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Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Plivensia

International non-proprietary name: sirukumab

Procedure No. EMEA/H/C/004165/0000

Note

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

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List of abbreviations

ACR American College of Rheumatology
ADR Adverse drug reaction
AE adverse event
ANCOVA analysis of covariance
ANOVA analysis of variance
anti-TNF-IR anti-tumor-necrosis-factor- agent-inadequate responder(s)
CCP cyclic citrullinated peptide
CDAI Clinical Disease Activity Index
CI confidence interval
CMH Cochran-Mantel-Haenszel (test)
CO Crossover
CQ chloroquine
CRP C-reactive protein
DAS28 Disease Activity Index Score 28
DBL database lock
DMARD disease modifying antirheumatic drugs
EE early escape
ESR erythrocyte sedimentation rate
ER exposure-response
EULAR European League Against Rheumatism
FACIT-fatigue Functional Assessment of Chronic Illness Therapy-fatigue
HAQ-DI Health Assessment Questionnaire-Disability Index
HCQ hydroxychloroquine
IL interleukin
ITT Intention to treat
JSN joint space narrowing
LDA Low Disease Activity
LE late escape
LOCF last observation carried forward
LoQ list of questions
LS means Least-squares means
LTE long-term extension
mAb monoclonal antibody
MCR Major Clinical Response
MCS Mental Component Score
MTX methotrexate
NSAIDs nonsteroidal anti-inflammatory drugs
PK pharmacokinetics
PTY patient-years
PD pharmacodynamics
q1w every week
q2w every 2 weeks
q4w every 4 weeks
PCS Physical Component Score
RA rheumatoid arthritis
RF rheumatoid factor
SC subcutaneous
SD standard deviation
SCS Summary of clinical safety
SDAI Simplified Disease Activity Index
SF-36 36-item short form health survey
SmPC Summary of product information
SSZ sulfasalazine
TF Treatment Failure
TNF tumor necrosis factor alpha
US United States
VAS visual analogue scale
vdH-S van der Heijde-modified Sharp (score)

1. Recommendation

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for Plivensa, a medicinal product in the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, ***or who were intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs***) is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. .

The major objection precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

As a consequence of the design of the main studies the comparison of incidence of major safety outcomes to placebo beyond 18 weeks exposure is likely confounded. This means that the long-term safety of sirukumab cannot be considered as well characterized. Due to this limitation, as illustrated by the observed potential imbalance in mortality rate between exposed and not exposed patients, it is crucial that a reassuring long-term safety profile is confirmed after a potential approval of a marketing authorization. This requires robust estimation of the risk for all relevant safety outcomes in comparison to a relevant active comparator. The Applicant should discuss different alternatives for a post marketing study program, eg. a randomized controlled study and/or observational study/ies. Any study proposal should be accompanied by a study synopsis for a relevant study design of sufficient detail to allow a feasibility assessment.

The discussion should include (but not necessarily be limited to) aspects such as:

- The adequate patient population

- Relevant study outcomes

- Suitable comparator(s) (eg other IL6 antibodies or anti-tnf alfa)

- Feasability of recruiting sufficient number of patients. This should include a discussion on the feasibility to enroll patients to an interventional study with safety as a primary aim in the context of the observed apparent imbalance in mortality.

- Time lines

Proposal for questions to be posed to additional experts

N/A

Inspection issues

The European Medicines Agency Compliance and Inspection Service has reviewed the manufacturer information contained in the application form (Module 1) and available from the EEA National Competent Authorities and determined that all relevant sites have valid manufacturing authorizations or valid GMP certificates as appropriate. Hence, no GMP inspections are deemed necessary at this stage within the scope of this MAA evaluation procedure.

New active substance status

Based on the review of the data the CHMP considers that the active substance sirukumab contained in the medicinal product Plivensia is to be qualified as a new active substance.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The indication for RA currently proposed by the applicant is as follows:

Plivensia in combination with methotrexate (MTX), is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to one or disease-modifying anti-rheumatic drugs (DMARDs) (see section 5.1). In these patients, Plivensia can be given as monotherapy when treatment with MTX is inappropriate for safety or tolerability reasons.

2.1.2. Epidemiology

RA prevalence in the adult population is estimated to be approximately 0.5-1% in developed populations (*Gabriel and Michaud, Arthritis Research & Therapy 2009*).

According to the data provided by the applicant, patients with RA have about a 50% increased risk of premature mortality and their life expectancy is decreased by 3 to 10 years compared with the US general population. A longitudinal cohort study performed in the UK found that, after adjusting for age and sex, patients with RA had an increased risk of mortality, with a mortality rate of 31.71 per 1000 person-years (Hazard Ratio [HR]: 1.56; 95% CI:1.51- 1.62) compared with 12.35 for controls. Increased mortality in patients with RA is largely due to premature cardiovascular disease.

2.1.3. Biologic features; aetiology and pathogenesis

The applicant has provided data supporting that IL-6 plays a major role in the pathophysiology of RA stating that this is confirmed by the efficacy of IL-6 and IL-6 receptor inhibitors in preclinical studies of experimental arthritis and clinical studies of patients with inflammatory arthritis. The effectiveness of the anti-IL-6 receptor mAb, tocilizumab, in reducing joint swelling and tenderness, improving physical function, and reducing the rate of radiographic progression was demonstrated in pivotal registration studies, leading to its approval. Unlike tocilizumab, sirukumab inhibits IL-6 by binding specifically to the cytokine IL-6 with high affinity.

2.1.4. Clinical presentation, diagnosis and prognosis

Rheumatoid arthritis is a chronic, systemic, autoimmune inflammatory disease in adults that leads to swelling and tenderness of the joints in the hands, feet, wrists, elbows, knees, and ankles. If the inflammation is left untreated, it results in significant joint damage culminating in disability and joint deformity.

