummy, parallel group, non-inferiority study comparing SC (162mg weekly) to IV (8mg/kg every 4 weeks) tocilizumab in combination with a non-biologic DMARD in 1,262 subjects with moderate to severe RA.
- The primary efficacy endpoint was ACR20 at Week 24 with non-inferiority of the SC compared to the IV considered established if the difference between them was ≥ 12% for the lower limit in the 95% confidence interval.
- The trial population was appropriate for this indication and the non-inferiority margin was considered clinically acceptable to show a treatment difference.

- Patients were 83% female, aged between 18 and 86 years and had similar baseline demographics, disease characteristics (mean tender joint count of 27 out of 68 joints and mean swollen joint count of 15 out of 66 joints) and concomitant DMARD use (about 80% of patients in both groups were on methotrexate).
- About 30% of patients in each group started new rheumatoid arthritis treatments during the study but these were evenly matched.
- The results showed non-inferiority was established with the ACR20 response in the per protocol population being 69.4% on SC versus 73.4% on IV (difference of -4.0%, 95% CI -9.2 to +1.2%) with the lower limit of the 95% CI being greater than the non-inferiority margin of -12%.
- The response over time was similar for the two groups. Secondary efficacy endpoints showed no significant difference in ACR50/70, DAS remission, DAS28, HAQ-DI or SF-36 for SC versus IV.
- A non-statistically significant difference by weight group appeared with those ≥100kg having a lower response for ACR20 on SC (52.8%) but a higher response on ACR50 and ACR70, compared to IV dosing.
- Patients <60kg had no difference in ACR20 between SC and IV dosing but a lesser response on ACR50 and ACR70 for SC versus IV dosing.

7.1.1.1. *Study design, objectives, locations and dates*

In the previous submission, efficacy data were presented up to a clinical cut-off of 16 January 2012, as beyond this point data were too sparse to make any meaningful assessment. The final report has now been submitted, which presents efficacy data up to Week 97. All Week 97 analyses are exploratory in nature with no formal comparisons between treatment arms.

The study consisted of a 24-week DB period followed by a 72-week OLE period with a 1 week dose interruption (Week 24-25) before the first dosing in the OL period at Week 25 At the baseline visit, patients were randomised to one of two groups for the 24 week DB period:

- Group A: TCZ 162 mg SC weekly and placebo IV infusion every 4 weeks + DMARD
- Group B: TCZ 8 mg/kg IV every 4 weeks and placebo SC weekly + DMARD

Subcutaneous injections of TCZ and placebo were given using a pre-filled syringe (PFS).

At Week 24, patients from the SC arm were re-randomised in a ratio of 11:1 to SC and IV, respectively, whilst patients from the IV arm were re-randomised in a ratio of 2:1 to IV and SC, respectively:

- Group A1: TCZ 162 mg SC weekly + DMARD (SC arm)
- Group A2: TCZ 8 mg/kg IV every 4 weeks + DMARD (SC IV switch arm)
- Group B1: TCZ 8 mg/kg IV every 4 weeks + DMARD (IV arm)
- Group B2: TCZ 162 mg SC weekly + DMARD (IV SC switch arm)

The first treatment for the OL period was started at Week 25. The maximum duration of OL treatment was 72 weeks. Efficacy parameters were assessed at Weeks 37, 49, 73, and 97 or at the early withdrawal visit. All patients continued to receive at least one permitted traditional DMARD at the stable pre-entry dose throughout the study as prescribed by the treating physician.

7.1.1.2. *Efficacy variables and outcomes*

The efficacy analyses presented in this CSR were performed to assess the maintenance of the efficacy response seen at the end of the DB period (primary efficacy endpoint ACR20 at Week 24). The main time points of interest are Weeks 24, 49, and 97.

7.1.1.3. *Randomisation and blinding methods*

Randomisation and re-randomisation occurred via an interactive voice response system. Re-randomisation for the open label phase was via a permuted block without stratification. The extension phase of the study was open label.

7.1.1.4. *Analysis populations*

The primary analysis for Study WA22762 was based on the per protocol (PP) population. The PP population was also used for the longer term analyses of efficacy (up to Week 49) in the open label extension for consistency with the Week 24 analyses and because WA22762 was a non-inferiority study. However in the final 2 year report the re-randomised ITT population (hereafter referred to as ITT) was used for analyses of efficacy parameters, safety laboratory parameters and vital signs data.

> *Evaluator's comment: The sponsor stated that:Since there was no formal testing carried out on the data at Week 97, it was felt that the ITT population would be more informative than the PP.*

7.1.1.5. *Participant flow*

Of the 572 patients who completed Week 24 in the SC arm, 524 were re-randomised to SC TCZ and 24 to IV TCZ (SC IV switch). Of the 564 patients who completed Week 24 in the IV arm, 377 were re-randomised to IV TCZ and 186 to SC TCZ (IV SC switch). Between 14% and 17% withdrew from each of the re-randomised arms for a variety of safety (AE) and non-safety reasons (subject or legal guardian decision to withdraw or due to insufficient therapeutic response).

7.1.1.6. *Major protocol violations/deviations*

In October 2011, an unscheduled inspection at the Lithuanian trial centre discovered critical findings related to GCP, including the late reporting of SAEs and AEs of special interest for one patient who subsequently died and instances of non-compliance with the 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). At the time of the report, 12 patients were randomised at the site; 10 patients were ongoing and two had withdrawn (one deceased and one due to non-safety reasons). Appropriate corrective and preventative actions were undertaken. All randomised patients were included in the safety population, the 11 re-randomised patients were included in the ITT population, and 9 of the re-randomised patients were included in the PP population.

> *Evaluator's comment: Based on the relatively small number of patients involved, performance of corrective and preventative action, and inclusion of the patients in the safety population, it is not expected that these GCP failings would have had a major impact on the study results.*

7.1.1.7. *Baseline data*

The ITT population in the OLE study was similar to that in the DB phase from both a demographic and disease characteristic perspective. The majority of patients in each treatment arm were female (75%-84%), white (74%-83%), with a mean age from 52.1-54.7 years.

7.1.1.8. *Results for the primary efficacy outcome*

At Week 24 in the original 2 group analysis, the non-inferiority of weekly SC TCZ compared with IV TCZ every 4 weeks was demonstrated (ACR20 responders 69.4% versus 73.4%, and 67.7% versus 70.2% for the PP and ITT populations respectively). The ACR20 response rate was maintained and comparable in the SC and IV arms at Week 49 (79% versus 78%) and Week 97 (84% versus 83%) (See Figure 1 and Table 3 below). Maintenance of effect was also observed in patients who switched at Week 25 from IV to SC (84% and 89% at Weeks 49 and 97, respectively) or SC to IV (71% and 83% at Weeks 49 and 97, respectively) although the latter group started from a lower baseline and was based on a small number of patients.

Figure 1: Plot of the percentage of Patients with ACR20 response by visit (ITT Population, WA22762)

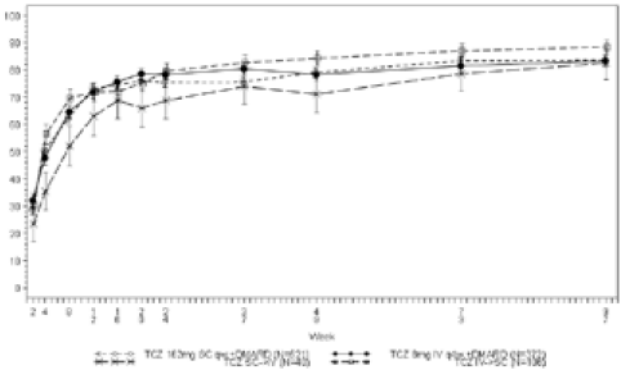


Table 3: Overview of efficacy results up to Week 97 (ITT Population, WA22762)

	No. of Patients (%)			
	162 mg SC qw +DMARD n=521	8 mg/kg IV q4w +DMARD n=372	IV-SC n=186	SC-IV n=48
ACR20 response rate [Section 5.2.1]				
Week 24	391/518 (76%)	291/372 (78%)	148/186 (80%)	33/48 (69%)
Week 49	397/502 (79%)	278/355 (78%)	150/178 (84%)	32/45 (71%)
Week 97	377/451 (84%)	264/317 (83%)	146/165 (89%)	33/40 (83%)
ACR50 response rate [Section 5.2.2]				
Week 24	263/518 (51%)	196/372 (53%)	97/186 (52%)	23/48 (48%)
Week 49	278/502 (55%)	206/355 (58%)	104/178 (58%)	22/45 (49%)
Week 97	295/451 (65%)	198/317 (63%)	111/165 (67%)	23/40 (58%)
ACR70 response rate [Section 5.2.3]				
Week 24	143/518 (28%)	114/372 (31%)	52/186 (28%)	7/48 (15%)
Week 49	173/502 (35%)	130/355 (37%)	66/178 (37%)	13/45 (29%)
Week 97	202/451 (45%)	133/317 (42%)	78/165 (47%)	15/40 (38%)
Decrease in HAQ-DI ≥ 0.22 [Section 5.4]				
Week 24	383/516 (74%)	277/371 (75%)	137/186 (74%)	33/47 (70%)
Week 49	383/499 (77%)	267/354 (75%)	141/177 (80%)	30/44 (68%)
Week 97	347/445 (78%)	250/317 (79%)	130/162 (80%)	26/39 (67%)
Decrease in HAQ-DI ≥ 0.30 [Section 5.4]				
Week 24	347/516 (67%)	254/371 (69%)	120/186 (65%)	28/47 (60%)
Week 49	347/499 (70%)	247/354 (70%)	124/177 (70%)	28/44 (64%)
Week 97	322/445 (72%)	219/317 (69%)	115/162 (71%)	22/39 (56%)
DAS28-ESR remission (<2.6) [Section 5.6]				
Week 24	198/517 (38%)	137/370 (37%)	68/185 (37%)	17/47 (36%)
Week 49	217/498 (44%)	156/352 (44%)	85/176 (48%)	17/45 (38%)
Week 97	238/446 (53%)	142/306 (46%)	90/162 (56%)	20/40 (50%)
Withdrawal due to lack of therapeutic response [Section 5.7] *				
	9/521 (1.7%)	11/372 (3.0%)	3/186 (1.6%)	2/48 (4.2%)

7.1.1.9. *Results for other efficacy outcomes*

As seen for the primary efficacy variable, response rates for ACR50[1], ACR70, HAQ-DI[2], and DAS28-ESR[3] were maintained for the duration of the study, and comparable in each of the treatment arms (see Table 3 above). Switching from IV to SC TCZ did not affect response rates while the variability in response for patients switching from SC to IV was probably affected by the small patient numbers in this group. Withdrawal due to lack of therapeutic response occurred for 9 (1.7%) patients in the SC group, 1 (3.0%) in the IV group, 3 (1.6%) in the IV to SC switch group, and 2 (4.2%) in the SC to IV switch group.

7.1.1.10. *Analyses of Baseline body weight*

Patients weighing ≥ 100kg had lower ACR20, ACR50, and ACR70 responses than those weighing < 60kg and 60 to 100kg for the SC and IV groups, with the IV group recording the lowest response rates in the ≥ 100 kg group. Within weight categories, responses were generally comparable across the treatment groups, although there was increased variability in the ≥ 100 kg group because of small patient numbers (see Table 4, below). In the patients who switched administration route the results were also more variable, again probably reflecting the low number of patients particularly in the SC then IV switch and ≥ 100kg groups.

Table 4: ACR20, ACR50, and ACR70 response rates at Week 97, by body weight at Baseline (ITT Population, WA22762)

ACR Response by Body Weight at Baseline	Number of Patients (%)			
	SC TCZ (N = 521)	IV TCZ (N = 372)	IV-SC switch (N = 186)	SC-IV switch (N = 48)
ACR20				
< 60 kg	94 (88.7%)	68 (91.9%)	33 (80.5%)	9 (81.8%)
60-100 kg	258 (83.2%)	177 (84.7%)	102 (91.9%)	21 (80.8%)
≥ 100 kg	25 (71.4%)	19 (55.9%)	11 (84.6%)	3 (100.0%)
ACR50				
< 60 kg	72 (67.9%)	52 (70.3%)	26 (63.4%)	5 (45.5%)
60-100 kg	204 (65.8%)	134 (64.1%)	79 (71.2%)	16 (61.5%)
≥ 100kg	19 (54.3%)	12 (35.3%)	6 (46.2%)	2 (66.7%)
ACR70				
< 60 kg	52 (49.1%)	43 (58.1%)	21 (51.2%)	3 (27.3%)
60-100kg	138 (44.5%)	85 (40.7%)	54 (48.6%)	11 (42.3%)
≥ 100kg	12 (34.3%)	5 (14.7%)	3 (23.1%)	1 (33.3%)

[1] ACRχ; American College of Rheumatology Criteria Response: A measurement, recording improvement in disease state of rheumatoid arthritis, with χ = corresponding with a global improvement of at least that number (as a percentage).
[2] HAQ-DI; Stanford Health Assessment Questionnaire-Disability Index: 20 Question patient reported assessment of rheumatoid arthritis. Fries JF et al. Measurement of patient Outcomes in arthritis. Arthritis and Rheumatism, 23, 1980, pp.137-145.
[3] DAS28-ESR; Disease Activity Score 28-Erythrocyte Sedimentation Rate: Combined index to measure rheumatoid arthritis disease activity using swollen/tender joint number with ESR blood test. van der Heijde et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis. 1990 Nov; 49(11): 916-920.

7.1.2. **Study NA25220 (Pivotal efficacy study)**

The following is a summary of clinical efficacy from the previous evaluation overview:

- Results were based on the primary analysis after Week 24 and an interim analysis of the OLE period up to a clinical cut-off date of 28 May 2012.
- The latest report contains the final results of the OLE up to Week 96 and focuses primarily on the period from Week 24 to Week 96 (clinical cut-off date of 27 November 2013).
- Study NA25220 was a multicentre, multinational, randomised, double blind, placebo controlled, parallel group study comparing SC tocilizumab (162mg every 2 weeks) to placebo in combination with a non-biologic DMARD in 656 subjects with moderate to severe rheumatoid arthritis.
- The trial population was similar to Study WA22762.
- Patients were 85% female, aged between 18 to 82 years and had similar baseline demographics, disease characteristics (mean tender joint count of 28 out of 68 joints and swollen joint count of 18 out of 66 joints) and history of previous DMARD use.
- The primary efficacy endpoint of ACR20 at week 24 by ITT analysis was superior on tocilizumab at 60.9% versus 31.5% on placebo (difference of 29.5%, 95% CI: 22%-37%). The effect was maintained to week 52.
- Secondary efficacy endpoints (ACR50/70, DAS28, DAS remission, CRP, HAQ-DI and SF-36) were all superior on tocilizumab compared to placebo.
- An effect by weight was seen with the ACR20/50/70 responses being all less for those ≥ 100kg (ACR20: 38.5% on tocilizumab versus 27.3% on placebo).

7.1.2.1. ***Study design, objectives, locations and dates***

The study consisted of a 24-week DB period followed by a 72-week OLE period. At the baseline visit, patients were randomised in a 2:1 ratio to one of two groups for the 24-week DB period while continuing to receive stable background DMARDs:

- Group A: TCZ 162 mg SC every 2 weeks (PFS)
- Group B: placebo SC every 2 weeks

From Week 12 to 24, escape treatment (TCZ 162 mg weekly) was allowed for patients in either arm who had < 20% improvement in SJC and TJC count from baseline. This therapy was continued until the end of study (Week 96).

At Week 24, all patients remaining in the study who had not received escape therapy were re-randomised in a 1:1 ratio as follows:

- Group A1: TCZ 162 mg SC every 2 weeks (AI)
- Group A2: TCZ 162 mg SC every 2 weeks (PFS)
- Group B1: TCZ 162 mg SC every 2 weeks (AI)
- Group B2: TCZ 162 mg SC every 2 weeks (PFS)

The first treatment for the OL period was started at Week 25. After re-randomisation, patients initiating escape treatment (TCZ 162 mg weekly) used the same product they were assigned at Week 24 (PFS or AI). After Week 48, escape treatment was allowed for patients who had < 70% improvement in SJC and TJC from baseline.

The maximum duration of OL treatment was 72 weeks. Efficacy parameters were assessed at Weeks 37, 49, 73, and 97 or at the early withdrawal visit. All patients continued to receive at

least one permitted traditional DMARD at the stable pre-entry dose throughout the study as prescribed by the treating physician.

7.1.2.2. *Efficacy variables and outcomes*

The efficacy analyses presented in this CSR were performed to assess the maintenance of efficacy (primary efficacy endpoint ACR20 at Week 24) in patients re-randomised to remain in the TCZ PFS arm. The OLE study also evaluated the efficacy of TCZ when administered using the AI, efficacy in patients who switched from placebo to TCZ using the PFS or AI, and efficacy in patients in the 24-week study who received escape therapy with weekly SC injections of TCZ administered using the PFS.