The diagnosis is based on an assessment of swollen and/or tender joints, measurement of acute phase reactants (CRP, SR), serology (anti-CCP, RF-positivity) and radiographic evaluation of hands and feet.

2.1.5. Management

Control or reversal of the systemic inflammation in RA is the most important therapeutic goal. International treatment guidelines advocate a treat-to-target approach with the aim of achieving long-term remission or at least low disease activity, and an emphasis on regular, frequent assessment of

disease activity driving changes in therapy. Even patients who are considered to be in clinical remission can have subclinical synovitis and progress to structural damage of cartilage and bone. Prevention of structural damage remains a key objective for new disease-modifying treatments and reinforces the importance of disease control.

Traditional therapeutic approaches include nonsteroidal anti-inflammatory drugs NSAIDs, conventional non-biologic disease-modifying antirheumatic drugs (cDMARDs), and corticosteroids. Current European guidelines (*EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update*) recommend that the cDMARD MTX is part of the first line treatment strategy unless there are contraindications, in which case sulfasalazine or leflunomide should be considered as part of the (first) treatment strategy. If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another csDMARD strategy should be considered but when poor prognostic factors are present, addition of a biologic DMARD (bDMARD) should be considered. In patients responding insufficiently to MTX and/or other csDMARD strategies, bDMARDs should be commenced with MTX. If a first bDMARD has failed, patients should be treated with another bDMARD. Currently, approved biologic therapeutics for RA includes the following modes of action: TNFα inhibition, IL-6 receptor inhibition, IL-1 receptor inhibition, T-cell co-stimulation blockade, and B-cell depletion.

None of the approved drugs can achieve treatment target, i.e. remission or at least low disease activity, in all patients. In addition, many patients discontinue their DMARD or never become candidates for DMARDs because of safety reasons. Biologic and non-biologic DMARDs have a safety profile that includes the risk of serious infections and other consequences of immunosuppression such as a potential for malignancy. However, depending on the medical history and comorbidities, one biologic may be suited better to certain patients than others.

Overall, despite multiple treatment options being available for the treatment of adult patients with moderately or severely active RA, there still remains a considerable unmet need in this chronic disease that requires lifelong therapy. New therapies that provide efficacy in combination with an acceptable safety profile could be candidates for fulfilling this unmet need.

2.2. About the product

2.3. The development programme, compliance with CHMP guidance and scientific advice

A total of 14 interventional studies with sirukumab were completed or are ongoing.

Prior to the initiation of the Phase 3 program, scientific advice was obtained from European national competent authorities including the Medicines & Healthcare products Regulatory Agency (MHRA, United Kingdom), the Paul Ehrlich Institute (PEI, Germany), and the Medical Products Agency (MPA, Sweden), as well as from the Food and Drug Administration (FDA, United States). The target population and study endpoints were discussed. With respect to the analyses of progression of structural damage, there were concerns regarding the handling of missing data. For the monotherapy study ARA3005 it was, among other things, commented that the EU adalimumab monotherapy is only approved for patients intolerant to MTX or when continued treatment with MTX is inappropriate, but not for MTX inadequate responders. Based on the feedback obtained, the ARA3005 study population was stratified by the reason that subjects were not taking MTX, to allow for pre-specified subgroup analyses.

In the advice from Paul-Ehrlich-Institut, 03 November 2015, it was recommended to propose one dose regimen for the MAA but to define situations for which a higher dose may be justified (e.g. patients with higher body weight, enhanced IL-6 levels at baseline, or with monotherapy treatment).

A Paediatric Investigation Plan for sirukumab in the Juvenile Idiopathic Arthritis indication was agreed with the Paediatric Committee (EMEA-001043-PIP01-10-M03, decision P/0150/2017).

CHMP comment

The development program for sirukumab was largely consistent with EMA guidelines in this therapeutic field (see clinical AR for details). Overall, the applicant seems to have integrated previous scientific advice into their development program. ***The applicant is currently proposing that for those patients being treated with Plivensia 50 mg every 4 weeks monotherapy who are not responding adequately by weeks 12 to 16 (after 3 to 4 doses), the dosage of Plivensia can be escalated to 100 mg every two weeks monotherapy.***

2.4. General comments on compliance with GMP, GLP, GCP

The Applicant confirms that all clinical trials evaluated in this submission carried out within or outside the European Union meet the ethical requirement of Directive 2001/20/EC of the European Parliament and of the Council of 4 April2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

2.5. Type of application and other comments on the submitted dossier

- Legal basis: The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, a complete and independent application (NCE) and a Biotech medical product.
- Accelerated procedure - NA
- Conditional approval - NA
- Exceptional circumstances - NA
- Biosimilar application - NA
- 1 year data exclusivity - NA
- Significance of paediatric studies - NA

3. Scientific overview and discussion

3.1. Introduction

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, a complete and independent application (NCE) and a Biotech medical product. The application concerns Sirukumab, a human anti-IL-6 monoclonal antibody (mAb), for the indication treatment of RA. The wording of the indication proposed by the applicant is as follows:

Plivensia in combination with methotrexate (MTX), is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have either

responded inadequately to, or who were intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs) (see section 5.1). In these patients, Plivensia can be given as monotherapy when treatment with MTX is inappropriate for safety or tolerability reasons.

None of the currently approved RA drugs can achieve the treatment target, i.e. remission or at least low disease activity, in all patients. In addition, many patients discontinue their DMARD or never become candidates for DMARDs because of safety reasons. However, depending on the medical history and comorbidities, one DMARD may be suited better to certain patients than others. In summary, despite multiple treatment options being available for the treatment of adult patients with RA, there still remains a considerable unmet need in this chronic disease that requires lifelong therapy.

At the time of the initial application, there was one IL-6 blocker approved for the RA indication; tocilizumab. According to the applicant, unlike tocilizumab, sirukumab inhibits IL-6 by binding specifically to the cytokine IL-6 with high affinity.

3.2. Quality aspects

3.2.1. Introduction

Sirukumab (also known as CNTO 136) is a recombinant human anti-interleukin 6 (IL-6) monoclonal antibody of the immunoglobulin G1 kappa (IgG1κ) class with a molecular weight of approximately 150,000 daltons. Sirukumab binds with high affinity and specificity to human IL-6 and as a result inhibits IL-6-mediated signalling and the biological effects of IL-6. Data is presented to support use of sirukumab for the treatment of moderately to severely active rheumatoid arthritis in adult patients.

Sirukumab drug substance is formulated at 100 mg/mL in acetate, sorbitol, polysorbate 20 buffer.

The sirukumab finished product is provided in the form of a sterile solution in a single-use prefilled syringe (PFS), which can be assembled into either an autoinjector or a passive needle guard. Plivensia is administered by subcutaneous injection.

3.2.2. Active Substance

General Information

Sirukumab is a fully human monoclonal immunoglobulin G1 (IgG1) containing kappa light chains. The intact molecule contains 1324 amino acid residues, which sequence was deduced from cDNA sequence and confirmed by peptide mapping and intact mass spectrometry. Sirukumab is a glycoprotein with multiple glycoforms, each containing 2 N-glycans (1 on each heavy chain) at asparagine 299 (Asn-299) in the CH2 region of the heavy chain. The N-glycans are primarily complex, biantennary structures containing 4 N-acetylglucosamine, 3 mannose, and 1 fucose residues with galactose heterogeneity. The different structures have different molecular masses, and they are paired in different combinations on the sirukumab molecule. As a result, sirukumab displays microheterogeneity in terms of mass (147,222 to 147,546 Da).

Manufacture, characterisation and process controls

Process and scale

Sirukumab active substance is manufactured at Jansen Sciences UC, Ireland in a process from a working cell bank (WCB), consisting of perfusion cell culture followed by purification (including Direct Product Capture, low pH hold, various chromatography steps,virus removal filtration, concentration

and diafiltration) and formulation. Proven Acceptable Ranges (PARs) of critical process parameters and non-critical process parameters have been identified. Bioreactors are used for production and harvests of several bioreactors may be combined for Direct Product Capture batches as well as further downstream batches.

The container and closure used for storage and shipping of intermediate drug substance meet the relevant EU / Ph.Eur requirements. Extraction studies were performed and extractable compounds did not result in toxicological safety concern.

The different unit operations in manufacturing process are described in sufficient level of details, and adequately justified. Information on target set limits and proven acceptable ranges for both non-critical and critical process parameters is detailed in the dossier.

Control of materials

The host cell line (NS0/1) used for expression of sirukumab is a murine myeloma cell line The final clone selected was C1377B

The MCB was generated in accordance with cGMP. The WCB lots were generated in accordance with cGMP. The growth medium contained no animal derived materials.

Testing and characterisation of MCB lot and WCB lots were performed according to the ICH Q5D guideline. No raw materials derived from animal origin are used during active substance manufacture. Specifications of raw materials (compendial and non-compendial) are provided.

Control of critical steps and intermediates

A list is provided of In-Process Controls (IPCs) tests and the associated acceptance criteria, or predefined instructions, established based on the control of active substance critical quality attributes (CQAs) at critical steps and intermediates to ensure product quality and consistency during the active substance manufacturing process. In addition, a list of process monitoring tests (PMTs) is provided to assess process consistency at less critical steps in the process. Holding times and temperatures of the several stages have been stated but no data on cumulative storage (worst case) of these materials has been provided.

Process evaluation and/or validation

The sirukumab commercial manufacturing process was validated at the commercial facility. Acceptance criteria for IPCs and process parameters were established based on data obtained from process characterisation studies and reduced-scale studies. Process validation for Sirukumab included:

- General commercial process validation
- Consistency of the active substance
- Cell substrate and bioreactor characterisation Reprocessing steps
- Holding times of materials during the process
- Chromatography resin cleaning and resin life time and establishment of commercial protocols for end of life of resin material used during commercial production.
- Ultrafiltration/Diafiltration membrane cleaning and life time and establishment of commercial protocols for end of life of membrane material used during commercial production.
- Control / purging of impurities Shipping qualification of active substance to finished product manufacturing site

Manufacturing development

A detailed description has been provided on the manufacturing process development, including the history of process development at each of the manufacturing stages, comparability studies, an impurity risk evaluation, process control strategy development, analytical history and the description of the quality management system. A comprehensive comparability strategy was designed and executed in accordance with the guidance in ICH Q5E. Any differences observed were adequately justified and comparability was shown.

Control strategy

The process control strategy was based on identification of critical quality attributes (CQAs)and includes an integrated control of process parameters, material attributes, IPCs, release and stability tests, process validation and procedural control.

The CQAs are considered relevant for monoclonal antibodies, the used process and the degradation profile. All CQAs are controlled, either through tests in the active substance specification, IPCs or have been established to be related to Critical Process Parameters (CPPs), which are also controlled.

All stages of the process were reviewed for CPPs and proven acceptable ranges were established based on experiments (reduced-scale or full scale). Elements of Quality by Design were used, such as the performance of Design of Experiments (DoE) of several process steps. However, no design space or regulatory flexibility is claimed. A comprehensive overview of all PARs has been provided, although actual results of DoE studies are not included. A similar exercise has been performed for control of critical material attributes (raw materials, cell banks, liquid media and purification columns).

An impurity criticality assessment has been performed by the applicant. A history of the development of analytical procedures is provided.