7.1.2.3. *Randomisation and blinding methods*

Randomisation and re-randomisation occurred via an interactive voice response system. The extension phase of the study was open label.

7.1.2.4. *Analysis populations*

Efficacy analyses in the OLE study were performed separately for the ITT population and the escape patients. The ITT population analysed in the OLE study excludes all patients who withdrew or received escape therapy prior to Week 24. Patients who received escape therapy after re-randomisation were included in the ITT population up until the time of escape.

Evaluator's comment: As acknowledged by the sponsor, during the OLE phase of the study there is potential for bias in reporting for all subjective endpoints (TJC, SJC, visual analogue scale (VAS), and Heath Assessment Questionnaire (HAQ)).

7.1.2.5. *Sample size*

Not relevant for the OLE. For the DB phase of the study, the expected ACR20 response was 23% and 46% in patients treated with placebo and SC TCZ, respectively. The sample size of 400 patients in the TCZ arm and 200 patients in the placebo arm was estimated to provide greater than 90% power to detect this difference with a significance level of 5%.

7.1.2.6. *Statistical methods*

No hypothesis testing was performed during the OLE period. All analyses are exploratory; no formal analyses were performed to compare between treatment arms.

7.1.2.7. *Participant flow*

Of the 410 patients (93.6%) who completed Week 24 in the TCZ arm (including 70 who received escape therapy), 338 were re-randomised to OL treatment (170 to TCZ PFS, 168 to TCZ AI). Of the 209 patients (95.9%) who completed Week 24 in the placebo arm (including 88 who received escape therapy) 119 were re-randomised to OL treatment (60 to TCZ PFS, 59 to TCZ AI). More patients from the initial TCZ arm withdrew during the OLE phase (10.6% on TCZ PFS, 14.9% on TCZ AI) than those initially on placebo (15.0% on TCZ PFS, 3.4% on TCZ AI).

7.1.2.8. *Major protocol violations/deviations*

During the OLE, 2 patients in the TCZ PFS arm and 1 escape patient in the initial placebo arm were withdrawn from the study due to a protocol violation. The most common violations reported during the OLE involved concomitant medication dosing deviations.

7.1.2.9. *Baseline data*

The ITT population in the OLE study was similar to that in the DB phase. The majority of patients were female (> 82%), with a mean age of around 52 years (range 18-82 years) and had similar baseline demographics, RA duration (mean 10-11 years) and previous DMARD use. Characteristics were generally well balanced across the 4 re-randomised treatment arms. Escape patients had similar baseline demographics to the overall safety population (all patients

who received at least one dose of study drug and had at least one post dose safety assessment in the DB phase).

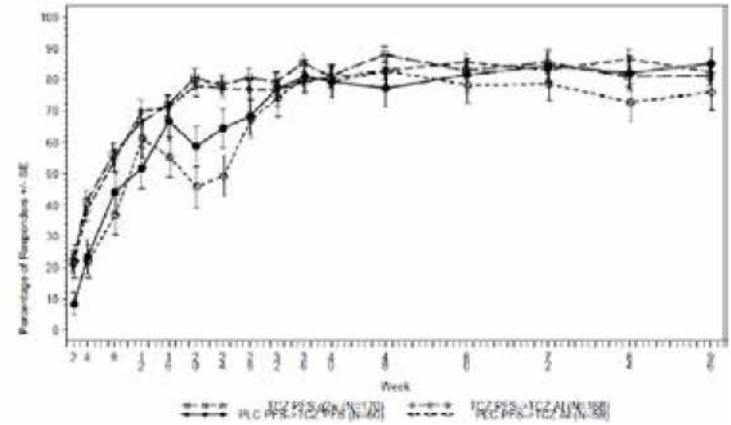
7.1.2.10. *Results for the primary efficacy outcome*

At Week 24 in the original 2 group analysis, the superiority of SC TCZ PFS every 2 weeks compared with placebo was demonstrated (ACR20 responders 60.9% versus 31.5%, respectively). The ACR20 response rate was maintained in patients remaining on TCZ PFS at Week 48 (88%), Week 72 (85.4%), and Week 96 (81.1%). Maintenance of effect was also observed in patients who switched at Week 24 from TCZ PFS to TCZ AI (82.9%, 83.0%, and 82.4% at Weeks 48, 72, and 96, respectively). In patients who switched from placebo PFS to TCZ PFS OR TCZ AI, a rapid improvement in ACR20 response was seen reaching levels comparable to patients on TCZ for the entire duration of the study by about Week 32 (See Table 5 and Figure 2, below).

Table 5: ACR20 response at Weeks 12, 24, 48, 72, and 96 (ITT Population, NA25220)

Efficacy Endpoint Study Week	No. of Patients (%) TCZ PFS q2w (N = 170)	TCZ PFS q2w → TCZ AI q2w (N = 169)	Placebo PFS q2w → TCZ PFS q2w (N = 60)	Placebo PFS q2w → TCZ AI q2w (N = 59)
ACR20 response [Section 6.2.1]				
Week 12	112/169 (66.3)	117/168 (69.6)	31/60 (51.7)	36/59 (61.0)
Week 24	133/170 (78.2)	130/168 (77.4)	38/59 (64.4)	29/59 (49.2)
Week 48	139/158 (88.0)	131/158 (82.9)	44/57 (77.2)	48/58 (82.8)
Week 72	129/151 (85.4)	122/147 (83.0)	43/51 (84.3)	44/56 (78.6)
Week 96	116/143 (81.1)	112/136 (82.4)	40/47 (85.1)	41/54 (75.9)

Figure 2 Percentage of Patients with ACR20 response by visit (ITT Population, NA25220)



7.1.2.11. *Results for other efficacy outcomes*

As seen for the primary efficacy variable, response rates for ACR50, ACR70, HAQ-DI, and DAS28 Remission (< 2.6) were maintained for the duration of the study (after an initial improvement for those originally on placebo), and were generally comparable in each of the treatment arms (see Table 6, below).

Table 6: Summary of efficacy at Weeks 12, 24, 48, 72, and 96 (ITT Population, NA25220)

Efficacy Endpoint Study Week	No. of Patients (%) TCZ PFS q2w (N = 170)	TCZ PFS q2w → TCZ AI q2w (N = 168)	Placebo PFS q2w → TCZ PFS q2w (N = 60)	Placebo PFS q2w → TCZ AI q2w (N = 59)
ACR50 response [Section 5.2.2]				
Week 12	64/169 (37.9)	53/168 (31.5)	13/60 (20.0)	14/59 (23.7)
Week 24	91/170 (53.5)	82/168 (48.8)	14/59 (23.7)	12/59 (20.3)
Week 48	130/158 (83.3)	83/168 (58.8)	27/57 (47.4)	29/59 (49.3)
Week 72	99/151 (64.9)	96/147 (65.3)	30/51 (58.8)	28/56 (50.0)
Week 96	98/143 (67.1)	89/136 (65.4)	32/47 (68.1)	29/54 (51.8)
ACR70 response [Section 5.2.3]				
Week 12	36/169 (21.3)	21/168 (12.5)	3/60 (5.0)	2/59 (3.4)
Week 24	44/170 (25.9)	41/168 (24.4)	5/59 (8.5)	6/59 (10.2)
Week 48	55/158 (34.8)	55/158 (34.8)	21/57 (36.8)	17/58 (29.3)
Week 72	63/151 (41.7)	59/147 (40.1)	18/51 (37.3)	17/56 (30.4)
Week 96	70/143 (49.0)	64/136 (47.1)	18/47 (38.3)	21/54 (38.9)
DAS28 Remission (<2.6) [Section 5.2.5]				
Week 12	42/169 (24.9)	36/168 (21.7)	3/60 (5.0)	3/57 (5.3)
Week 24	50/170 (29.4)	51/168 (30.3)	2/59 (3.4)	3/59 (5.1)
Week 48	69/156 (44.2)	73/157 (46.5)	20/57 (35.1)	19/57 (33.3)
Week 72	77/151 (51.0)	80/143 (55.9)	22/50 (44.0)	19/55 (34.5)
Week 96	73/142 (51.4)	71/134 (53.0)	23/47 (48.9)	24/53 (45.3)
Decrease in HAQ-DI ≥0.30 [Section 5.2.7]				
Week 12	96/169 (56.8)	72/168 (42.9)	32/60 (53.3)	26/59 (42.4)
Week 24	107/169 (63.3)	91/168 (54.2)	28/59 (47.5)	28/59 (47.5)
Week 48	110/158 (69.6)	86/158 (54.4)	32/57 (56.1)	30/59 (50.8)
Week 72	100/151 (66.2)	89/147 (59.9)	28/51 (54.9)	35/56 (62.5)
Week 96	96/143 (67.1)	84/136 (61.8)	32/47 (68.1)	31/54 (57.4)
Withdrawal Due to Lack of Therapeutic Response [Section 5.2.12]				
	1/170 (<1%)	1/168 (<1%)	0	0

Radiography assessments (mTSS) at Weeks 24 and 48 demonstrated less progression in patients initially randomised to TCZ compared with those initially randomised to placebo. The mean change from baseline in the van der Heijde mTSS at Week 24 was 0.46 in the pooled TCZ arm and 0.91 in the pooled placebo arm. At Week 48, mean changes were 0.64 and 1.48, respectively. Other measures of radiographic progression (annualised progression rate, proportion of patients without radiographic progression (mTSS score ≤ 0.5) were also lower in patients initially randomised to TCZ. Results for the 4 treatment arms were more variable because of the smaller group sizes, but generally reflected the pooled 2 group comparison.

7.1.2.12. *Efficacy in escape patients*

Patients not responding to placebo or TCZ PFS every 2 weeks were switched to TCZ weekly. ACR20 responses were higher following the switch for those initially on placebo (86% at 48 Weeks post switch) compared with those initially on TCZ every 2 weeks (54% at 48 Weeks post switch). Responses post-switch for placebo patients were comparable to the responses seen in patients initially randomised to TCZ PFS every 2 weeks. Responses were sustained for up to 84 weeks (see Table 7 below).

Table 7: Summary of efficacy following escape therapy

Efficacy Endpoint Study Week	TCZ PFS qw (prior Placebo q2w) N = 91 No. of Responders/n (%)	TCZ PFS qw (prior TCZ q2w) N = 98 No. of Responders/n (%)	TCZ PFS q2w[a] N=170 No. of Responders/n (%)
ACR20 response			
4 Weeks after Escape	48/91 (52.7)	26/76 (34.2)	69/169 (40.8)
12 Weeks after Escape	62/86 (72.1)	52/89 (58.4)	112/169 (66.3)
24 Weeks after Escape	60/78 (76.9)	42/75 (56.0)	133/170 (78.2)
48 Weeks after Escape	67/78 (85.9)	43/80 (53.8)	139/158 (88.0)
84 Weeks after Escape	57/66 (86.4)	34/54 (63.0)	116/143 (81.1)
ACR50 response			
4 Weeks after Escape	16/91 (17.6)	3/76 (3.9)	20/169 (11.8)
12 Weeks after Escape	34/86 (39.5)	17/89 (19.1)	64/169 (37.9)
24 Weeks after Escape	40/78 (51.3)	20/75 (26.7)	91/170 (53.5)
48 Weeks after Escape	50/78 (64.1)	27/80 (33.8)	100/158 (63.3)
84 Weeks after Escape	40/66 (60.6)	22/54 (40.7)	96/143 (67.1)
ACR70 response e			
4 Weeks after Escape	5/91 (5.5)	2/76 (2.6)	6/169 (3.6)
12 Weeks after Escape	13/86 (15.1)	7/89 (7.9)	36/169 (21.3)
24 Weeks after Escape	22/78 (28.2)	11/75 (14.7)	44/170 (25.9)
48 Weeks after Escape	24/78 (30.8)	13/80 (16.3)	55/158 (34.8)
84 Weeks after Escape	31/66 (47.0)	11/54 (20.4)	70/143 (49.0)

7.1.2.13. *Analyses of baseline body weight*

Patients weighing ≥ 100 kg had lower ACR20, ACR50, and ACR70 responses at Week 96 than those weighing < 60 kg and 60 to 100kg. Within weight categories, responses were generally comparable across the treatment groups, although there was a lot of variability in the ≥ 100 kg group because of small patient numbers (see Table 8 below).

Table 8: ACR20, ACR50, and ACR70 response rates at Week 96, by body weight (ITT Population, NA25220)

ACR Response by Body Weight	TCZ PFS q2w (N = 170) No. of Responders/n (%)	TCZ PFS q2w → TCZ AI q2w (N = 168) 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	32/34 (94.1)	37/44 (84.1)	10/12 (83.3)	14/14 (100)
60 to < 100 kg	82/102 (80.4)	71/86 (82.6)	26/31 (83.9)	26/39 (66.7)
≥ 100 kg	2/7 (28.6)	4/6 (66.7)	4/4 (100)	1/1 (100)
ACR50 response				
< 60 kg	28/34 (82.4)	33/44 (75.0)	8/12 (66.7)	14/14 (100)
60 to < 100 kg	67/102 (65.7)	54/86 (62.8)	21/31 (67.7)	14/39 (35.9)
≥ 100 kg	1/7 (14.3)	2/6 (33.3)	3/4 (75.0)	0/1 (0.0)
ACR70 response				
< 60 kg	24/34 (70.6)	23/44 (52.3)	3/12 (25.0)	11/14 (78.6)
60 to < 100 kg	45/102 (44.1)	39/86 (45.3)	12/31 (38.7)	10/39 (25.6)
≥ 100 kg	1/7 (14.3)	2/6 (33.3)	3/4 (75.0)	0/1 (0.0)

7.2. Other efficacy studies

7.2.1. Study MRA229JP

The following is a summary of clinical efficacy from the previous evaluation and overview:

- Study MRA229JP was a supportive, multicentre, randomised, double blind, double dummy, parallel group, non-inferiority study comparing SC tocilizumab (162mg every 2 weeks) to IV tocilizumab (8mg/kg every 4 weeks) in 346 Japanese subjects with RA.
- The primary efficacy endpoint was ACR20 at week 24 with non-inferiority of the SC compared to the IV considered established if the difference between them was < -18% for the lower limit in the 95% confidence interval.
- Patients were 83% female, aged between 20 and 75 years.
- The results showed non inferiority was established with the ACR20 response being 79.2% on SC versus 88.5% on IV (difference of -9.4%, 95% CI -17.6 to -1.2%) with the lower limit of the 95% CI being greater than the non-inferiority margin of -18%.
- The time course of response for ACR20/50/70, ACR components and DAS28 was similar in both groups.

A synopsis was submitted for the combined 24 week blind and 84 week open-label phases of the study. The OL phase compared 162mg SC TCZ administered every 2 weeks via a PFS or AI. In total, 278 subjects completed the 108 week study. In the combined SC group, the Week 108 ACR20/50/70 response rates were 92.5%, 80.6%, and 61.6% respectively and the mean DAS28 score was 1.92.

7.2.1.1. *Self-injection*

This was performed by 82 subjects using either the PFS or the AI. No major difference between the ACR 20/50/70 response rates or DAS28 scores were detected before and after the start of self-injection.

7.2.1.2. *Baseline body weight*

In response to a Delegate's question in the post-ACPM negotiation letter, the sponsor provided ACR response rates by weight at Week 24. No patients weighed ≥ 100 kg. ACR responses were comparable for SC TCZ and IV TCZ in patients weighing < 60kg, but were consistently lower in SC TCZ every 2 weeks compared with IV TCZ 8 mg/kg in patients weighing ≥ 60kg (Table 9, below).

Table 9: ACR Response at Week 24 by Body Weight as Randomized (PP Population, MRA229JP)

	8 mg/kg TCZ IV N=156	162mg q2w TCZ SC N=159
ACR20 at Week 24		
<60 kg	88.8%	81.0%
≥60 kg	87.5%	73.7%
ACR50 at Week 24		
<60 kg	62.9%	66.1%
≥60 kg	80%	55.3%
ACR70 at Week 24		
<60 kg	37.1%	39.7%
≥60 kg	52.5%	28.9%

Evaluator's comment: The combined SC group Week 108 results were comparable to the combined SC/IV group results at Week 24 in the DB phase of the study (ACR20/50/70 response rates of 89.4%, 72.1%, and 49.7%, respectively, mean DAS28 score of 2.38).

7.2.2. Study ML28338

The CSR for the long-term extension (LTE) study ML28338 is still in preparation, so preliminary results have been presented only. This study was a Phase IIIb, multicentre, open label, single arm, LTE study of the WA22762 and NA25220 core studies conducted in the US. The primary objective of the study was to evaluate the long-term safety of SC TCZ therapy (162 mg once weekly or every 2 weeks) with regard to adverse events (AEs) and clinical laboratory assessments including immunogenicity. Long term efficacy was a secondary objective. Patients who received SC TCZ in the core study continued with the same dosage (SC TCZ 162 mg weekly or every 2 weeks) while patients who received IV TCZ in the core study switched to SC TCZ 162 mg weekly (study WA22762 only). A total of 218 patients were enrolled; 148 patients from study WA22762 and 70 patients from study NA25220. One patient did not receive any treatment leaving a total of 217 patients who received at least one dose of SC TCZ (n = 44 SC TCZ every 2 weeks, n = 173 SC TCZ weekly). ACR20 response rate at baseline was 52.3% and 42.2% for SC TCZ every 2 weeks and weekly respectively. There was an increase in response rate at Week 12 (72.7% and 59.0%), with rates stabilising for Weeks 24 to 48 (in the range of 59% to 67%). ACR50/70 response rates were lower but showed a similar pattern. Patient numbers on SC TCZ every 2 weeks were too low for interpretation of later response rates. Patients on SC TCZ weekly maintained their ACR20/50/70 response rates out to Week 84.

7.2.3. Study WA18696

Study WA18696 was submitted as a condition of registration from evaluation PM-2008-02563-3 and relates to IV administration of TCZ in patients with RA. It does not have direct relevance to the main purpose of this evaluation.

7.3. Evaluator's conclusions on clinical efficacy

Results from the open label extensions of the pivotal WA22762 and supportive MRA229JP studies showed that the comparable efficacy demonstrated for weekly (WA22762) or 2 weekly (MRA229JP) SC and 4-weekly IV TCZ during the DB phase of the studies (based on ACR 20/50/70, DAS28 and so on) was maintained for up to 2 years in patients remaining on SC TCZ

or IV TCZ for the total duration of the study and for those switching from IV to SC or SC to IV TCZ. Patients weighing ≥ 100 kg were noted to have a lower response for ACR20 on SC TCZ but a higher response for ACR50 and ACR70, compared to IV dosing at Week 24. At Week 97, patients weighing ≥ 100 kg again had lower response rates compared with lighter patients, with the IV group having lower response rates than the SC group in the ≥ 100 kg group. Patient numbers in the ≥ 100 kg switch groups were too small for reliable interpretation.

In the pivotal NA25220 study, patients who commenced and remained on 2 weekly SC TCZ had no reduction in efficacy during the up to 96 weeks of follow up. Patients switching from placebo to SC TCZ at Week 24 responded rapidly, reaching comparable levels to those on continuous TCZ after approximately 8 weeks of treatment, and maintaining this response for the duration of the study. At Week 96, patients weighing ≥ 100 kg had lower response rates compared with lighter patients, but the patient numbers were very low (maximum of 7 patients) making interpretation of these results difficult. However the results were consistent with those reported at Week 24 when the patient numbers were higher in the ≥ 100 kg group (26 patients).

Study ML28338 (LTE of US patients completing either WA22762 or NA25220) provided further supportive evidence of the long-term efficacy of SC TCZ.

It is noted that the ACR20/50/70 response rates at weeks 24, 48/49, and 96/97 were similar for patients receiving SC TCZ weekly in study WA22762 and SC TCZ twice weekly in study NA25220. Although these studies were not designed to be directly compared, the patient populations in both studies were similar (moderate to severe RA with an inadequate response to DMARDS). The dosage selection for the pivotal studies was based on PD profiles, however in view of the similar efficacy responses for the two dosage regimens, the sponsor will be asked to comment on this finding and whether there are any planned or existing studies directly comparing clinical outcomes for the two SC dosing regimens. Whether the dosing model for SC TCZ is appropriate was also raised by the ACPM following the original submission.

In study MRA229JP self-injection was undertaken by 82 patients. No difference in efficacy was noted between the ACR 20/50/70 response rates or DAS28 scores achieved with self-injection versus those achieved when TCZ was administered by a healthcare professional.

8. Clinical safety

As agreed with the TGA at a pre-submission meeting on October 1, 2014, the sponsor has submitted updated data from the SC TCZ clinical trial program beyond that submitted in the previous application (Studies WA22762, NA25220, MRA229JP, and ML28338), post-marketing safety data from regions where SC TCZ has marketing approval and specific analyses on hypersensitivity and anaphylaxis to TCZ to address the concerns of the risks for serious hypersensitivity and/or anaphylactic reactions in the home setting (see Table 10, below).

Table 10: Summary of sources of data for SC TCZ safety

Clinical trial	Follow up	SC TCZ exposure				Home use allowed†
		DB Period		OLE Period		
		Tx Arm	n=	Tx Arm	n=	
WA22762 (SUMMACTA)	2 years (Week 97)	SC TCZ qw	631	IV TCZ then SC TCZ qw switch	186	after 4 injections
NA25220 (BREVACTA)	2 years (Week 96)	TCZ PFS every 2 weeks	438	Placebo then TCZ PFS every 2 weeks switch	61	after 6 injections
		Placebo escaper	90	Placebo then TCZ AI every 2 weeks switch	59	
ML28338 (LTE of WA22762 & NA25220) (data cut-off 26/8/14)	Up to an additional 84 weeks‡	-	-	SC TCZ qw	173	as per WA22762
				SC TCZ every 2 weeks	44	
MRA229JP	2 years (Week 108)				346δ	After 7 injections in the OL period
Post-marketing		Overall SC TCZ exposure				
Roche Global Safety Database (data cut-off 10/10/14)λ		20,920 patients (4,045 from clinical trials and 16,875 from post-marketing experience) 17,380 PYs (3,716 from clinical trials and 13,664 from post-marketing experience)				
Research Report		Nil				

‡ only 11/217 (5.1%) remained; 56/217 (25.8%) had 72 weeks further exposure; †Allowed under the protocol after a differing number of injections at the clinical site; δ333 received at least one SC injection of TCZ; λwhich includes data from the two included PBRERs (11 October 2013 to 10 October 2014).

The clinical safety from each source will be reviewed separately; the implications for home use are discussed later.

The following is a summary of clinical safety from the previous evaluation and overview:

- The two pivotal studies (WA22762 & NA25220) had exposure to SC tocilizumab for up to 1 or 2 years.
- Treatment emergent adverse events were similar between SC and IV groups at an overall 84% on SC versus 80% on IV from the first pivotal study with administration site adverse events being more common on SC dosing (14.9 versus 7%) as expected (mostly erythema, pruritus and pain) but no difference by body weight.
- Deaths occurred in one patient on SC from shock and two on IV from idiopathic pulmonary fibrosis and sepsis or septic arthritis in the pivotal study with 4 deaths occurring in the second pivotal study (three sepsis, one angina).

- Serious adverse events and discontinuations due to adverse events occurred at a similar rate with no apparent difference between the groups.
- Increases in hepatic transaminases were observed but at a similar rate in SC and IV groups.
- Decreases in neutrophil and platelet counts also occurred at a similar rate in both groups.
- Neutralising anti-tocilizumab antibodies occurred in 1.6% on SC versus 1.7% on IV from the pivotal study.
- The Japanese study, unlike the two pivotal studies, indicated IgE anti-tocilizumab antibodies were higher on SC than IV (14.5 versus 5.2%) with injection site reactions being more common in people positive for IgE anti-tocilizumab antibodies.
- Injection site reactions were more common on SC than IV (11.6% versus 2.4%) and serious infections were slightly higher (2.5% versus 1.7%).
- Anaphylaxis occurred in two people on IV and serious hypersensitivity reactions occurred in four on SC versus three on IV.
- In the fortnightly dosing study, injection site reactions occurred in 6.9%.

8.1. Studies providing evaluable safety data

The following pivotal studies provided evaluable safety data: Study WA22762 and Study NA25220. Additional safety data was provided in Study MRA229JP (synopsis only submitted) and Study ML28338 (The sponsor will be requested to provide the CSR when it is available in future).

There were no pivotal studies that assessed safety as a primary outcome.

8.2. Patient exposure

8.2.1. Pivotal studies

Mean and median exposure in Study WA22762 was longer for SC administration of TCZ than for IV administration (1.38 and 1.72 years versus 1.12 and 1.44 years, respectively). A further mean (median) 1.20 (1.33) years and 1.19 (1.29) years of SC and IV TCZ exposure, respectively, were added from the switch arms during the OL phase of the study (see Table 11 below).

Table 11: Extent of Exposure† to Trial Treatment (Safety Population, WA22762)

	SC TCZ N = 631	IV-SC TCZ switch N = 186	IV TCZ N = 631	SC-IV TCZ switch N = 48
Extent of exposure (years)				
Mean	1.38	1.20	1.12	1.19
Median	1.72	1.33	1.44	1.29
Min-Max	0.0-1.8	0.1-1.4	0.1-1.8	0.1-1.4
Total PY Exposure† to Treatment	873.7	224.0	707.2	57.0
PY Study Duration‡ (used for AE rates)	1013.3	255.8	816.5	66.2

† Exposure per SC injection = the difference between the dates of a patient's injection and their subsequent injection (capped at 7 days). SC Extent of exposure = Sum of the exposure for all injections + 7 days.

Total patient years exposure is the sum of the exposure across all patients in the treatment group divided by 365.25. ‡Duration in study (years) = (date of last assessment - date of first dose + 1) / 365.25

In Study NA25220 the total patient years (PY) of exposure was 404.3 PY (n=437 patients) in the TCZ PFS arm, 211.6 PY in the TCZ PFS-to-AI arm (n=168 patients), 75.6 PY in the placebo-to-TCZ PFS arm (n=61 patients), and 78.7 in the placebo-to-TCZ AI arm (n=59 patients). This is based on the duration of actually received treatment over the 96 weeks of the study in the TCZ PFS treatment arm, but limited to TCZ exposure during the OL period for the other 3 treatment arms. For escape patients, exposure to TCZ weekly was 126.5 PY in the prior TCZ arm (n=98 patients) and 129.3 PY in the prior placebo arm (n=91 patients).

8.2.2. Other studies

Only Study ML28338 gave patient exposure data with a total PY duration of 251.3 PY for the overall population.

8.3. All adverse events irrespective of study treatment

8.3.1. Pivotal studies

Overall in Study WA22762, the vast majority of patients had at least 1 AE, with incidence similar across the treatment groups (88% on IV, 92% on SC, 81% on SC IV, & 87% on IV SC). Administration site conditions were more common in the SC (20.8%) and IV SC (14.5%) patients than in the IV (12.0%) and SC IV (8.3%) patients. Rates for AEs were comparable in the SC and IV TCZ arms. Rates were also similar for IV SC switch patients. Duration of exposure and event numbers were low in the SC IV switch patients with wide CIs, but rates were generally comparable to the other treatment arms (see Table 12, below).

Table 12: Overview of adverse events: Rate (95% CI) per 100 PY (safety population, WA22762)

	162 mg SC qw + DMARD	8 mg/kg IV q4w + DMARD	SC-IV	IV-SC
PY Duration	1013.26	816.53	66.19	255.75
All AEs (Section 7.3)				
No. of events	4214	3336	180	1010
Rate per 100 PY [95% CI]	415.89 [403.42;428.64]	408.56 [394.81;422.66]	271.93 [233.66;314.69]	394.92 [370.94;420.05]
Deaths (Section 7.4)				
No. of events	4	4	0	2
Rate per 100 PY [95% CI]	0.39 [0.11;1.01]	0.49 [0.13;1.25]	0.00 [0; 5.57]	0.78 [0.09;2.82]
SAEs (Section 7.5)				
No. of events	148	126	6	50
Rate per 100 PY [95% CI]	14.61 [12.35;17.16]	15.43 [12.85;18.37]	9.06 [3.33;19.73]	19.55 [14.51;25.78]
AEs leading to withdrawal (Section 7.6)				
No. of events	91	80	2	16
Rate per 100 PY [95% CI]	8.98 [7.23;11.03]	9.80 [7.77;12.19]	3.02 [0.37;10.91]	6.26 [3.58;10.16]

Most events occurred at a similar rate per 100 PY (95% CI) in the continuous SC and IV treatment arms, for example:

- infection and infestation events: 108.7 (102.3, 115.3) versus 105.6 (98.6, 112.9)
- serious infection: 4.0 (2.8, 5.4) versus 3.9 (2.7, 5.5)

- adjudicated malignancies (including NMSC AEs): 0.9 (0.4, 1.7)versus 0.7 (0.3, 1.6)
- hypersensitivity reactions: 8.8 (7.1, 10.8) versus 14.8 (12.3, 17.7)
- serious hypersensitivity reactions (reported as an SAE): 0.5 (0.2, 1.2) versus 0.2 (0.03, 0.9)
- injection site reactions (ISRs): 26.1 (23.0, 29.4) versus 33.6 (27.1, 41.3)

In the IV to SC switching arm, event rates were generally similar to the rates in the continuous IV and SC treatment arms (wide and overlapping 95% CIs) with the exception of ISRs (higher at 93.45 (82.0, 106.1)) and hypersensitivity reactions (lower at 3.91 (1.9, 7.2)). Very few events were reported in the SC to IV arm because of the limited PY exposure.

There was a trend towards higher AE rates and numerically higher infections in patients weighing ≥ 100 kg at baseline.

In Study NA25220, a similar proportion of patients had at least 1 AE in each of the treatment arms (73.5% TCZ PFS, 74.4% TCZ PFS switched to TCZ AI, 73.8% placebo switched to TCZ PFS, and 79.7% placebo switched to TCZ AI). The proportion of escape patients with AEs were slightly higher (84.6% placebo switched to TCZ PFS weekly, 83.7% TCZ every 2 weeks switched to TCZ PFS weekly).

Infections and infestations were the most common AEs (URTIs), followed by gastrointestinal disorders, investigations (ALT and AST increased), and musculoskeletal and connective tissue disorders. The types and percentage of AEs were generally similar in each of the TCZ arms. The overall rates per 100 PY for AEs were generally comparable between the 2 continuous TCZ arms, and lower but comparable in the 2 placebo switch arms (Table 13 below). These rates are all lower than reported in the interim OLE report.

Table 13: Overview of adverse events: Rate (95% CI) per 100 PY (safety population, Study NA25220)

	TCZ PFS q2w (N = 437)[a]	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 PY	404.34	211.61	75.55	73.65	82.80
Any AE (Section 7.3)					
No. of events	1438	612	174	197	293
Rate per 100 PY (95% CI)	355.64 (337.50, 374.51)	289.22 (266.75, 313.07)	230.32 (197.37, 267.21)	250.47 (216.71, 287.99)	353.86 (314.50, 396.79)
Deaths (Section 7.4)					
No. of events	4	3	1	0	0
Rate per 100 PY (95% CI)	0.99 (0.27, 2.53)	1.42 (0.29, 4.14)	1.32 (0.03, 7.38)	0 (0.00, 4.59)	0 (0.00, 4.46)
SAEs (Section 7.5)					
No. of events	46	23	2	0	12
Rate per 100 PY (95% CI)	11.38 (8.33, 15.17)	10.87 (6.89, 16.31)	2.65 (0.32, 9.56)	0 (0.00, 4.59)	14.49 (7.49, 25.32)
Withdrawals due to AE (Section 7.6)					
No. of events	16	10	1	1	4
Rate per 100 PY (95% CI)	3.96 (2.26, 6.43)	4.73 (2.27, 8.69)	1.32 (0.03, 7.38)	1.27 (0.03, 7.08)	4.83 (1.32, 12.37)

Escape patients had types and rates of AEs similar to TCZ PFS every 2 weeks arm, and was comparable in the prior TCZ (331.90 (95% CI 300.91, 365.21)) and prior placebo (360.48 (95% CI: 328.49; 394.74)) arms.

Due to the low number of events reported for most AESIs and the limited PY exposure in the prior placebo arms, meaningful comparison was limited. Rates per 100 PY (95% CI) were comparable in the TCZ PFS, and TCZ PFS switched to AI treatment arms for the following events:

- infection and infestation events: 87.06 (78.20, 96.64) versus 85.54 (73.53, 98.95)
- serious infection: 3.96 (2.26, 6.43) versus 1.89 (0.52, 4.84)
- adjudicated malignancies (including NMSC AEs): 0.99 (0.27, 2.53) versus 0.95 (0.11, 3.41)

- hypersensitivity reactions:5.69 (3.61, 8.54) versus 4.25 (1.94, 8.07)
- injection site reactions (ISRs): 22.01 (17.68, 27.09) versus 15.60 (10.73, 21.90)

8.3.2. Other studies

Across the entire study period of Study MRA229JP 340 subjects (98.3%) experienced 2,473 AEs. The most common AEs (PTs) were: nasopharyngitis (46.5%), upper respiratory tract infection (21.1%), blood cholesterol increased (20.2%), pharyngitis (15.0%), low density lipoprotein increased (18.5%), blood triglycerides increased (13.3%), alanine aminotransferase increased (13.0%), stomatitis (11.3%), eczema (11.3%), gamma-glutamyltransferase increased (10.7%), white blood cell count decreased (10.7%), and injection site erythema (10.7%).

In the 82 subjects who self-injected, the AE rates 12 weeks before and 12 weeks after the start of self-injection were similar (54.9% (77 events in 45 of 82 subjects) versus 58.5% (85 events in 48 of 82 subjects), respectively).