Characterisation

Elucidation of structure and other characteristics

The sirukumab human IgG1 Mab is comprised of 2 identical HCs and 2 identical kappa light chains connected by disulfide bonds in a heterodimeric structure.

The predicted amino acid sequence for sirukumab was confirmed. Carbohydrate structure has been examined and structural assignments confirmed.All expected disulfide linkages for an IgG1 antibody were detected.The observed molecular masses for intact sirukumab,matched the expected masses. The higher order structure and thermal stability of sirukumab was typical for an IgG1 antibody.

Degradation pathways have been identified. Comprehensive biological characterisation of Sirukumab was conducted to demonstrate the mechanism of action.Sirukumab is a monoclonal antibody with an intact human IgG1 Fc-domain and thus, in principle, is able to interact with Fcγ receptors. Since Sirukumab's antigenic binding target is a soluble protein (and not a cell surface protein), it would not be expected to induce antibody dependent cellular cytotoxicity (ADCC) or to activate complement.

Impurities

Mechanisms contributing to the heterogeneity of sirukumab are described and levels are well controlled.The potential contaminants are either tested and monitored by in-process control, and/or release testing with acceptance criteria, or controlled by means of characterisation/validation.

Control of Active substance

Specification

The specification of the active substance includes control of identity, purity and impurities, potency and other general tests.

The test methods for identity, general properties, quantity, charge heterogeneity, purity, potency and microbiological contamination were selected to ensure the levels of these CQAs are kept within predefined limits. These specifications for the active substance are aligned with regulatory guidance and are part of an integrated control strategy to ensure product quality and process consistency.

Statistical analyses of release and stability data from relevant active substance were used to set the acceptance criteria. The proposed active substance acceptance criteria were tied to safety and efficacy assessments from clinical studies as well as product and process understanding. The applicant has proposed tightening of the acceptance criterion for bioactivity for DS release and stability as well as DP release and stability in accordance with the request by the rapporteurs. This is found acceptable.

Analytical procedures

The analytical procedures used to test the active substance are described in detail in the relevant sections. Compendial methods are performed in accordance with the current European Pharmacopoeia. Summaries of the analytical procedures used during development are provided, including relevant validation reports.

The determination of the bioactivity (relative potency) of sirukumab test articles is based on the ability of sirukumab antibody to neutralise IL-6 dependent growth of murine hybridoma cells in a cell-based bioassay.

Batch analyses

Batch analyses data, for sirukumab active substance lots used during clinical development and for product manufactured at the commercial manufacturing facility are provided. The batch analyses data demonstrate that sirukumab active substance can be manufactured reproducibly.

Reference standards

Reference materials were used throughout the development process and analytical results (of specification tests and additional characterisation procedures) have been provided of the materials.

Stability

The stability studies were performed per ICH Guidelines Stability Testing of New Active substances and Products (Q1A) and Stability Testing of Biotechnological/Biological Products (Q5C). Stability studies are conducted at the recommended storage condition and at elevated temperatures in order to assess the effect of these conditions on quality of the active substance.

Sufficient stability data has been presented of the active substance to substantiate the proposed shelf life period.

3.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The marketing authorisation application concerns the 50 mg solution for injection in PFS fitted with passive needle guard and in pre-filled pen. The same PFS, as well as the identical solution for injection, is used for both presentations.

The composition of Plivensia 50 mg/syringe is 50 mg Sirukumab/mL, sorbitol, Glacial acetic acid, sodium acetate trihydrate, polysorbate 20 (Table 6). These excipients are commonly used in the formulation of biopharmaceuticals and comply with Ph. Eur compendia.

The development program for sirukumab assessed two different strengths, 50 mg and 100 mg.

The excipients used in the finished product are the same as those used in the active substance. No additional excipients are included. The compendial grades and functions of the individual excipients used are described. No excipients of human or animal origin or novel excipients are used.

A rationale for each of the formulation components is provided. The formulation composition and dosage form were developed as part of an extensive development effort.The finished product manufacturing processes for the 50 and 100 mg/syringe finished product were established based on platform knowledge with similar products in the same commercial facility. The data gathered from the development and Phase 3 clinical manufacturing batches was used to define the commercial processes for the two finished product presentations, the respective control strategies, and process validation plans.

CQAs have been identified for the finished product. A formal risk assessment was performed according to internal procedures to establish an appropriate set of controls for the finished product CQAs. The control elements listed below are placed at control points that have a major influence on product conformance to specifications for finished product CQAs: process parameters, material controls, IPCs, release tests, stability tests, characterisation testing, process validation, Procedural controls. The list of controls associated with the finished product manufacturing process steps for each finished product CQA is provided.

Most of the procedures used for testing the finished product are the same procedures that are used for testing the active substance (i.e. identity, purity and product impurities, potency, quantity). Changes to the procedures that are used for testing both the active substance and the finished product are described in detail.

The container closure system utilized for the finished product is a PFS. The syringe is demonstrated to be compatible with the finished product. The PFS in combination with a device is discussed in the applicable device sections.

The finished product contains no preservatives and is sterile-filtered before aseptic filling into the sterile primary packaging components. Container closure integrity tests of the PFS and device assembly were used to validate the integrity of the container closure system and its ability to prevent the ingress of microbial contamination to the final product. Additional studies were performed to ensure microbial integrity of the finished product following exposure to physical stresses during production and shipment. The results showed no failures of the container closure system.

Manufacture of the product and process controls

Prefilled syringe

The 50 mg/syringe finished product is manufactured at Cilag AG (Cilag), Schaffhausen, Switzerland site. The frozen active substance (100 mg/mL is thawed and mixed followed by dilution with a dilution buffer to create the finished product solution (50 mg/mL). The finished product solution (50 mg/mL) is sterile filtered, filled into prepared syringes and stoppered. IPCs are monitored during manufacturing. The process step in which an IPC is measured, the test, and its associated acceptance criteria are provided.