A total of 954 AEs were reported by 179 (82.5%) of the 217 patients in Study ML28338 giving an overall rate of 379.66 (95% CI: 355.95, 404.54) events per 100 PY.

8.4. Treatment related adverse events (adverse drug reactions)

8.4.1. Pivotal studies

For Study WA22762, treatment related adverse events were not specifically tabulated separately (reported in line listings), with the exception of hypersensitivity events which were 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.

Treatment related adverse events for Study NA25220 were similar to those for Study WA22762.

8.4.2. Other studies

Across the entire study period of Study MRA229JP 334 subjects (96.5%) experienced 1,921 ADRs. No further information was provided.

No treatment related AEs were reported for Study ML28338.

8.5. Deaths and other serious adverse events

8.5.1. Pivotal studies

In total, 10 deaths were reported during Study WA22762: 4 each in the SC and IV treatment arms and 2 in the IV SC switch arm. All but one occurred in the OL phase of the study and 5 of the deaths (2 in the SC, 2 in the IV and 1 in IV SC switch arm) were considered related to the study treatment. Cause of death was given as shock, acute respiratory distress syndrome, sepsis in two patients and simply ‘death’ in another.

Overall, 195 patients reported a total of 330 SAEs, with incidence similar across the treatment groups (13% on IV and 14% on SC). The most frequently reported SAEs by SOC were infections and infestations, musculoskeletal and connective tissue disorders, and nervous system disorders. Hypersensitivity SAEs were more common in the SC patients (3 patients or 0.5%) than in the IV patients (1 patient or 0.2%).

Rates for SAEs and deaths were comparable in the SC and IV TCZ arms. Rates were also similar for IV SC switch patients. Duration of exposure and event numbers were low in the SC IV switch patients with wide CIs, but rates were generally comparable to the other treatment arms (Refer to Table 12 above).

Nine deaths were reported during Study NA25220: 4 during the DB phase, 1 during the interim OL phase (previously reported and evaluated) and 4 after the interim analysis of the OL phase. Of these 4 deaths, two were considered related to study treatment (pyrexia of unknown origin (TCZ PFS then AI switch arm), MI (placebo then TCZ PFS switch arm)), and 2 unrelated (myocardial infarction (placebo then TCZ PFS then AI switch arm), myocardial infarction (TCZ PFS arm)). One patient in the escape arm died (upper GI haemorrhage, considered unrelated to treatment).

Overall, 63 patients reported 82 SAEs across the DB and OL phases of the study, with incidence similar in the TCZ PFS and the TCZ PFS then TCZ AI switch arms (8.2% versus 10.1%). There were few SAEs and the limited PY exposure in the prior placebo arms limiting meaningful comparison. The most frequently reported SAEs by SOC were infections and infestations, gastrointestinal disorders, and cardiac disorders. Most types of SAEs were reported in ≤2 patients. A further 30 patients on escape therapy had SAEs (16 (16.3%) on prior TCZ, 14 (15.4%) on prior placebo).

8.5.2. **Other studies**

One death occurred during Study MRA229JP (in the open-label period). There were 107 SAEs in 22.3% (77 of 346 subjects) of the subjects. The most frequently reported SAEs by SOC were infections and infestations which occurred in 8.7% (30 of 346 subjects) of the subjects.

In Study ML28338 a total of 37 SAEs in 23 patients (10.6%) were reported giving an overall rate of 14.72 (95% CI: 10.37, 20.30) SAEs per 100 PY. There were no deaths during the study.

8.6. Discontinuation due to adverse events

8.6.1. **Pivotal studies**

In Study WA22762 AEs leading to withdrawal were observed in 91 (14.4%) patients in the SC arm and 80 (12.7%) patients in the IV arm. The most common AEs that led to withdrawal were hypersensitivity, infections, and elevated transaminases. Rates for AEs leading to withdrawal were comparable in the SC and IV TCZ arms. Rates were also similar for IV SC switch patients. Duration of exposure and event numbers were low in the SC IV switch patients with wide CIs, but rates were generally comparable to the other treatment arms (See Table 12 above).

AEs leading to withdrawal from Study NA25220 were reported for 16 (3.7%) TCZ PFS patients, 8 (5.4%) TCZ PFS to AI switch patients and 1 patient each (1.7%) in the placebo to TCZ PFS switch and placebo to TCZ AI switch arms. The most common reasons for withdrawal included neutropenia, and increased ALT. Twelve patients in the escape arm (5 on prior TCZ, 7 on prior placebo) were withdrawn.

8.6.2. **Other studies**

In Study MRA229JP there were 44 AEs in 36 subjects leading to withdrawal of the investigation product and a further 299 adverse events in 181 subjects leading to modification of the dosing interval or temporary suspension of treatment. The most common SOCs were infections and infestations.

Sixteen patients (7.4%) in Study ML28338 experienced an AE that led to withdrawal from treatment.

8.7. Adverse events of special interest

8.7.1. Immunogenicity

8.7.1.1. *Pivotal studies*

In Study WA22762 anti-TCZ antibodies were detected in only a small proportion of patients in the SC (1.6%), IV (1.1%), and IV SC (0.5%) arms and only 2 patients (both on SC TCZ) had positive anti-TCZ IgE antibodies. None of the patients had an anaphylactic or serious hypersensitivity reaction. 1 patient (in the IV arm) had a clinically significant hypersensitivity reaction, and 2 patients in the SC arm had non-serious ISRs (injection site erythema). No patient with anti-TCZ antibodies was withdrawn from study due to insufficient therapeutic response or met the criteria of "loss of efficacy".

The proportions of patients in Study NA25220 with anti-TCZ antibodies post-baseline were consistently low and similar across the treatment arms: 8 of 432 patients (1.9%) in the TCZ PFS arm, 1 of 168 patients (0.6%) in the TCZ PFS to AI switch arm, 1 of 61 patients (1.7%) in the placebo to TCZ PFS switch arm, no patients in the placebo to TCZ AI switch arm, and 3 of 218 patients (1.4%) in the placebo arm. Among escape patients, 3 (3.3%) patients in the prior placebo arm and 1 (1.0%) patient in the prior TCZ arm had anti-TCZ antibodies. Four patients had positive anti-TCZ IgE antibodies (3 in the TCZ PFS arm and 1 in the TCZ PFS to AI switch arm). None of the patients had an anaphylactic, or serious or clinically significant hypersensitivity reaction, or injection site reaction. No patient with anti-TCZ antibodies experienced loss of efficacy or withdrew from the study due to lack of efficacy.

8.7.1.2. *Other studies*

Overall in Study MRA229JP anti-TCZ antibodies (screening method) were detected in 6 of 173 (3.5%) patients in the SC TCZ group (all during the BD phase) and in 1 of 173 (0.6%) patients in the IV TCZ group (after switch to SC administration) during the 108-week study. Sixteen subjects (4.8%) experienced a post-injection systemic reaction, but there were no events of anaphylaxis reported.

Data from Study ML28338 was not yet available.

8.7.2. Injection site reactions

8.7.2.1. *Pivotal studies*

In Study WA22762 a total of 264 ISRs were observed in 77 (12.2%) patients in the SC arm and 91 ISRs were observed in 15 (2.4%) patients in the IV arm (who only received SC injections of placebo during the 24 weeks of the DB phase of the study). This resulted in a comparable rate of ISRs in both arms (26.05 (23.01, 29.39) versus 33.63 (27.08, 41.29) events per 100 PY). None of the ISR symptoms in either arm were reported as an SAE and none led to withdrawal from treatment. In the switch arms, no ISR AEs were reported in the SC IV arm (as expected as there were no SC injections during the OL phase), and 12 patients had 239 ISR AEs in the IV SC arm (93.45 (81.98, 106.08) events per 100 PY). The higher rate in the IV to SC switch arm was largely due to multiple ISR AEs (between 31 and 75 events each) reported by 5 patients.

In Study NA25220 ISRs were more common in the TCZ PFS arm than in the TCZ PFS to AI switch arm (22.01 (17.68; 27.09) versus 15.60 (10.73; 21.90)), with very few events in either of the prior placebo arms. The most commonly reported ISRs were injection site erythema, and injection site pain.

8.7.2.2. *Other studies*

There were 57 injection site reactions in Study MRA229JP (all mild) in 13.2% (44 of 333 subjects) of the subjects. In the 82 subjects who self-injected, the incidence rate of administration site reactions was higher after the start of self-injection, but the reactions were all mild, and none of the subjects discontinued self-injection owing to injection site reactions.

A total of 29 ISRs in 6 (2.8%) of 217 patients were reported in Study ML28338.

8.7.3. Infection of any nature

8.7.3.1. *Pivotal studies*

The overall rate (95% CI) of infection and infestation AEs in Study WA22762 was comparable in the SC, IV, and IV SC arms (108.66 (102.34, 115.27) versus 105.57 (98.64, 112.86) versus 96.97 (85.28, 109.82) events per 100 PY, respectively). Rates were numerically lower in the SC IV arm (84.60 (63.91, 109.86) events per 100 PY) but the 95% CIs are wide and overlapping.

In Study NA25220 the overall rate (95% CI) of infection and infestation AEs was comparable in the TCZ PFS, TCZ PFS to TCZ AI switch, and placebo to TCZ PFS switch arms (87.06 (78.20; 96.64) versus 85.54 (73.53; 98.95) versus 90.01 (69.90; 114.11) events per 100 PY, respectively). Rates were numerically lower in the placebo to PFS to TCZ AI switch arm (59.76 (43.91; 79.46) events per 100 PY) but the 95% CIs are overlapping.

8.7.3.2. *Other studies*

Overall rates of infection were not discussed in the non-pivotal studies.

8.7.4. Serious infections

8.7.4.1. *Pivotal studies*

The overall rate (95% CI) of serious infection AEs in Study WA22762 was comparable in the SC and IV arms (3.95 (2.82, 5.38) versus 3.92 (2.68, 5.53) events per 100 PY, respectively). Rates were numerically higher in the IV SC arm (6.65 (3.87, 10.64) events per 100 PY) but the 95% CIs are wide and overlapping. There was a single serious infection (diverticulitis) reported in the SC IV arm (1.51 (0.04, 8.42) events per 100 PY). The most common serious infections occurring in ≥ 2 patients in either SC or IV arm were: cellulitis (8 patients SC versus 1 patient IV, respectively), pneumonia (4 patients versus 6 patients), septic shock (3 patients versus. 1 patient), urinary tract infection (3 patients versus 1 patient), gastroenteritis (2 patients versus 2 patients), peritonitis (2 patients versus 0 patient), wound infection (0 patient versus 3 patients), bacterial arthritis (0 patient versus 2 patients), infective arthritis (1 patient versus 2 patients), and infective bursitis (0 patient versus 2 patients). The most common serious infections in the IV SC switch arm (occurring in ≥ 2 patients) were pneumonia (4 patients) and cellulitis (2 patients).

In Study NA25220 there were few serious infections, but the rate (events per 100 PY) was numerically higher in the TCZ PFS arm (3.96 (2.26; 6.43)) compared with the TCZ PFS to TCZ AI switch arm (1.89 (0.52; 4.84)). The only events occurring in more than 1 patient were: pneumonia, sepsis, lower respiratory tract infection, and pulmonary tuberculosis which each occurred in 2 patients, all on the TCZ PFS arm. Fifteen escape patients (8 in the prior TCZ arm (8.2%) and 7 in the prior placebo arm (7.7%)) experienced serious infections with cellulitis (6 patients) and pneumonia (3 patients) being the only events occurring in more than 1 patient.

8.7.4.2. *Other studies*

Infection was not discussed in Study MRA229JP.

In Study ML28338 the rate of serious and/or medically significant infections was 4.38 events per 100 PY.

8.7.5. Opportunistic infections

8.7.5.1. *Pivotal studies*

In Study WA22762 seven opportunistic infections were reported during the study: 4 events in 3 patients in the SC arm (atypical pneumonia, bronchopulmonary aspergillosis, oropharyngeal candidiasis, and pharyngeal abscess) and 2 events in 2 patients in the IV arm (genital herpes zoster and lepromatous leprosy). The overall rate of opportunistic infection AEs was

comparable in the SC and IV arms (0.39 (95% CI: 0.11, 1.01) versus 0.24 (95% CI: 0.03, 0.88) events per 100 PY, respectively).

In Study NA25220 four opportunistic infections were reported during the study: 1 during the DB phase (coccidioidomycosis in a patient in the placebo arm), and 3 during the OL phase (oesophageal candidiasis in a patient in the TCZ PFS arm, coccidioidomycosis in a patient in the TCZ PFS to AI switch arm, and atypical pneumonia in a patient in the TCZ PFS to AI switch arm).

8.7.5.2. *Other studies*

Opportunistic infection was not discussed.

8.7.6. Malignancy

8.7.6.1. *Pivotal studies*

The overall rate (95% CI) of adjudicated malignancy in Study WA22762 including NMSC AEs was comparable in the SC, IV and IV SC arms (0.89 (0.41, 1.69) versus 0.73 (0.27, 1.60) versus 0.78 (0.09, 2.82) events per 100 PY). One adjudicated malignancy event was reported in the SC IV switch arm after the switch to IV therapy (1.51 (0.04, 8.42) events per 100 PY). While the rate was numerically higher in the SC to IV switch arm, the 95% CIs are wide and overlap with the rates in the other treatment.

In Study NA25220 eight malignancies were reported during the study, 3 during the DB phase (all in the TCZ PFS arm), and 5 in the OL phase (1 in the TCZ PFS, 2 in the TCZ PFS to AI and 2 in the placebo to AI switch arms). Six malignancies were reported in escape patients: 4 in the prior placebo arm and 2 in the prior TCZ arm.

8.7.6.2. *Other studies*

Malignancy was not discussed in Study MRA229JP.

In Study ML28338 two malignancies in 2 patients were reported (0.80 (95% CI 0.10, 2.88) per 100 PY).

8.7.7. Anaphylaxis and hypersensitivity

8.7.7.1. *Pivotal studies*

No anaphylactic events were identified in Study WA22762. Hypersensitivity reactions were lower in the SC arm than in the IV arm (8.78 (7.05, 10.81) versus 14.82 (12.30, 17.71) events per 100 PY). There were 10 events in the IV SC arm and 1 in the SC IV arm (3.91 (1.88, 7.19) versus 1.51 (0.04, 8.42) events per 100 PY). Most of the hypersensitivity reactions were not considered clinically significant (did not result in withdrawal from the study drug). Rates for clinically significant hypersensitivity events were comparable in the SC and IV arms (1.18 (0.61, 2.07 versus 1.47 (0.76, 2.57) events per 100 PY). No clinically significant hypersensitivity events were reported for either switch arm. Seven hypersensitivity events were reported as an SAE: 5 in the SC arm and 2 in the IV arm (0.49 (95% CI 0.16, 1.15) versus 0.24 (0.03, 0.88) events per 100 PY). Ten additional potential hypersensitivity events (5 each in the SC an IV arms) occurred more than 24 hours after study drug administration.

In Study NA25220 no anaphylactic events were identified and only 1 clinically significant hypersensitivity reaction was reported (TCZ PFS arm). Overall, 36 hypersensitivity reactions were reported and while numerically higher in the TCZ PFS arm, rates were generally similar across the treatment arms with wide and overlapping 95% CIs. Five escape patients (2 (2.0%) in the prior TCZ arm and 3 (3.3%) in the prior placebo arm) had at least 1 hypersensitivity event during the study.

8.7.7.2. *Other studies*

No anaphylactic reaction events were reported in the 84-week open-label period of Study MRA229JP during which all patients received SC TCZ. One severe anaphylactic reaction was reported following the second IV TCZ infusion in the DB phase of the study.

No anaphylaxis or serious and/or clinically significant hypersensitivity events were reported in Study ML28338. Six potential hypersensitivity events were reported (2.39 (95% CI 0.88, 5.20) per 100 PY).

8.7.8. **Hepatic events**

8.7.8.1. *Pivotal studies*

In Study WA22762 two patients had 3 serious hepatic adverse events, both in the IV arm. These events were hepatic encephalopathy (two events occured in same patient) and hepatic steatosis in another patient. All serious hepatic AEs were Grade 3 and considered by the investigator as being not related to study treatment.

In Study NA25220 hepatic events of special interest were defined as a combination of the hepatic failure, fibrosis and cirrhosis SMQ wide and hepatitis, non-infectious SMQ Wide. No serious hepatic events were reported during the study. Non-serious events were reported for 6 patients (1.4%) in the TCZ PFS arm (hepatic steatosis (3 patients) and biliary dyskinesia, cholelithiasis, and hepatic cyst (1 patient each)), 4 patients (2.4%) in the TCZ PFS to AI switch arm (cholelithiasis, hepatitis, hypertransaminasaemia and hyperbilirubinemia), 1 patient (1.6%) in the placebo to TCZ PFS switch arm (hypertransaminasaemia), and 3 patients (5.1%) in the placebo to TCZ AI switch arm (hypertransaminasaemia, hyperbilirubinaemia, and biliary colic). One escape patient in the prior placebo arm developed acute cholecystitis.

8.7.8.2. *Other studies*

There was no discussion of hepatic events in Study MRA229JP.

No serious and/or medically significant hepatic events were reported from Study ML28338.

8.7.9. **Stroke**

8.7.9.1. *Pivotal studies*

Four patients in the SC group of Study WA22762 and 10 patients in the IV group experienced a serious stroke AE. Of these, 4 occurred during the 24 week DB period (in the IV arm), 2 occurred before a clinical cut-off date of 16 January 2012 (interim OLE phase) (in the SC arm) and the remaining 8 occurred during the remainder of the OLE period. Two were considered related to study treatment (1 CTC Grade 3 haemorrhagic stroke and 1 CTC Grade 4 ischemic stroke). No serious stroke AEs were reported in the IV SC or SC IV switch arms.

In Study NA25220 no stroke events were reported in any of the 4 re-randomised treatment arms or in escape patients. One patient in the TCZ PFS arm experienced a Grade 4 transient ischemic attack but recovered with treatment; the event was considered unrelated to study treatment.

8.7.9.2. *Other studies*

Stroke events were not discussed in Study MRA229JP.

In Study ML28338 five events in 4 patients were reported (1.99 (95% CI 0.65, 4.64) per 100 PY).

8.7.10. Myocardial Infarction

8.7.10.1. *Pivotal studies*

Two patients in the SC arm of Study WA22762 and 1 patient in the IV SC switch arm experienced serious myocardial infarction (MI) AEs. One event occurred during the DB period and 2 during the OL period. All serious MI AEs were considered by the investigators as being not related to study treatment.

In Study NA25220 one patient each in the TCZ PFS, TCZ PFS to AI switch, and placebo to TCZ PFS arms and 2 escape patients had a serious MI event. Only one event was considered by the investigator to be related to study drug (placebo to TCZ PFS switch treatment arm).

8.7.10.2. *Other studies*

In Study MRA229JP MI AEs were not discussed.

Study ML28338 saw no MI and/or acute coronary syndrome events reported.

8.8. Laboratory tests

8.8.1. Liver function

8.8.1.1. *Pivotal studies*

In Study WA22762 marked shifts (that is from normal at baseline to > 3 to 5 times ULN or >5 times ULN or from raised ULN but < 3 x normal at baseline to > 5 x ULN) were experienced by a similar proportion of patients for both ALT ((7.3% SC versus 6.2% IV) versus (9.1% IV SC versus 10.4% SC IV)) and AST ((1.7% SC versus 1.3% IV) versus (2.1% IV SC versus 0.0% SC IV)).

The incidence of marked shifts in ALT and AST in Study NA25220 (that is, from normal at baseline to either between 3 times to 5 times normal ULN or above 5 times normal ULN and from raised ULN below 3 times normal ULN at baseline to more than 5 times normal ULN) was low in all treatment arms. Most of the ALT and AST elevations represented single or non-consecutive occurrences. None of the elevations in transaminases were associated with simultaneous elevations in total bilirubin of > 2 ULN.

8.8.2. Kidney function

None of the studies discussed renal function.

8.8.3. Haematology

8.8.3.1. *Pivotal studies*

Amongst patients in Study WA22762, newly occurring Grade 3 or 4 neutropaenia was experienced by a similar proportion in both the SC and IV arms (6.0% versus 6.7%), and by 3 (1.6%) in the IV to SC switch arm. There were no occurrences in the SC to IV switch arm. No patient with Grade 3 or 4 neutropenia experienced a serious infection in the SC or IV arm, and 1 patient in the IV to SC switch arm had a serious infection of laryngitis.

Newly occurring Grade 2, 3 or 4 thrombocytopaenia was rare, occurring in ≤ 0.5% of patients in the SC or IV treatment groups, with no occurrences in the IV to SC or SC to IV switch groups. Thrombocytopenia was not associated with any serious bleeding events.

In Study NA25220 newly occurring Grade 3 or 4 neutropaenia was reported by a small proportion of patients in each of the treatment arms: 8 patients (4.7%) in the TCZ PFS arm, 9 patients (5.4%) with TCZ PFS then AI switch arm, 2 patients (3.3%) in placebo then TCZ PFS switch arm, and 5 patients (8.5%) in the placebo then TCZ AI arm). Most occurred at single or non-consecutive visits. None of the patients with neutropenia developed a serious infection.

Newly occurring Grade 2 or 3 thrombocytopaenia was uncommon occurring in 1 patient (0.6%) in the TCZ PFS treatment group and 2 patients (1.2%) in the TCZ PFS then AI switch treatment group. There were no occurrences in the prior placebo groups. Thrombocytopenia was not associated with any serious bleeding events.

8.8.4. Lipids

8.8.4.1. *Pivotal studies*

In Study WA22762 an increase in total cholesterol from < 200 mg/dL at baseline to ≥ 200 mg/dL at the last observation was more common in the switch arms (IV to SC (27.4%) and SC to IV (34.9%)) than in the continuous treatment arms (SC 26.1% and IV 21.0%). The SC to IV result should be interpreted with caution as it is based on 48 patients. Decreases in HDL from ≥ 40 mg/dL at baseline to < 40 mg/dL at the last observation was reported in a similar proportion of SC (3.2%) and IV (3.9%) patients.

Newly occurring post baseline shifts in Study NA25220 from ≤ 200 mg/dL to worsened values ≥ 240 mg/dL were observed for 10.0%, 6.0%, 1.7%, and 8.5% of patients respectively in the TCZ PFS, TCZ PFS to AI, placebo to TCZ PFS, and placebo to TCZ AI switch arms. Decreases in HDL from ≥40 mg/dL at baseline to < 40 mg/dL at the last observation was reported for 1.8%, 2.4%, 3.3%, and 5.1% of patients in the TCZ PFS, TCZ PFS to AI, placebo to TCZ PFS, and placebo to TCZ AI switch arms respectively.

8.9. Other reports

8.9.1. Drug Safety Report: Characterisation of anaphylaxis events in tocilizumab patients

The Roche safety database ARISg[4] was searched for all cases within the anaphylactic reaction SMQ[5,6] using the preferred term (PT) 'hypersensitivity' with a cut-off date of 10 April 2013.[7] Preclinical data, company sponsored clinical trials and published literature were also searched. All cases identified from the ARISg search were medically reviewed internally by the Marketing Authorisation Holder (MAH) and were also medically reviewed by an external panel of clinical experts (adjudicators) in anaphylaxis.

8.9.2. Preclinical / Toxicological evidence

No evidence was found for a major risk of cytokine release syndrome (which has similar clinical manifestations to anaphylaxis) in nonclinical animal models (that is, in monkeys) after repeated subcutaneous and intravenous injections of tocilizumab for a period of 6 months or in vitro models using human whole blood cells.

8.9.3. Company clinical (trial) database results

TCZ subcutaneous formulation: No cases of anaphylaxis have been reported in the ongoing clinical trial program to date.

TCZ intravenous formulation: Anaphylactic reactions reported from sponsor studies are summarised in Table 12 (below). The overall incidence was 0.298%, with the lowest incidence in the adult RA studies (0.198%). The high rate in the AS studies (1.408%) was the result of a

[4] ARISg; Adverse Reaction Information System Global
[5] SMQ; Standardised MedDRA Query
[6] MedDRA; Medical Dictionary for Regulatory Activities
[7] An algorithmic search is a combination of search terms from various sub-categories of the broad search terms to further refine the identification of cases of interest. Algorithmic search methodology yields greater sensitivity compared to the narrow search and greater specificity compared to the broad search.

cluster of 5 cases reported from Bulgaria. All cases in all indications fully resolved with treatment.

Table 12 Incidence Proportion of Anaphylactic Reactions Associated with TCZ following IV Infusion in Company Clinical Trial Database

	No. of Patients	No. of Anaphylaxis cases	Incidence Proportion*
Adult IV Rheumatoid Arthritis Programme	5,042	10	0.198%
Ankylosing Spondylitis Programme	355	5	1.408%
Juvenile Idiopathic Arthritis IV Programme	300	2	0.667%
Overall	5,697	17	0.298%

* Incidence proportion is calculated by dividing number of anaphylaxis case by the total number of patients in clinical trials

8.9.4. Company safety database (ARISg)

ARISg[8] contains all SAEs, all AEs of special interest (including non serious events) from clinical trials of TCZ (irrespective of reporter causality assessment, therefore includes the cases reported in the previous section of this document) and all spontaneous reports of AEs from countries where TCZ is marketed.

8.9.4.1. *All cases*

In total 732 cases were identified of which 122 cases were assessed by the external adjudicators as 'anaphylaxis to (Tocilizumab) TCZ' cases, using Sampson's criteria[9] based on the reported information within the case. The remaining 610 cases were adjudicated as either not anaphylaxis or unevaluable. With an estimated cumulative patient exposure to TCZ between April 2005 and April 2013 of 234,146 patients, the un-adjudicated anaphylaxis incidence proportion is 0.31% (732/234,146) and the externally adjudicated incidence proportion is 0.052% (122 cases out of 234,146 estimated cumulative exposure patients).

A total of 1215 AEs were reported for these 732 cases of which 679 AEs (55.9%) in 528 individuals (72.1%) were serious. The most frequent PTs reported were hypersensitivity (n = 274) followed by anaphylactic reaction (n = 152) dyspnoea (n = 111) rash (n = 70), and pruritus (n = 62).

Of the 732 cases, 378 were study cases (329 medically confirmed) and 354 were spontaneous cases (300 medically confirmed). The most common indications for TCZ use were RA (77.5%) juvenile arthritis (7.1%) and ankylosing spondylitis (1.5%). The highest number of cases was reported from the USA (n = 144 cases) followed by Japan (n = 77 cases) Brazil (n = 74 cases) Canada (n = 59 cases) and Germany (n = 52 cases). The majority of cases were reported in adults (n = 450) followed by elderly patients (n = 123 cases), children (n = 26 cases), adolescents (n = 10 cases) and infants (n = 3 cases). The age was unknown in 120 cases.

[8] ARISg Adverse Reaction Information System Global. 'ARISg is the world's leading pharmacovigilance and clinical safety system, with more than 300 companies maintaining their critical drug safety data in ARISg worldwide'.

[9] Sampson's criteria for anaphylaxis: Clinical criteria for the diagnosis of anaphylaxis. Second symposium on the definition and management of anaphylaxis: Summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Sampson A et al. Journal of Allergy and Clinical Immunology, Volume 117 , Issue 2, 391-397.

These cases have been reported (see Table 13 below) in the PSURs as follows:

Table 13: Comparison of incidence proportions for anaphylaxis events from the safety database per PSUR period.

	Qualifying Patients				Incidence Proportions		
PSUR #	Number of Anaphylaxis cases (N) in SMQ Narrow (N=72)	Number of Anaphylaxis cases (N) in Externally Adjudicated 'Anaphylaxis-to-TCZ' (N=122)	Number of Anaphylaxis cases (N) in All cases within Algorithmic SMQ + PT Hypersensitivity (N=732)	Patients	SMQ Narrow (N=72)	Externally Adjudicated 'Anaphylaxis-to-TCZ' (N=122)	All cases within Algorithmic SMQ + PT Hypersensitivity (N=732)
1	13	15	43	10,022	1.30%	1.50%	4.29%
2	3	3	27	10,960	0.27%	0.27%	2.46%
3	3	5	27	19,422	0.15%	0.26%	1.39%
4 *	12	20	81	24,852	0.48%	0.80%	3.26%
5	12	21	87	30,086	0.40%	0.70%	2.89%
6	7	11	67	35,790	0.20%	0.31%	1.87%
7	3	6	105	40,689	0.07%	0.15%	2.58%
8	5	13	140	46,521	0.11%	0.28%	3.01%
9 **	14	28	155	15,804	0.89%	1.77%	9.81%
Grand Total	72	122	732	234,146	0.031%	0.052%	0.31%

* DHCPL issued during PSUR-04 (08/2010)

** TCZ exposure calculations changed between PSUR 8 to 9, which led to apparent decrease in exposure during PSUR 9, even though overall exposure is increasing with each consecutive PSUR period

8.9.4.2. *Adjudicated anaphylaxis cases*

For the 122 adjudicated anaphylaxis cases there were 241 events reported of which 196 AEs (81.3%) in 116 individuals (95.1%) were serious. The most frequent PTs reported were anaphylactic reaction (n = 42), anaphylactic shock (n = 26), hypersensitivity (n = 24), dyspnoea (n = 19), and hypotension (n = 16).

Of the 122 cases, 51 were study cases (48 medically confirmed) and 71 were spontaneous cases (65 medically confirmed). The highest number of cases was reported from the USA (n = 29 cases) followed by Japan (n = 17 cases), Australia (n = 8), Brazil and Germany (n = 7 cases each), and Canada and Poland (n = 5 cases each). The majority of cases were reported in adults (n = 87) followed by elderly patients (n = 19 cases), children (n = 7 cases), and adolescents (n = 2 cases). The age was unknown in 7 cases. Anaphylaxis events occurred most commonly on the 2nd (36.9%) or 3rd (18.0%) infusion, but 1 case followed the 20th infusion (0.8%). Infusion number information was not reported for 22.1% of events. Of anaphylaxis events where the infusion number was known (n = 95), 57% (n = 54), 80% (n = 76), and 91% (n = 86) occurred by infusion number 2, 3 and 5 respectively (see Table 14 below). The majority of events occurred during the infusion (55.7%) or within 24 hours of the infusion (33.6%). Fatal anaphylaxis has been reported 4 times (3 medically confirmed).

Table 14: Anaphylaxis event by infusion number (n = 122 cases).

Infusion number	Number of events	% Including NR	% Excluding NR
1	9	7.4%	9.5%
2	45	36.9%	47.4%
3	22	18.0%	23.2%
4	8	6.6%	8.4%
5	2	1.6%	2.1%
6	2	1.6%	2.1%
7	2	1.6%	2.1%
9	1	0.8%	1.1%
10	1	0.8%	1.1%
13	1	0.8%	1.1%
15	1	0.8%	1.1%
20	1	0.8%	1.1%
Not reported (NR) if events were associated with infusion	27	22.1%	--
Grand Total	122	100.0%	100.0%

Evaluator's comment: While the majority of anaphylaxis events occur with the first 4 to 5 infusions, similar data has not been reported for other hypersensitivity reactions. The sponsor will be asked to provide these data for the SC and comparator arms (for all hypersensitivity, clinically significant hypersensitivity, and serious hypersensitivity events) for studies WA22762 and NA25220. Based on the sponsor's application letter, there has only been one case of adjudicated anaphylaxis to SC TCZ up to 10 October 2014. It was not clear from the Drug Safety Report (with a data cut-off of 10 April 2013) whether this case forms one of the 122 adjudicated cases, or arose after the cut-off date. The sponsor will be asked to clarify this and also to provide details regarding how many of the 732 potential anaphylaxis cases and 122 adjudicated anaphylaxis cases were on SC TCZ.

8.9.4.3. *Sponsor produced addendum to summary of clinical safety*

The sponsor produced an addendum to the original Summary of Clinical Safety, which contained analyses not presented. In particular, they analysed clinical and post-marketing safety data on hypersensitivity reactions and anaphylaxis events in RA patients treated with the SC and IV formulations of TCZ. The methodology for searching ARISg was the same as reported in the Drug Safety Report reported above but the data cut-off date was 10 October 2014. Hypersensitivity and anaphylaxis events in patients exposed to IV and SC TCZ are presented in Table 15 and Table 16 below:

Table 15: Global Safety Database, global reporting proportions and rates of hypersensitivity in patients exposed to IV and SC tocilizumab (cut-off 10 October 2014)

	IV [a] (N=403,018)	SC [b] (N=20,920)
Postmarketing exposure (PYs)	343,512	17,380
Hypersensitivity SMQ (Narrow)		
No. cases	2749	305
Reporting proportion (per 100 patients)	0.7	1.5
Reporting rate [95% CI] (per 100 PY)	0.8 [0.77, 0.83]	1.8 [1.56, 1.96]
PT hypersensitivity (serious events)		
No. cases	148	11
Reporting proportion (per 100 patients)	0.04	0.05
Reporting rate [95% CI] (per 100 PY)	0.04 [0.04, 0.05]	0.06 [0.03, 0.11]

PT = preferred term. Cases for which the route of administration of TCZ was unknown or not IV or SC were excluded from the analysis. [a]Includes patients who received only IV or whose most recent administration of TCZ was IV. [b]Includes patients who received only SC or whose most recent administration of TCZ was SC.