Generally, the description of the manufacturing process for PFS is given in sufficient detail where the proposed target values and/or PARs are listed for both critical and non-critical process parameters. The claimed PARs are considered satisfactorily supported by data.

PFS assembly in Autoinjector or Passive Needle Guard

The PFS are assembled into an autoinjector or passive needle guard.

The autoinjector components and subassemblies are received from qualified suppliers and are stored in quarantine until release. Autoinjector components and subassemblies are visually inspected for identity, defects, and damage, and undergo functional/dimensional tests according to applicable standard operating procedures. The parts are released for assembly with prefilled syringe (PFS) upon successful inspection. The assembly of the labelled PFS in the autoinjector (PFS-AI) is performed with auto-injector components and subassemblies A and B, using a semi-automated or fully automated process. Both processes were successfully validated. A tamper-evident label is applied after assembly. There is inspection of all critical assembly steps performed manually or by in-line sensors and detectors. After assembly with PFS, functional performance testing of the auto-injector is performed during release testing.

The passive needle guard components (plunger rod and needle guard subassembly) are received from the manufacturer ready for assembly with the PFS. Passive needle guard components are visually inspected for identity, defects, and damage according to the applicable standard operating procedures. The PFS, PFS label, plunger rods, and needle guard subassemblies are introduced into a semi - automated or fully automated assembly line. There is inspection of all critical assembly steps performed by in-line sensors and detectors. After assembly, the specified device functionality is checked as part of release testing.

Process Validation

Process validation studies were executed. During execution of the process validation runs, the control of CPPs was verified within predefined ranges to demonstrate the ability to control CPPs within the

specified ranges. The results of process characterization (additional in-process sampling beyond IPCs), product characterisation (qualified, non-routine tests used to characterize the finished product), and enhanced sampling (during process qualification) testing were also evaluated.

*Manufacturing process development*The comparability study demonstrated that the changes during development would not be expected to adversely impact the safety and efficacy of sirukumab.

Product specification

The specification of the active substance includes control of identity, purity and impurities, potency and other general tests
The proposed tests for control of drug product are acceptable. Descriptions of methods used for analysis are provided in sufficient detail. All non-compendial analytical procedures are satisfactorily validated in accordance with the ICH Q2 requirements.

Generally, the specifications proposed for control of drug product are considered acceptable. In accordance with the request by the rapporteur, further data have been provided supporting the proposed specifications for control of purity. The product-related substances and impurities in the finished product include the same product-related substances and impurities that are applicable to the active substance, as well as product-related impuritys applicable specifically to the finished product.

Batch analyses

Batch analyses data for the different batches of finished product used during development was presented.

Reference standard

See active substance section.

Stability of the product

Data are presented to provide the rationale and justification for the finished product shelf life claim 24 months when stored at the recommended temperatureof 2-8 °C and protected from light. The PFS batches are stored at 2-8 °C and subsequently assembled with an auto-injector (PFS-AI) or a passive needle guard. The manufacturing date of the PFS batch is taken as the manufacturing date of PFS-AI and passive needle guard.

In addition, supportive data regarding accelerated temperature, stressed temperature, characterisation stability resultsphotostability of finished product, temperature cycling of finished product, biochemical and functional stability of combination products (PFS-AI, PFS-U) are presented.Overall it can be agreed that the provided information is sufficient to support the proposed 24-month shelf life at 2-8 °C.

Adventitious agents

The information provided on non-viral adventitious agents is sufficient. No materials of animal origin have been used to prepare the MCB or WCB or in the manufacturing process of sirukumab. No virus particles were detected in the cell banks, other than retrovirus-like particles.

Viral clearance studies were performedforrelevant steps Appropriate model viruses were used for validation. Scaled down models were used for the different manufacturing steps. The small-scale chromatography models are appropriately validated. Verification of the ability of resins at lifetime limits to remove representative model viruses was completed. The results presented confirm that viral clearance remains satisfactory up till the end of resin life time.

The results of the virus clearance studies show acceptable reduction of the model virus studied.

3.2.4. Discussion on chemical, pharmaceutical and biological aspects

As a general remark, the Plivensia dossier is of good quality and in the D120 LoQ no Major objections were identified. There were, however, some Other Concerns raised, partly due to lack of detail and also lack of justification for some proposals and statements made by the applicant but all of them have been appropriately addressed by the applicant and no Other concerns are unresolved.

The DS and DP manufacturing process description and process controls are in general described with a sufficient level of details included. Raw materials are sufficiently described and controlled. MCB and WCB are adequately described and characterised and the description of the production of future WCB´s is considered acceptable. The reporting from the characterisation of the end-of-production cells have been extended to comply with the recommendations in the ICH Q5A guideline and the results are acceptable. As requested by the Rapporteurs, it has been clarified if viruses were detected or not in the co-cultivation assay.

Critical process parameters were identified and the process was appropriately validated.

Sirukumab has been extensively characterised.

The DS and DP specifications proposed by the applicant are deemed suitable to control the quality of DS and DP at commercial scale manufacturing. The applicant has given an acceptable description of the actions taken if a batch falls out of trend. The proposed shelf lifes for both DS and DP are supported by the performed stability studies.

3.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of Plivensia is considered to be in line with the quality of other approved monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications.

Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

The overall quality of Plivensia is considered acceptable when used in accordance with the conditions defined in the SmPC.

In conclusion, based on the review of the quality data provided, the CHMP considers that the marketing authorisation application for Plivensia **is approvable** from the quality point of view.

3.3. Non clinical aspects

Sirukumab (CNTO 136) is a fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that binds specifically to human IL-6 with high affinity (K_D = 0.175 pM), thereby neutralizing the biological activity of IL-6 molecules.

In vitro

In a series of in vitro bioassays sirukumab was shown to block the interaction of IL-6 with its receptor. Additional in vitro studies showed that sirukumab neutralized IL-6-mediated cellular responses including cell proliferation (EC50 = 1.17 ng/ml), and IL-6-induced intracellular signaling (STAT3 phosphorylation, EC50 = 0.53 µg/ml) in THP-1 cells. Additionally, sirukumab inhibited human IL-6-induced MCP-1 secretion in U937 cells (EC50 = 1.66 ng/ml) as well as the synthesis of downstream proteins such as acute phase protein serum amyloid A (SAA) in HepG2 human hepatoma cells (EC50 = 7.26 ng/ml). In a bioassay utilizing classical IL-6-mediated signaling, sirukumab potently inhibited IL-6/IL-6R trans-signaling mediated stimulation of MCP-1 production in primary human umbilical vein cells (EC50 = 59 ng/ml). In ex vivo studies, a single dose of sirukumab (0.5, 5 mg/kg, IP) was found to block human IL-6-induced SAA production in serum of Balb/c mice.

Cross-reactivity studies using a 7TD1 cell proliferation assay revealed that sirukumab neutralizes cynomolgus monkey and other non-human primate IL-6, but sirukumab did not neutralize dog, guinea-pig, rat, or mouse IL-6. The EC_{50} for sirukumab neutralization of human IL-6 (0.8 ng/mL) was similar to that of cynomolgus monkey IL-6 (0.3 ng/mL). Thus, cynomolgus monkey was selected as a pharmacologically relevant species for the toxicology and pharmacokinetics evaluation of sirukumab.

The immunological characteristic of sirukumab with a human IgG1 backbone indicate that sirukumab could be capable of Fc-mediated functions such as antibody-dependent-cell-mediated cytotoxicity (ADCC) or complement dependent cell cytotoxicity (CDC). However, sirukumab's antigenic binding target is the soluble IL-6 cytokine and native IL-6 bound to cell surface expressed IL-6R was not recognized by sirukumab, suggesting that sirukumab would not trigger ADCC and CDC. In accordance with current guidelines (ICH S6 (R1)), an evaluation of ADCC and CDC is generally not needed for mAbs directed against non-membrane bound targets.

In vivo

Since sirukumab did not neutralize murine IL-6, the surrogate anti-mouse IL-6 monoclonal antibody (CNTO 345, 1, 5 mg/animal/week, IP) was characterized in vitro (K_D = 40 pM) and subsequently tested in in vivo studies to demonstrate efficacy in a mouse model of collagen-induced arthritis.

Secondary pharmacodynamics

Cardiovascular disease is a significant co-morbidity for patients with rheumatoid arthritis. A secondary pharmacodynamics study, designed to mimic the early stages of atherosclerosis was performed to assess the effect of sirukumab in an in vitro human surrogate system using primary human arterial endothelial cells (EC) and smooth muscle cells (SMC) co-cultured under atheroprone hemodynamic flow and in the presence of inflammatory mediators. Transcriptomic pathway analysis of both EC and SMC demonstrated that sirukumab could suppress inflammation by decreasing adhesion molecule gene expression and NF-κB-dependent genes and promote vasculoprotective responses by increasing eNOS and KLF2 expression, suggesting that therapies targeting IL-6 signaling (e.g. sirukumab) is effective in

suppressing inflammation or promoting vascular health and may provide vascular protection in patients with RA.

Safety pharmacology

In line with ICH S6(R1) safety pharmacology endpoints (cardiovascular, respiratory, CNS [clinical observations, body temperature]) were evaluated as part of the repeat-dose toxicity studies in cynomolgus monkeys up to 6 months, which in turn is an acceptable approach. In the dose-range tested (10-50 mg/kg, IV/SC), no sirukumab related adverse effects were observed on cardiovascular, respiratory or CNS functions.

3.3.1. Pharmacokinetics

The pharmacokinetics of sirukumab was evaluated in a non-GLP single-dose PK comparability study in cynomolgus monkeys after subcutaneous administration (10 mg/kg, SC) to compare a liquid formulation of sirukumab with a lyophilized formulation. Toxicokinetics after repeated administration were evaluated as part of the GLP compliant toxicity studies in cynomolgus monkeys after subcutaneous (50 mg/kg, SC twice weekly) and intravenous administration (10, 50 mg/kg, IV once weekly) of sirukumab up to six months. In addition, sirukumab concentrations were measured in serum and milk of maternal monkeys and in serum of fetal/infant monkeys in eEFD and ePPND studies.

Anti-sirukumab antibodies were tested in cynomolgus monkeys following both single- or repeat-dose of sirukumab.

Since sirukumab did not display pharmacological activity in rodents, the pharmacokinetics of the surrogate anti-mouse IL-6 antibody CNTO 345 (40, 100 mg/kg, IV and SC once or twice weekly) was determined after repeated dosing in mice.

The serum concentration of sirukumab following SC treatment with 50 mg in humans was C_{max} = 4.26 µg/ml and $AUC_{0\text{-}28d}$ = 83.52 µg.day/mL

Methods of analysis

The serum concentrations of sirukumab in cynomolgus monkey were measured by a validated electrochemi-luminescent based immunoassay (ECLIA). A qualified ECLIA method was also used in the detection of the murine surrogate antibody CNTO 345 concentrations in mouse serum.

Absorption

Single-dosing in cynomolgus monkeys

Following a single subcutaneous injection of sirukumab (10 mg/kg, SC, n=10/group) in male cynomolgus monkeys, a similar systemic exposure (Cmax values 61.40 ± 17.05 µg/mL and 60.94 ±11.15 µg/mL) was observed for the lyophilized and liquid formulations, respectively. After single SC administration of 50 mg/kg, sirukumab was slowly absorbed. Maximum concentrations of sirukumab in monkey serum were reached at a median time (T_{max}) of 3 to 5 days. The mean half-life of sirukumab ranged from 12.2 to 13.7 days after single SC dosing. The sirukumab PK profile appears, thus, comparable between the liquid and lyophilized formulations in cynomolgus monkeys.