Using the Hypersensitivity SMQ (Narrow) search strategy, 305 cases were reported in patients receiving SC TCZ (proportion 1.5 per 100 patients; 1.8 (95% CI: 1.56, 1.96) cases per 100 PY), and 2,749 in patients receiving IV TCZ (proportion 0.7 per 100 patients; 0.8 (95% CI: 0.77, 0.83) cases per 100 PY). Using the more restricted and specific PT Hypersensitivity (serious cases only) search strategy, 11 cases were reported in patients receiving SC TCZ (proportion 0.05 per 100 patients; 0.06 (95% CI: 0.03, 0.11) cases per 100 PY), and 148 in patients receiving IV TCZ (proportion 0.04 per 100 patients; 0.04 (95% CI: 0.04, 0.05) cases per 100 PY).

Table 16: Global Safety Database, global reporting proportions and rates of anaphylaxis in patients exposed to IV and SC tocilizumab (cut-off 10 October 2014)

	TCZ IV [a] (N=403,018)	TCZ SC [b] (N=20,920)
PYs exposure	343,512	17,380
Anaphylactic Reaction SMQ (Algorithmic)		
No. cases	701	23
Reporting proportion per 100 patients	0.17	0.11
Reporting rate [95% CI] per 100 PY	0.20 [0.19, 0.22]	0.13 [0.08, 0.20]

PT = preferred term. Cases for which the route of administration of TCZ was unknown or not IV or SC were excluded from the analysis. [a]Includes patients who received only IV or whose most recent administration of TCZ was IV. [b]Includes patients who received only SC or whose most recent administration of TCZ was SC.

In total, 23 anaphylactic reactions were reported in patients receiving SC TCZ (proportion 0.11 per 100 patients; 0.13 (95% CI: 0.08, 0.20) cases per 100 PY), and 701 in patients receiving IV TCZ (proportion 0.17 per 100 patients; 0.20 (95% CI: 0.19, 0.22) cases per 100 PY).

8.9.5. Literature review

Epidemiology data on the rates of anaphylaxis in the general population and in patients with RA treated with biologic therapy are limited. The sponsor identified a small number of publications which estimated a population-based lifetime prevalence of anaphylaxis to range from 0.05% to 2.0% and the average annual incidence rate of anaphylaxis to range from 210 to 498 per 1,000,000 PY in the USA, with the annual incidence rate increasing over time (from 469 per 1,000,000 PY in 1990 to 589 per 1,000,000 PY in 2000). The data on deaths due to anaphylaxis are even more limited, with an estimate of 4.8 deaths per 1,000,000 PY, of which approximately one quarter are thought to be drug-induced. These estimates varied with the source of the data (higher in the USA), definition of anaphylaxis used, collection methodologies, and time period analysed. The literature was also searched for serious infusion reactions or anaphylaxis / anaphylactoid reactions following treatment with biological therapies. Two reports of anaphylaxis during clinical studies on abatacept were found (1 from SC and 1 from IV route of administration), and 7 reports of infusion reactions on infliximab. A further 24 serious infusion reactions occurring during or within 2 hours after infliximab infusion completion were identified in a post-marketing study.

8.9.6. Research Report: Rates for anaphylaxis for patients with rheumatoid arthritistreated with tocilizumab or other biologics: an analysis based on health claims data (Report 1063062, December 2014)

Due of limited epidemiology data on the rates of anaphylaxis in patients with RA treated with biologic therapy, the sponsor conducted a retrospective cohort study of anaphylaxis in multiple cohorts of RA patients treated with commonly used biologics, including adalimumab, etanercept, golimumab, certolizumab pegol (SC formulation), infliximab, TCZ (IV formulation only as SC formulation not approved at the time the study was conducted) and abatacept (both IV and SC formulation).

The data source for the study was the Truven Healthcare MarketScan Commercial Claims and Encounters (Commercial) and the Medicare Supplemental and COB (Medicare) Database (from January 2000 to September 2013) which contains information on the Medicare population with supplemental insurance paid for by employers.

Anaphylaxis and fatal anaphylaxis within 7 days of drug administration (where able to be ascertained) were the primary endpoints. Anaphylaxis within 14 and 30 days of drug administration were used as sensitivity analyses.

Two definitions of anaphylaxis were used:

1. Algorithmic definition based on the Mini-Sentinel initiative. This is the more specific definition which was used for the primary analysis.
2. Algorithmic definition of anaphylaxis of hospitalised and non-hospitalised events based on the Sampson criteria. In order to qualify as anaphylaxis more than one ICD9 code required. This is the more sensitive definition which was used for the secondary analysis.

Fatal anaphylaxis cases were based on the in-hospital death variable. This would have underestimated fatalities as according to the US Centres for Disease Control, only 30% of all deaths occur in a hospital setting.

8.9.6.1. *Results*

The largest cohorts (patient numbers) were for Enbrel SC (32,382), Humira SC (29,942), and Remicade IV (16,790) and the smallest for Orencia SC (2,004), Actemra IV (2,605), and Cimzia SC (3,054). The majority of patients were female (74-82%), with a mean age of 49 to 54 years. Up to 1.6% (using Sampson criteria) had a previous history of anaphylaxis (<0.15% if using mini-sentinel criteria).

Incidence rates of anaphylaxis within 7-days of the infusion for the three IV drugs are presented in Table 17, below. Overall incidence rates were higher using the sensitive definition (0.11) than the specific definition (0.04) and were generally consistent for each individual drug based on overlapping CIs. Anaphylaxis rates within 14 or 30 days changed little for the specific definition, but increased 2 to 5-fold with the sensitive definition. Rates remained consistent between drugs.

Table 17: Incidence rates (per 100 PY) of anaphylaxis events occurring within 7 days and at any time following infusion in adult RA patients treated with IV biologics.

			Anaphylaxis Definition			
			≤ 7 days		Any Time	
	N	Approximate PYs	Mini-sentinel Specific Definition n, IR (95% CI)	Sampson Criteria[a] Sensitive Definition n, IR (95% CI)	Mini-sentinel Specific Definition n, IR (95% CI)	Sampson Criteria[a] Sensitive Definition n, IR (95% CI)
Tocilizumab IV	2,603	1,750	1 0.06 (0.001, 0.32)	2 0.12 (0.01, 0.42)	1 0.06 (0.001, 0.32)	13 0.75 (0.40, 1.28)
Infliximab IV	16,786	11,836	6 0.05 (0.019, 0.11)	15 0.13 (0.07, 0.21)	9 0.08 (0.035, 0.14)	54 0.56 (0.35, 0.60)
Abatacept IV	7,629	6,559	1 0.02 (0.0004, 0.08)	6 0.09 (0.03, 0.20)	2 0.03 (0.004, 0.11)	35 0.54 (0.38, 0.75)
All patients	27,018	20,156	8 0.04 (0.017, 0.078)	23 0.11 (0.073, 0.17)	12 Not reported	102 Not reported

[a]Based on hospitalised and non-hospitalised events.

For drugs administered via the subcutaneous route, exact timing of administration was not always ascertainable; therefore incidence rates of anaphylaxis occurring at any time following drug prescription are presented in Table 18 below. Consistent with the IV results, event numbers and rates were higher with the sensitive definition compared with the specific definition. Rates were generally comparable across the individual drugs although the point estimates were higher for certolizumab (0.93) and abatacept (0.58) for the sensitive definition. Rates of anaphylaxis were also comparable across the SC and IV formulations when the "Any Time" time frame was used (final 2 columns of Table 17 above).

Table 18: Incidence rates (per 100 PY) of anaphylaxis events occurring at any time following treatment with SC biologics in adult RA patients

			Anaphylaxis Definition	
	N	Approximate PYs	Mini-sentinel Specific Definition n, IR (95% CI)	Sampson Criteria[a] Sensitive Definition n, IR (95% CI)
Abatacept SC	2,003	1,044	0 0 (0.0, 0.35)	6 0.58 (0.21, 1.27)
Adalimumab SC	29,937	32,810	8 0.02 (0.01, 0.05)	104 0.32 (0.26, 0.39)
Etanercept SC	32,375	39,180	8 0.02 (0.009, 0.04)	125 0.32 (0.27, 0.38)
Certolizumab SC	3,053	2,287	2 0.09 (0.011, 0.05)	21 0.93 (0.58, 1.42)
Golimumab SC	4,016	3,496	1 0.03 (0.001, 0.32)	14 0.40 (0.22, 0.68)

[a]Based on hospitalised and non-hospitalised events.

Overall there were few cases of fatal anaphylaxis within 7 days of the primary event (2 using the specific definition (1 each for IV TCZ and adalimumab SC), 28 using the sensitive definition) (see Table 19, below). Rates were comparable across drugs, time windows and definitions with all confidence intervals overlapping.

Table 19: Incidence rates (per 100 PY) of fatal anaphylaxis events occurring within 7 days of anaphylaxis event in adult RA patients.

			Anaphylaxis Definition	
			Mini-sentinel Specific Definition	Sampson Criteria* Sensitive Definition
	N	Approximate PYs	n, IR (95% CI)	n, IR (95% CI)
Tocilizumab IV	2,603	1,750	1 0.057 (0.001, 0.32)	1 0.057 (0.001, 0.32)
Infliximab IV	16,786	11,836	0 0 (0.0, 0.031)	3 0.026 (0.005, 0.075)
Abatacept IV	7,629	6,559	0 0 (0.0, 0.056)	7 0.11 (0.043, 0.22)
Abatacept SC	2,003	1,044	0 0 (0.0, 0.35)	1 0.097 (0.002, 0.54)
Adalimumab SC	29,937	32,810	1 0.003 (0.00008, 0.017)	4 0.012 (0.003, 0.031)
Etanercept SC	32,375	39,180	0 0 (0.0, 0.009)	10 0.026 (0.012, 0.047)
Certolizumab SC	3,053	2,287	0 0 (0.0, 0.16)	1 0.044 (0.001, 0.25)
Golimumab SC	4,016	3,496	0 0 (0.0, 0.11)	0 0 (0.0, 0.11)
All patients	98,759	99,004	2 0.0020 (0.00025, 0.0073)	28 0.028 (0.019, 0.041)

*Based on hospitalised and non-hospitalised events.

8.10. Post-marketing experience

Two Periodic Benefit-Risk Evaluation Reports (PBRERs) were submitted covering the periods 11 October 2013 to 10 April 2014, and 11 April 2014 to 10 October 2014. Since the international birth date (11 April 2005) to 10 October 2014 the estimated cumulative market exposure to tocilizumab is 399,041 patients (equivalent to 323,111 PYs) of which 382,166 patients (95.8%) received intravenous tocilizumab and 16,875 patients (estimated 13,664 PYs) received subcutaneous tocilizumab. A further 24,897 patients received TCZ while participating in clinical trials (34,065.1 PYs on IV TCZ and 3,715.7 PYs on SC TCZ).

During the combined periods, the following actions were taken:

- Stevens-Johnson syndrome (SJS) was identified as a new adverse drug reaction resulting in the update of the core data sheet (CDS), SPC, PIL, and Informed Consent Forms and other relevant clinical trial documents for a number of ongoing studies.
- A drug safety report (DSR) was prepared for autoimmune disorders, but the signal was refuted by the MAH following a thorough assessment.
- The SC formulation of tocilizumab was approved in the European Union for the treatment of moderate to severely active RA in adult patients who have had an inadequate response to one or more DMARDs.

Serious hypersensitivity reactions and anaphylaxis are considered events of interest for TCZ (Table 20, below). During the period of the PBRERs, no new notable findings related to these events were identified and the safety profile of SC TCZ was found to be comparable with the safety profile of IV TCZ (with the exception of injection site reactions which were more common with SC TCZ).

Table 20: Cumulative rates of serious hypersensitivity reactions (PBRER 11/4/14 to 10/10/14).

	Events per 100 PY (95% CI)	
	IV all exposure population (02 May 2012)	SC all exposure population (4MSU† Data Cut October 2012)
Rates of Serious Hypersensitivity‡	0.27 (0.20, 0.36)	0.37 (0.14, 0.81)
Rates of Anaphylaxis	0.05 (0.02, 0.10)	0 (0.00, 0.23)

†Four-Month Safety Update; ‡Serious hypersensitivity events were defined as all SAEs that occurred during or within 24 hours of a dose and which were not judged 'unrelated' to treatment by the investigator, regardless of whether or not they were consistent with hypersensitivity.

No other newly identified safety risks were identified, and post-marketing data were considered to be consistent with the safety profile observed in the clinical trial data. Of note, there was no data specifically related to home-based use of SC TCZ in these reports.

8.11. Safety of home-based therapy

The sponsor has provided long term safety data for patients receiving SC TCZ in clinical trials and post-marketing data in support of the safety of home-based therapy. However while the data does address the relative safety of subcutaneous administration of TCZ versus intravenous TCZ, for the majority of the data it was not reported whether SC administration occurred in a home setting or a healthcare setting. While the clinical trial protocols all allowed home administration after demonstrated competence in self-administration (or administration by a caregiver) at the clinical site, only the Japanese study (MRA229JP) reported AEs separately for patients before and after the start of self-injection. Similarly for the post-marketing data, safety of SC TCZ (versus IV TCZ) has been presented, but it is not reported separately for clinical site and home-based administration (the sponsor will be asked to provide this information). Therefore the decision regarding the safety of home-based therapy is being made on the basis of the relative safety of SC versus IV TCZ administration which has occurred primarily in the healthcare setting, not on demonstrated safety of SC TCZ in the home.

8.12. Risk management plan

In the Australian specific Risk Management Plan, the Important Identified Risks are:

- Serious infection
- Complications of diverticulitis (including GI perforation)
- Serious hypersensitivity reactions

The Important Potential Risks are:

- Neutropenia
- Thrombocytopenia
- Elevated hepatic transaminases
- Elevated bilirubin (essentially indirect)
- Immunogenicity
- Elevated lipids
- Malignancies
- Demyelinating disorders
- Viral reactivation

- CYP450 enzyme normalisation

Important Missing Information is:

- Increased mortality in the Japanese PMS compared to clinical study population
- Elderly
- Paediatric patients
- Effects during pregnancy
- Hepatic impairment
- Renal Impairment
- Combination with biologics
- Vaccinations

8.13. Evaluator's overall conclusions on clinical safety

- Injection site reactions with the TCZ PFS presentation occurred at a similar rate in both pivotal studies (26.1 (23.0, 29.4) versus 22.01 (17.68, 27.09) events per 100 PY for WA22762 and NA25220, respectively). These rates were comparable to the rate seen with IV administration of TCZ (33.6 (27.1, 41.3) events per 100 PY) in WA22762.
- Hypersensitivity reactions with the TCZ PFS presentation occurred at a similar rate in both pivotal studies (8.8 (7.1, 10.8) versus 5.69 (3.61, 8.54) events per 100 PY for WA22762 and NA25220, respectively), which was lower than the rate seen with IV administration (14.8 (12.3, 17.7)) in WA22762.
- Serious hypersensitivity reactions with the TCZ PFS presentation occurred at a similar rate in both pivotal studies (0.5 (0.2, 1.2) versus 0.00 (0.00, 0.91) events per 100 PY for WA22762 and NA25220, respectively), which was comparable to the rate seen with IV administration (0.2 (0.03, 0.9)) in WA22762.
- To date, only one (non-fatal) anaphylaxis event has been reported with SC TCZ administration. This needs to be put in the context of an estimated 13,664 PYs of post-authorisation exposure to SC TCZ, versus 309,447 PYs of post-authorisation exposure to IV TCZ with an estimated anaphylaxis rate of 0.05 (95% CI: 0.02, 0.10) events per 100 PY based on cumulative market exposure up till 10 October 2014. Based on the adult IV TCZ RA clinical trial program, the incidence proportion of anaphylactic reactions was 0.198%, while the overall adjudicated incidence proportion based on clinical trials in all indications and spontaneous reports was 0.052%.
- Based on a retrospective cohort study of anaphylaxis in multiple cohorts of RA patients treated with commonly used biologics, rates of anaphylaxis following IV administration were similar (overlapping 95% CIs) for TCZ, infliximab and abatacept. Only abatacept had both IV and SC formulations in the database, and anaphylaxis rates were comparable for both formulations.
- Of the 122 adjudicated anaphylaxis events following IV TCZ administration, 91% occurred in association with the first 5 infusions. It is not known whether this would also reflect the distribution of anaphylaxis events following SC administration.
- Development of antibodies is not a good predictor of hypersensitivity, anaphylaxis, or ISRs.
- When compared to the rates in the 24 week DB and interim OLE reports, the rate of AEs of hypersensitivity declined over the course of the pivotal studies.

- The AE profiles were comparable for the weekly and 2 weekly SC TCZ dosing regimens, and were consistent with the known safety profile of IV TCZ.
- Safety has not specifically been demonstrated for SC TCZ in the home-based setting.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of subcutaneous administration of tocilizumab in the proposed usage are:

- Comparable efficacy (non-inferiority) for subcutaneous tocilizumab 162 mg weekly and the approved intravenous dosing regimen (8 mg/kg IV 4 weekly) which is maintained for up to 2 years of follow up.
- Provides an alternative to intravenous dosing which may be preferable to patients with poor venous access.
- Potentially allows for the convenience of home administration in patients for whom this is considered appropriate by their health care professional.
- AE profile that is consistent with that known for the IV dosing regimen.