Repeat-dosing in cynomolgus monkeys

Both intravenous (10 and 50 mg/kg, IV once weekly) and subcutaneous (50 mg/kg, SC twice weekly) repeated administration of sirukumab in cynomolgus monkeys was evaluated in the 3- and 6-month toxicology studies. There was no apparent sex differences in the systemic exposure observed. After IV administrations, systemic exposure of sirukumab increased in an approximately dose proportional

manner over the dose range of 10 to 50 mg/kg. However, a reliable dose-response relationship is difficult to establish since only two dose groups were included in the studies presented.

The mean terminal half-life (t1/2) of sirukumab ranged from 10 to 19 days across all IV and SC dose groups. Moderate accumulation of sirukumab in monkey serum was observed after repeated dosing up to 6 months. Calculated drug accumulation ratios were 3.34 and 2.45 for once-weekly IV administrations at 10 and 50 mg/kg, respectively, and 3.19 for twice-weekly SC administrations at 50 mg/kg. The mean SC bioavailability of sirukumab was somewhat variable between studies and reached approximately 87% and 59% in the 3- and 6-month studies, respectively.

The clearance (Clss, mean ± SD) of sirukumab after 6 months of treatment was 4.60 ± 1.45 and 5.04 ± 1.68 mL/day/kg for the 10, and 50 mg/kg dose groups. After 3 months of treatment, the clearance of sirukumab was higher, reaching 8.53 ± 2.61 and 9.43± 1.40 mL/day/kg, respectively, at steady state.

CNTO 345 – murine surrogate anti-mouse IL-6 antibody

The PK profile of the surrogate anti-mouse IL-6 antibody, CNTO 345, was also assessed in a tolerability study conducted prior to fertility studies in mice. Following single- and repeat-dose SC and IV administration in mice (40, 100 mg/kg up to 25 days of dosing), CNTO 345 was absorbed with a T_{max} of 1 to 2 days after SC dosing. The systemic exposure (C_{max} and AUC values) following repeat (SC, q1w) injections, the clinical route of administration, appeared to increase in an approximate dose-proportional manner, with an estimated 2.6-fold accumulation in mean serum concentrations across the tested dose level of 40 and 100 mg/kg. Even though the systemic exposure of CNTO 345 was higher after repeated IV administration as compared to SC, the latter route of administration was selected in the subsequent toxicology studies in mice.

Distribution

The mean volume of distribution of sirukumab in cynomolgus monkeys was 102.45 ± 43.66 and 124.93 ± 71.14 ml/kg following single IV administration, of 10 and 50 mg/kg, respectively, for 3 months. These results indicate that the distribution of sirukumab was mainly confined to the vascular space in the body, typical of a IgG-based mAb. Therefore, standard biodistribution studies were not considered necessary for sirukumab.

Consistent with its nature as IgG, sirukumab was able to cross the placental barrier in developing monkey embryos. Fetal exposure to sirukumab was proportional to the increase in SC dose administered to the dams (see Toxicology section for further discussion).

Metabolism and Excretion

No specific metabolism and excretion studies were performed. Similar to other IgG1 mAbs, the expected consequences of metabolism of sirukumab are the degradation to small peptides and individual amino acids. The absence of metabolism and excretion studies is in accordance with ICH S6(R1).

Pharmacokinetic drug interactions

No non-clinical in vivo PK drug interaction studies with sirukumab were conducted. The effects of sirukumab treatment on CYP enzyme activities were evaluated in subjects with active RA in clinical study (see study report CNTO136ARA1001/ CSR). The potential effects of concomitant medications including MTX, DMARDs other than MTX, NSAIDs and corticosteroids on the PK of sirukumab were investigated through clinical population PK analysis.

Other pharmacokinetic drug interactions

Formation of anti-sirukumab antibodies (ADA) was only detected in the single dose SC monkey study in 2 out of 30 monkeys at day 56 after dosing. None of the maternal or infant monkeys in the prenatal and postnatal development study tested positive for anti-sirukumab antibodies. In addition, no animal tested positive for anti-sirukumab antibodies in the 3- and 6-month repeated dose toxicity studies.

3.3.2. Toxicology

Repeat dose toxicity

The repeat-dose toxicity of sirukumab has been evaluated in two GLP toxicity studies. Sirukumab was administered IV q1w at 10 or 50 mg/kg or SC b.i.w. at 50 mg/kg for 3 or 6 months to cynomolgus monkeys. There were no toxicologically significant effects. The T-cell dependent antibody response was studied after keyhole limpet hemocyanin (KLH) immunization. Sirukumab treatement was associated with a partial decrease in IgG and IgM response.

The mean steady-state C_{max} (2956.49 µg/mL) and $AUC_{0\text{-}7d}$ (13180.78 µg·day/mL) values in the 50 mg/kg/week SC dosing groups in the monkeys were 189- and 140-fold greater, respectively, than the mean steady-state C_{max} (15.68 µg/mL) and $AUC_{0\text{-}14d}$ (188.67 µg·day/mL; 94 µg·day/mL for one week interval) in subjects treated with 100 mg every 2 weeks; and were 694- and 628-fold greater, respectively, than the mean steady-state C_{max} (4.26 µg/mL) and $AUC_{0\text{-}28d}$ (83.52 µg·day/mL; 21 µg·day/mL for one week interval) at a dose of 50 mg every 4 weeks in subjects with rheumatoid arthritis.