9.2. First round assessment of risks

The risks of subcutaneous administration of tocilizumab in the proposed usage are:

- Comparable rates of injection site reactions, hypersensitivity reactions and anaphylaxis for SC and IV administration of tocilizumab, however the data for SC use is based on fewer PYs of follow-up (13,664 PYs versus 309,447 PYs, respectively).
- Non-serious hypersensitivity reactions may not be recognized (or reported) by the patient resulting in ongoing use of tocilizumab rather than permanent discontinuation of treatment. A subsequent, more serious reaction could then occur.
- A serious hypersensitivity reaction or anaphylaxis following SC usage of tocilizumab could occur in the home environment. Patients (and/or carers or other household members) may not be adequately prepared to deal with such an event, so there is the potential for delay in appropriate treatment which may, in the worst case scenario, result in a fatality. Patient specific safety and training materials need to be developed to address this.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of subcutaneous administration of tocilizumab is unfavourable given the proposed usage, but would become favourable if the changes recommended in the 'First round recommendations regarding authorisation' are adopted.

While comparable rates of injection site reactions, hypersensitivity reactions and anaphylaxis have been demonstrated for SC and IV administration of tocilizumab, the data for SC use is based on fewer PYs of follow-up and safety for home-based use has not been specifically presented. While the rates of serious hypersensitivity reactions and anaphylaxis following SC TCZ are low, it cannot be assumed that the outcomes for these events would be the same in the clinical and home environment. In clinical sites, access to professional assistance, resuscitation equipment and emergency drugs are usually readily available. The same cannot be said for a patient's home environment and delay in accessing appropriate treatment may result in an increased incidence of serious or fatal events.

10. First round recommendation regarding authorisation

The evaluator recommends:

> *Approval of the registration of a subcutaneous formulation of tocilizumab for the existing adult rheumatoid arthritis indication subject to modification of the PI, CMI, and RMP.*

While there is a recognized potential for serious hypersensitivity reactions and anaphylaxis with the use of biologic agents, it is a rare event that can occur with any of the currently registered products. If an event occurs in the healthcare environment (the current situation with the IV formulation) appropriate treatment can be initiated immediately, ensuring the best chance for a full recovery. However registration of the subcutaneous formulation will provide the opportunity for home use with no healthcare professional supervision. Under these circumstances early signs of hypersensitivity may not be recognized resulting in treatment delays and an increased risk of adverse outcomes. Additionally non-serious hypersensitivity which, if recognized, would result in permanent discontinuation of treatment may not be appreciated by the patient resulting in continued use and an increased risk of a subsequent serious hypersensitivity reaction.

There are currently 5 biologic agents with subcutaneous formulations registered for use in adult patients with rheumatoid arthritis, four TNF inhibitors: etanercept, adalimumab, certolizumab, golimumab and one T-cell costimulation blocker: abatacept. Each of these products has allergic reactions or hypersensitivity mentioned in the precautions section of the PI, but only abatacept reports a fatal case of anaphylaxis. Within the limitations of the data available, the incidence of anaphylaxis appears similar for the currently registered biologic agents with subcutaneous formulations and tocilizumab. However there have been deaths due to suspected severe allergic reactions on tocilizumab and a more conservative approach to home administration is considered appropriate. The 'dosage and administration' section of the PI is therefore proposed to be modified such that the first 5 subcutaneous injections are administered under the supervision of a qualified healthcare professional. This suggestion is based on the assumption that the distribution of anaphylaxis events following SC administration would reflect the distribution following intravenous infusion, and data from the Company Safety Database which demonstrated that 91% of anaphylaxis events following tocilizumab infusion (where the infusion number was known) occurred by infusion number 5. This also reflects what occurred in the Phase III clinical trials of SC tocilizumab, where self-administration at home was allowed after 4-7 injections at the clinical site (including demonstrated competence in self-administration).

11. Clinical questions

11.1. Efficacy

1. The PP population was used for the longer-term analyses of efficacy (Week 49) for consistency with the Week 24 analyses reported in the Week 24 CSR, which were based on the PP population because WA22762 was a non-inferiority study. Please provide analyses for the efficacy variables presented in Table 10 of the CSR using the PP population to allow comparison with the Week 24 and 49 results.
2. It is noted that the ACR20/50/70 response rates at weeks 24, 48/49, and 96/97 were similar for patients receiving SC TCZ weekly in study WA22762 and SC TCZ 2-weekly in study NA25220. Although these studies were not designed to be directly compared, the patient populations in these studies were similar (moderate to severe RA with an inadequate response to DMARDS). The dosage selection for the pivotal studies was based on PD profiles, however in view of the similar efficacy responses for the two dosage

regimens, please comment on this finding and advise whether there are any planned or existing studies directly comparing clinical outcomes for the two SC dosing regimens.

3. In the pre-submission meeting dossier sent by the sponsor to the TGA in an email on 29 August 2014 and in the slide set attached to the revised TGA official meeting record sent in an email dated 6 November 2014, it was stated that the final CSR for study ML28338 would be provided for evaluation. In the Summary of Clinical Safety Addendum it was stated that the CSR "*is still in preparation*". If available, the sponsor is requested to provide this report for evaluation.

11.2. Safety

4. While the majority of anaphylaxis events occur with the first 4 to 5 infusions, similar data has not been reported for other hypersensitivity reactions. Please provide these data (for all hypersensitivity, clinically significant hypersensitivity, and serious hypersensitivity events) for studies WA22762 and NA25220.
5. Based on the application letter and submission data there has only been one case of adjudicated anaphylaxis to SC TCZ up to 10 October 2014. It is not clear from the Drug Safety Report (with a data cut-off of 10 April 2013) whether this case forms one of the 122 adjudicated cases, or arose after the cut-off date. Please clarify this, and provide details regarding how many of the 732 potential anaphylaxis cases and 122 adjudicated anaphylaxis cases were on SC TCZ.
6. While the clinical trial protocols all allowed home administration after demonstrated competence in self-administration (or administration by a caregiver) at the clinical site, AEs have only been reported separately for the Japanese study (MRA229JP) for patients before and after the start of self-injection. Please provide information for studies WA2262, NA25220 and ML28338 regarding the number of patients who administered SC TCZ at home, when this took place (after how many visits), and the amount of PYs of exposure to SC TCZ at home, self-injection at the clinical site, and healthcare practitioner injection at the clinical site. Please also provide information on the occurrence of hypersensitivity reactions and anaphylaxis for each of these exposure periods. Where possible, please also provide this information for the post-marketing data.

12. Second round evaluation of clinical data submitted in response to questions

12.1. Efficacy

12.1.1. **Question 1**

· *The PP population was used for the longer-term analyses of efficacy (Week 49) for consistency with the Week 24 analyses reported in the Week 24 CSR, which were based on the PP population because WA22762 was a non-inferiority study. Please provide analyses for the efficacy variables presented in Table 10 of the CSR using the PP population to allow comparison with the Week 24 and 49 results.*

12.1.1.1. ***Sponsor's response***

The sponsor provided the requested analyses on the PP population (see Table 21 below).

Table 21: WA22762 Overview of efficacy results up to Week 97 (PP Population)

	No. of Patients (%)			
	162 mg SC qw n= 473	8 mg/kg IV q4w n= 338	IV-SC n= 161	SC-IV n= 44
ACR20 response rate				
Week 24	355/470 (76%)	263/338 (78%)	130/161 (81%)	29/44 (66%)
Week 49	365/455 (80%)	254/322 (79%)	128/153 (84%)	31/42 (74%)
Week 97	348/412 (85%)	244/290 (84%)	126/142 (89%)	31/38 (82%)
ACR50 response rate				
Week 24	238/470 (51%)	176/338 (52%)	85/161 (53%)	22/44 (50%)
Week 49	259/455 (57%)	187/322 (58%)	89/153 (58%)	21/42 (50%)
Week 97	270/412 (66%)	182/290 (63%)	96/142 (68%)	22/38 (58%)
ACR70 response rate				
Week 24	128/470 (27%)	105/338 (31%)	45/161(28%)	7/44 (16%)
Week 49	158/455 (35%)	118/322 (37%)	56/153 (37%)	13/42 (31%)
Week 97	182/412 (44 %)	122/290 (42%)	64/142 (45%)	14/38 (37%)
Decrease in HAQ-DI ≥ 0.22				
Week 24	343/468 (73%)	249/337 (74%)	123/161 (76%)	30/43 (70%)
Week 49	344/452 (76%)	245/321 (76%)	124/152 (82%)	28/41 (68%)
Week 97	318/407 (78%)	231/290 (80%)	112/139 (81%)	26/37 (70%)
Decrease in HAQ-DI ≥0.30				
Week 24	307/468 (66%)	229/337 (68%)	107/161 (67%)	26/43 (61%)
Week 49	315/452 (70%)	227/321 (71%)	108/152 (71%)	27/41 (66%)
Week 97	293/407 (72%)	201/290 (69%)	98/139 (71%)	22/37 (60%)
DAS28-ESR remission (< 2.6)				
Week 24	181/469 (39%)	123/336 (37%)	61/160 (38%)	16/43 (37%)
Week 49	199/452 (44%))	142/320 (44%)	75/152 (49%)	15/42 (36%)
Week 97	221/407 (54%)	128/280 (46%)	76/140 (54%)	19/38 (50%)
Withdrawal due to lack of therapeutic response *				
	7/473 (1.5%)	11/338 (3.3%)	3/161 (2.3%)	1/44 (1.9%)

ACR = American College of Rheumatology; DAS28 = disease activity score 28; DMARD = disease-modifying anti-rheumatic drug; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire-Disability Index; ITT = intent to treat.

* Based on data collected during the open-label phases up to the end of the study.

12.1.1.2. ***Evaluator's comment***

Compared with the analyses on the ITT population (Table 21 above), the primary and secondary efficacy endpoint results for the PP population were very similar (most differences within 0%-2%) at Weeks 24, 49 and 97 for each of the treatment groups, with maintenance of efficacy for the duration of follow-up within each group. More variability was seen in the patients who switched from the SC to IV formulation, most likely due to the small patient numbers. This response is acceptable.

12.1.2. **Question 2**

- *It is noted that the ACR20/50/70 response rates at weeks 24, 48/49, and 96/97 were similar for patients receiving SC TCZ weekly in study WA22762 and SC TCZ 2-weekly in study NA25220. Although these studies were not designed to be directly compared, the patient populations in these studies were similar (moderate to severe RA with an inadequate response to DMARDS). The dosage selection for the pivotal studies was based on PD profiles, however in view of the similar efficacy responses for the two dosage regimens, please comment on this finding and advise whether there are any planned or existing studies directly comparing clinical outcomes for the two SC dosing regimens.*

  Sponsor's response: The sponsor stated that the "Pharmacodynamic (PD), efficacy, and safety results from placebo-controlled study periods of core studies to support the starting dose of TCZ SC QW were extensively discussed in the original submission (PM-2012-04162-1-3) and in the Sponsor's prior pre-ACPM response (dated 18 November 2013)." They further emphasised the design differences between study WA22762 and NA25520 that made comparison of the results inappropriate. In particular, patients in NA25520 who had an inadequate response to SC TCZ every 2 weeks were allowed to escape to SC TCZ weekly and were excluded from the efficacy analysis. This occurred for 72/438 patients (16.4%)

prior to Week 24, and for 26/338 patients (7.7%) who were re-randomised at Week 24 (these latter patients were excluded from the efficacy analysis from the point of escape). The sponsor stated that:

'As a result, the patients included in the efficacy analysis in the TCZ SC EVERY 2 WEEKS group in study NA25220 were enriched with 'good responders' to TCZ SC EVERY 2 WEEKS therapy and such the response rates on TCZ EVERY 2 WEEKS may have been over-estimated.'

Evaluator's comment: This response is acceptable. On reviewing the ACPM 295 Ratified resolution, it appears that weekly dosing was deemed appropriate. The evaluator is satisfied that study WA22762 demonstrated that TCZ 162 mg SC weekly is non-inferior to the currently approved TCZ 8 mg/kg IV given every 4 weeks, and as such TCZ 162 mg SC weekly is the appropriate starting dose. While study NA25220 did show that many patients respond to SC TCZ every 2 weeks, it has only been shown to be superior to placebo. The Sponsor states there are no existing or planned studies to compare the safety and efficacy of SC TCZ every 2 weeks with SC TCZ weekly.

7. In the pre-submission meeting dossier sent by Roche to the TGA in an email on 29 August 2014 and in the slide set attached to the revised TGA official meeting record sent in an email dated 6 November 2014, it was stated that the final CSR for study ML28338 would be provided for evaluation. In the Summary of Clinical Safety Addendum, it was stated that the CSR "*is still in preparation*". If available, the sponsor is requested to provide this report for evaluation.

   Sponsor's response: The Sponsor provided the finalised CSR for study ML28338 (report no. 1063256) for evaluation. Study ML28338 was a multicentre open-label, long-term extension (LTE) study to evaluate safety (primary objective) and efficacy of SC TCZ in patients with moderate to severe RA who completed studies WA22762 or NA25220 and met the study ML28338 entry criteria (U.S. patients only). Patients on SC TCZ continued either weekly or every 2 weeks treatment, while those patients from study WA22762 who were on IV TCZ 8 mg/kg, switched to SC TCZ weekly therapy.

   A summary of the findings are presented here:

   - In total, 217 patients were exposed to SC TCZ for a mean of 0.93 years (range 0.08-1.59).
   - Of the 217 treated patients, 44 received SC TCZ every 2 weeks and the remaining 173 received weekly SC TCZ. Mean exposure increased to 2.6 years (range 1.35-3.36) when participation in both the core and LTE studies was considered.
   - AEs were reported by 179 patients (82.5%), with an event rate of 379.66 (95% CI: 355.95, 404.54) per 100 PY. The most common AEs were: URTI (19.8%), sinusitis (11.1%), and nasopharyngitis (10.1%).
   - AEs were considered to be treatment-related in 49 patients with 98 TEAEs. The most common TEAEs were: URTI (n = 11, 5.1%), ALT increased (n = 6, 2.8%), neutropenia (n = 6, 2.8%), neutrophil count decreased (n = 5, 2.3%), thrombocytopenia (n = 4, 1.8%), AST increased (n = 3, 1.4%), and sinusitis (n = 3, 1.4%).
   - A total of 37 SAEs were reported in 23 patients (10.6%). The most frequently reported SAEs by SOC were infections and infestations (3.2%), and nervous system disorders (2.3%). Only 4 SAEs in 3 patients were considered treatment-related: endocarditis, staphylococcal bacteraemia, thrombocytopaenia, and diverticular perforation.
   - Discontinuation as a result of AEs occurred in 16 patients (7.4%): 14 patients (8.1%) in SC TCZ weekly and 2 patients (4.5%) in SC TCZ every 2 weeks. Only staphylococcal bacteraemia occurred in more than 1 patient (n=2).
   - No deaths occurred during the study.

- Six patients experienced 29 ISRs; none were serious or lead to withdrawal from the study.
- There were no cases of anaphylaxis or serious hypersensitivity reaction.
- Serious and/or medically significant infections occurred in 8 patients.
- Neutralizing anti-tocilizumab antibodies occurred in 1 patient (0.5%).

Efficacy based on a number of validated measures was generally maintained throughout the study, although based on a decreasing number of patients.

Evaluator's comment: This LTE study was conducted in the subset of U.S. patients who had completed the core WA22762 and NA25220 studies. It provided safety data for an additional mean duration of SC TCZ exposure of 1.16 years. The rate and type of AEs and SAEs was generally consistent with those reported in the core studies, and patients continued to derive benefit from SC TCZ based on numerous validated efficacy measures.

12.2. Safety

1. While the majority of anaphylaxis events occur with the first 4 to 5 infusions, similar data has not been reported for other hypersensitivity reactions. Please provide these data (for all hypersensitivity, clinically significant hypersensitivity, and serious hypersensitivity events) for studies WA22762 and NA25220.

   Sponsor's response: The Sponsor provided the requested analyses. The following definitions were pre-specified for the reporting of hypersensitivity events[10]:

   Hypersensitivity events: defined as all AEs except injection site reactions (ISRs) that occurred during or within 24 hours of an infusion or injection and which were not judged "unrelated" to treatment by the investigator, regardless of whether or not they were clinically consistent with hypersensitivity.

   - Clinically significant hypersensitivity events: hypersensitivity events (as defined above) that led to withdrawal from treatment.
   - Serious hypersensitivity events: hypersensitivity events (as defined above) that were reported as serious.
   - Serious clinically significant hypersensitivity events: hypersensitivity events (as defined above) that were reported as serious and led to withdrawal from treatment.
   - Anaphylactic reactions: identified according to the Anaphylactic Reaction Standardized MedDRA Query (SMQ) (narrow) and the Roche standard Adverse Event Group Term (AEGT) basket based on Sampson's Criteria.

   Study WA22762

   IV TCZ (includes IV TCZ every 4 weeks, IV PLC, & SC IV TCZ switch patients): up to Week 97 (24 infusions), 63 AEs met the criteria of hypersensitivity in the IV TCZ and SC to IV TCZ switch group. Twenty five (39.7%) occurred with the 1st infusion, and the majority (55.6%) occurred by infusion number 3. Seven of the 63 AEs (11.1%) were clinically significant, with 4 occurring following 1st infusion, and only 1 considered serious (Table 22, below).

[10] Due to the double-dummy design up to Week 24, at the timepoints that both IV and SC treatment were given, a conservative approach was applied and any event meeting the above definitions of hypersensitivity was always attributed to TCZ (IV or SC) rather than to PLC. However, since SC was administered more frequently than IV, some AEs were attributed to PLC SC treatment as they occurred at a time when only PLC SC was given. In contrast, no AEs were attributed to PLC IV, as PLC IV was always administered together with TCZ SC.

Table 22: WA22762: All hypersensitivity events by IV infusion / SC injection number up to week 97

Infusion / injection No.	All IV TCZ (N=679)				All SC TCZ (N=817)			
	All Hypersensitivity		Clinically Significant	Clin Sig & Serious	All Hypersensitivity		Clinically Significant	Clin Sig & Serious
	N	%	N	N	N	%	N	N
1	25	39.7	4	1	21	21.6	1	1
2	4	6.3	0	0	8	8.2	2	1
3	6	9.5	0	0	6	6.2	1	0
4	0	0.0	0	0	2	2.1	1	0
5	2	3.2	0	0	3	3.1	0	0
6	3	4.8	0	0	2	2.1	0	0
7	2	3.2	1	0	3	3.1	0	0
8	5	7.9	0	0	2	2.1	0	0
9	1	1.6	0	0	1	1.0	1	0
10	3	4.8	0	0	0	0.0	0	0
11	1	1.6	0	0	2	2.1	0	0
12 +	11	17.5	2	0	47	48.5	6	0
TOTAL	63	100.0	7	1	97	100.0	12	2

SC TCZ: In the SC TCZ and IV SC TCZ switch group, 97 AEs met the hypersensitivity criteria: 21 (21.6%) occurred with the 1st injection, and the majority (51.5%) occurred by the 11th injection. Twelve of the 97 AEs (12.4%) were clinically significant, with 5 occurring between the 1st and 4th injection and 3 (all in 1 patient) occurring with the 29th injection. Only 2 clinically significant reactions were considered serious. There were 3 additional 'hypersensitivity' SAEs (all reported as cellulitis) which did not result in study withdrawal.

SC PLC: The SC PLC group reported 52 hypersensitivity AEs: 13 (25.0%) occurred with the 2nd infusion, and the majority (61.5%) occurred by infusion number 4. Five of the 52 AEs (9.6%) were clinically significant (all non-serious), and occurred as single events at 3rd, 4th, 8th, 14th and 19th injections. There was 1 "hypersensitivity" SAE (cellulitis) which did not result in study withdrawal.

Study NA25220

SC TCZ: (includes TCZ every 2 weeks, PLC-TCZ every 2 weeks switch, & TCZ weekly escape patients): up to Week 96, 48 AEs met the hypersensitivity criteria: 10 (20.8%) occurred with the 1st injection, and the majority (56.3%) occurred by the 11th injection. Three of the 48 AEs (6.3%) were clinically significant, occurring at the 14th injection and 2 at the 17th; all were considered non-serious (see Table 23 below). There was 1 hypersensitivity SAE (Ludwig angina) which did not result in study withdrawal.

SC PLC: The SC PLC group reported 12 hypersensitivity AEs: 6 (50.0%) occurred with the 1st infusion, and the majority (83.3%) occurred by the 2nd infusion. There were no clinically significant or serious events.

Table 23: NA25220: All hypersensitivity events by SC injection number up to Week 96.

injection No.	All SC TCZ (N=647)				PLC q2w (N=218)			
	All Hypersensitivity		Clinically Significant	Clinically Significant & Serious	All Hypersensitivity		Clinically Significant	Clinically Significant & Serious
	N	%			N	%		
1	10	20.8	0	0	6	50.0	0	0
2	3	6.3	0	0	4	33.3	0	0
3	2	4.2	0	0	0	0.0	0	0
4	0	0.0	0	0	1	8.3	0	0
5	2	4.2	0	0	0	0.0	0	0
6	0	0.0	0	0	1	8.3	0	0
7	1	2.1	0	0	0	0.0	0	0
8	1	2.1	0	0	0	0.0	0	0
9	3	6.3	0	0	0	0.0	0	0
10	0	0.0	0	0	0	0.0	0	0
11	2	4.2	0	0	0	0.0	0	0
12 +	24	50.0	3	0	0	0.0	0	0
TOTAL	48	100.0	3	0	12	100.0	0	0

Evaluator's comment: These results are consistent with the adjudicated anaphylaxis data from the company safety database. Hypersensitivity events, particularly those that were clinically significant and/or serious, were uncommon and generally resolved without sequelae. They occurred most commonly in the first 1-3 injections / infusions but did also occur intermittently thereafter during the 96 / 97 weeks of follow-up. While 17.5% of hypersensitivity events following IV TCZ occurred after 12 or more infusions (≈12+ months of exposure at every 4 weeks), up to 50% of hypersensitivity events following SC TCZ occurred after 12 or more injections (≈6+ months of exposure at every 2 weeks). It is also acknowledged that the definition of hypersensitivity used in this analysis is a conservative one, and that many of the events were not clinically consistent with hypersensitivity reactions. The response is noted.

2. Based on the application letter and submission data there has only been one case of adjudicated anaphylaxis to SC TCZ up to 10 October 2014. It is not clear from the Drug Safety Report (with a data cut-off of 10 April 2013) whether this case forms one of the 122 adjudicated cases, or arose after the cut-off date. Please clarify this, and provide details regarding how many of the 732 potential anaphylaxis cases and 122 adjudicated anaphylaxis cases were on SC TCZ.

   Sponsor's response: The sponsor advised that:

   - The single case of adjudicated anaphylaxis to SC TCZ up to 10 October 2014 was received after the Drug Safety Report cut-off and does not therefore form part of the 122 adjudicated anaphylaxis cases in that report,
   - 28 of the 732 potential anaphylaxis cases were potentially on SC TCZ (2 cases on known SC TCZ, the remaining 26 were on blinded study medication and could therefore have been receiving either TCZ or PLC), and
   - None of the 122 adjudicated anaphylaxis cases were on SC TCZ.

   The sponsor also advised that no additional adjudicated anaphylaxis cases have been identified up to the end of February 2015. Monitoring is ongoing.

   Evaluator's comment: The response is noted.

3. While the clinical trial protocols all allowed home administration after demonstrated competence in self-administration (or administration by a caregiver) at the clinical site, AEs have only been reported separately for the Japanese study (MRA229JP) for patients before and after the start of self-injection. Please provide information for studies WA2262, NA25220 and ML28338 regarding the number of patients who administered SC TCZ at home, when this took place (after how many visits), and the amount of PYs of exposure to SC TCZ at home, self-injection at the clinical site, and healthcare practitioner injection at the clinical site. Please also provide information on the occurrence of hypersensitivity reactions and anaphylaxis for each of these exposure periods. Where possible, please also provide this information for the post-marketing data.

   Sponsor's response: The sponsor provided the requested analyses. In each of the 3 studies (see Table 24 below), the vast majority of patients (84.5-94.3%) administered at least 1 injection at home. The exception was PLC patients in Study NA25220 (51.4%). The mean number of homes injections per patient was 48, 25 and 37 in studies WA22762, NA25220, and ML28338, respectively. The timing of commencement of self-injection at home is not specifically available, however it was largely driven by the study protocol:

   - WA22762: the first 4 SC injections during both the DB and OL periods were required to be conducted at the clinic.

- NA25220: the first 6 or 4 SC injections were to be done at the clinic during both the DB and OL phases for patients on SC every 2 weeks or escape therapy SC weekly injections, respectively.
- ML28338: only those patients enrolling from WA22762 on IV treatment were to have their first 4 SC TCZ injections administered at the study site.

Overall, the majority of injections were administered at home (62.4%), and most of these were self-administered by the patient (78.2%) (See Table 25 below).

Table 24: Number of SC injections per patient at home or clinic.

WA22762	TCZ SC QW N=817		Placebo SC QW N=631	
	Clinic	Home	Clinic	Home
# of Pts with ≥1 injection	817 (100%)	771 (94.3%)	631 (100%)	581 (92.1%)
Mean # of Injections/Pt	23.2	48.3	9.2	12.5
Median	23.0	57.0	9.0	15.0
Min – Max # of Injections/Pt	1 - 96	0 - 87	1 - 24	0 - 18
NA25220	TCZ SC (QW and Q2W) N=647		Placebo SC Q2W N=218	
	Clinic	Home	Clinic	Home
# of Pts with ≥1 injection	647 (100%)	547 (84.5%)	218 (100%)	112 (51.4%)
Mean # of Injections/Pt	22.1	25.3	8.1	1.3
Median	20.0	24.0	8.0	1.0
Min – Max # of Injections/Pt	1 - 90	0 - 79	2 - 12	0 - 5
ML28338	TCZ SC (QW and Q2W) N=217			
	Clinic		Home	
# of Pts with ≥1 injection	204 (94%)		204 (94%)	
Mean # of Injections/Pt	11.3		36.6	
Median	9.0		37.5	
Min – Max # of Injections/Pt	1 - 72		1 - 74	

Table 25: Total number of injections at home versus clinic

# of Injections	WA22762 N=1262		NA25220 N=656		ML28338 N=217	Total
	DB	OL	DB	OL	OL	
At Home	15,769 (57.5%)	31,561 (70.7%)	1,118 (16.8%)	15,571 (59.6%)	7,458 (76.4%)	71,490 (62.4%)
At Clinic	11,659 (42.5%)	13,063 (29.3%)	5,551 (83.2%)	10,533 (40.4%)	2,303 (23.6%)	43,116 (37.6%)
Total	**27,423**	**44,648**	**6,670**	**26,104**	**9,761**	**114,606**

The PYs of exposure to SC TCZ at home and at the clinical site was provided for each of the studies, along with the corresponding incidence rates of hypersensitivity events (see Table 26 below). In studies WA22762 and ML28338, PYs of exposure to SC TCZ were higher in the home than in the clinic (749.69 versus 359.23, and 153.0 vs. 48.6, respectively). In study NA25220, exposure was similar at home (477.28 PYs) and in the clinic (469.55 PYs), because the protocol specified that the first 6 (SC every 2 weeks) or 4 (SC QW (escape therapy)) injections had to be administered at the clinic for both the DB and OL periods. The number and rate of hypersensitivity events associated with home injections was much lower than for clinic injections, which is consistent with the earlier finding (see response to Safety Question (i) above) that hypersensitivity events occur most frequently after the first 1–3 injections. Results varied with respect to clinically significant hypersensitivity and serious hypersensitivity events, but the number of events was small and, as previously presented, many of these events were

not clinically consistent with hypersensitivity reactions. There were no events that met the criteria for anaphylaxis.

Table 26: Incidence rates of hypersensitivity events following SC injections at home versus clinic.

WA22762	TCZ SC QW (N=631) Clinic	TCZ SC QW (N=631) Home	Placebo SC QW (N=631) Clinic	Placebo SC QW (N=631) Home
Total exposure (PY)	359.23	749.69	109.67	149.98
All Hypersensitivity				
# of AEs	66	31	33	19
Rate (per 100PY)	18.37	4.14	30.09	12.67
(95% CI)	(14.21, 23.37)	(2.81, 5.87)	(20.71, 42.26)	(7.63, 19.78)
Clinically Significant Hypersensitivity				
# of AEs	10	2	2	3
Rate	2.78	0.27	1.82	2.00
(95% CI)	(1.33, 5.12)	(0.03, 0.96)	(0.22, 6.59)	(0.41, 5.85)
Serious Hypersensitivity				
# of AEs	2	3	0	1
Rate (per 100PY)	0.56	0.40	0	0.67
(95% CI)	(0.07, 2.01)	(0.08, 1.17)	(0.00, 3.36)	(0.02, 3.71)
Serious Clinically Significant Hypersensitivity				
# of AEs	2	0	0	0
Rate (per 100PY)	0.56	0	0	0
(95% CI)	(0.07, 2.01)	(0.00, 0.49)	(0.00, 3.36)	(0.00, 2.46)
NA25220	**TCZ SC (QW and Q2W) N=647 Clinic**	**TCZ SC (QW and Q2W) N=647 Home**	**Placebo SC Q2W N=218 Clinic**	**Placebo SC Q2W N=218 Home**
Total exposure (PY)	469.55	477.28	66.67	11.06
All Hypersensitivity				
# of AEs	40	8	12	0
Rate (per 100PY)	8.52	1.68	18.00	0
(95% CI)	(6.09, 11.60)	(0.72, 3.30)	(9.30, 31.44)	(0.00, 33.34)
Clinically Significant Hypersensitivity				
# of AEs	1	2	0	0
Rate (per 100PY)	0.21	0.42	0	0
(95% CI)	(0.01, 1.19)	(0.05, 1.51)	(0.00, 5.53)	(0.00, 33.34)
Serious Hypersensitivity				
# of AEs	1	0	0	0
Rate (per 100PY)	0.21	0	0	0
(95% CI)	(0.01, 1.19)	(0.00, 0.77)	(0.00, 0.00,5.53)	(0.00, 33.34)

Evaluator's comment: The provided analyses have clarified the safety of SC TCZ in the home based setting with respect to hypersensitivity events. The majority of patients administered ≥ 1 injection at home (mean of 25 to 48 injections depending on the study), and overall PYs of exposure to SC TCZ (looking at the 3 studies together) was higher in the home than in the clinic. The number and rate of hypersensitivity events associated with home injections was much lower than for clinic injections. This is consistent with the earlier finding (see response to Safety Question (i) above) that hypersensitivity events occur most frequently after the first 1–3 injections, and the fact that the administration of the first 4-7 injections occurred in the clinic as specified by the study protocols. The results were less clear cut with respect to clinically significant hypersensitivity and serious hypersensitivity events, but the number of events was small and many of these events were not clinically consistent with hypersensitivity reactions. There were no events that met the criteria for anaphylaxis. While the potential for a serious hypersensitivity or anaphylactic reaction to occur after home-based administration remains, the evidence presented to date (> 70,000 home-based SC

injections in clinical studies, and an estimated cumulative 34,413 patients on SC TCZ in the post-authorisation phase) suggests that the risk is low and consistent with the risk for other biologic agents with subcutaneous formulations registered for use in adult patients with rheumatoid arthritis.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of subcutaneous administration of tocilizumab in the proposed usage are unchanged from those identified in the first round assessment of benefits.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of subcutaneous administration of tocilizumab in the proposed usage are essentially unchanged from those identified in the first round assessment of benefits.

Additional data on rates of injection site reactions and hypersensitivity reactions after home based administration were presented for studies WA22762, NA25220, and ML28338. Overall the majority of injections were administered at home (62.4%), and most of these were self-administered by the patient (78.2%). The number and rate of hypersensitivity events associated with home injections was much lower than for clinic injections, which is consistent with the facts that hypersensitivity events occur most frequently after the first 1-3 injections, and that per-protocol, administration of the first 4-7 injections occurred in the clinic. While the potential for a serious hypersensitivity or anaphylactic reaction to occur after home-based administration remains, the evidence presented to date (> 70,000 home-based SC injections in clinical studies, and an estimated cumulative 34,413 patients on SC TCZ in the post authorisation phase) suggests that the risk is low and consistent with the risk for other biologic agents with subcutaneous formulations registered for use in adult patients with rheumatoid arthritis.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of subcutaneous administration of tocilizumab is favourable given the proposed usage. The subcutaneous formulation of tocilizumab 162 mg weekly has demonstrated non-inferiority to the approved intravenous dosing regimen (8 mg/kg IV 4 weekly), and has a comparable safety profile. The risk of a serious hypersensitivity or anaphylactic reaction occurring in the home appears to be low, and is comparable to the risks associated with the subcutaneous formulations of other registered biologic agents.

14. Second round recommendation regarding authorisation

The evaluator recommends approval of the registration of a subcutaneous formulation of tocilizumab for the existing adult rheumatoid arthritis indication subject to modification of the PI, CMI, and RMP as described elsewhere in comments on the PI and CMI. The risk of serious hypersensitivity reactions and anaphylaxis in the home should be clearly communicated to both healthcare professionals and patients, and patients need to be educated regarding the symptoms and signs of allergic / hypersensitivity reactions to tocilizumab so that appropriate action can be taken promptly, thus minimising potential adverse outcomes.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au