Genotoxicity and carcinogenicity

Genotoxicity and carcinogenicity tests have not been conducted with sirukumab. Repeat dose toxicity studies did not reveal the presence of proliferative changes.

A series of non-GLP experimental studies were conducted in squamous cell carcinoma (SCC) VII (SCC VII) tumor bearing C3H/HeN mice dosed with the anti-mouse IL-6 mAb (CNTO 345) to determine if inhibiting IL-6 signaling with CNTO 345 could influence various stages in tumor growth, promotion and progression. These studies produced conflicting results that were difficult to interpret and of unknown relevance to human safety.

Reproductive and developmental toxicity

Sirukumab produced no toxicity to the male or female reproductive organs in young (adolescent) male or female cynomolgus monkeys in the 3 or 6-month repeat-dose toxicity studies or in sexually mature male monkeys in the 6-month repeat-dose toxicity study. In addition to the general toxicology assessments, the sexually mature males had testicular measurements and semen samples collected pre-study, at 3- and 6-months during sirukumab treatment, and after a 3-month treatment-free period. No adverse effecs were observed.

In addition, an anti-mouse IL-6 mAb (CNTO 345) was utilized to evaluate fertility and general reproductive toxicity in male and female mice. There were no CNTO 345-related adverse observations in any of these studies.

To evaluate potential effects of sirukumab on embryo-fetal development, an expanded embryo-fetal developmental (eEFD) GLP toxicity study was conducted in cynomolgus monkeys at 10, or 50 mg/kg sirukumab, IV q1w from gestation day (GD) 20 (beginning of embryonic organogenesis) through 118 (mid-fetal period). There were no mortalities, and no maternal sirukumab-related effects. All fetuses obtained by scheduled C-section on GD140 (late fetal period) were alive and had no morphological

abnormalities. At C-section, sirukumab was present in the fetal serum at concentrations similar to that of the dams suggesting placental transfer of CNTO136 during fetal gestation. Embryo/fetal losses (GD20 – GD139) in this study were 20% (3/15), 0% (0/14) and 35.7% (5/14) in the control, 10 mg/kg and 50 mg/kg groups, respectively.

An enhanced prenatal and postnatal development (ePPND) GLP study was conducted with sirukumab in cynomolgus monkeys at 10 or 50 mg/kg, IV q1w. In maternal animals, there were no sirukumab-related toxicological significant changes. In infants, no sirukumab-related toxicological significant changes were identified in examinations at birth, clinical observations, body weights, morphological or functional development, skeletal evaluations, heart rate, ophthalmology evaluation, behavioral assessments, hematology, lymphocyte subset analysis, or the ability of the infants to mount a T-dependent antibody response to immunization with KLH. The only notable change in clinical chemistry was a decrease in mean serum globulin concentration, ranging from about -10 to -20% in the sirukumab-treated dams and infants. These changes were not considered adverse based on the extent and spontaneous resolution as sirukumab cleared from the serum. Embryo/fetal losses (GD20-GD139) occurred in 5.26% (1/19), 34.8% (8/23) and 10% (2/20) in the control, 10 mg/kg and 50 mg/kg groups, respectively. Maternal monkeys maintained high levels of sirukumab throughout the dosing period and infant monkeys were born with high levels of sirukumab in their serum suggesting that sirukumab crossed the placenta during gestation. Sirukumab was not detected in milk of maternal animals (except 1 monkey in the 50-mg/kg group) that had milk samples collected between lactation day (LD) 30 and 75.

3.3.3. Ecotoxicity/environmental risk assessment

Sirukumab is a recombinant protein and not considered a risk to the environment.

3.3.4. Discussion on non-clinical aspects

Pharmacology

Plivensia (sirukumab, CNTO 136) is a fully human immunoglobulin G1κ (IgG1κ) monoclonal antibody that binds specifically to human IL-6 and has been developed as an SC therapy for the treatment of rheumatoid arthritis.

The Applicant has presented non-clinical in vitro binding data demonstrating that sirukumab binds to human IL-6 with high affinity (KD = 0.175 pM) and specificity and prevents the binding of IL-6 to both transmembrane IL6-R and soluble IL-6R. Additional in vitro studies showed that sirukumab also neutralized IL-6-mediated cellular responses including cell proliferation, intracellular signalling (STAT-3 phosphorylation) and synthesis of downstream proteins as acute phase protein SAA and MCP-1 in human cell lines. In general, sirukumab blocked the biologic effect of IL-6 at concentrations below the maximum serum concentration reached in humans after SC treatment with 50 mg of sirukumab (Cmax= 4.26 µg/ml).

Sirukumab binds to and neutralizes human and non-human primate IL-6 but does not inhibit mouse, rat, dog, pig or guinea pig IL-6. Therefore, the cynomolgus monkey was selected as a pharmacologically relevant species for the toxicology and pharmacokinetics evaluation of sirukumab. In addition, in vivo studies with a surrogate murine anti-mouse IL-6 antibody were conducted to demonstrate pharmacologic efficacy in a mouse model of arthritis.

No sirukumab treatment-related adverse effects on safety pharmacology parameters were observed in the repeat dose toxicity studies in monkeys.

Pharmacokinetics

The PK profile of sirukumab was investigated in cynomolgus monkeys administered SC single-doses (10 mg/kg) and repeated-doses (50 mg/kg, SC twice weekly or 10, 50 mg/kg, IV once weekly) of sirukumab for up to 6 months. The available data indicate that the systemic exposure to sirukumab in monkeys increase in an approximately dose proportional manner with moderate accumulation of sirukumab (approximately 2.4 to 3.3-fold) in monkey serum after 3- and 6 months of treatment.

Typical of a IgG-based mAb, the mean volume of distribution of sirukumab in cynomolgus monkeys, indicated that the distribution of sirukumab was mainly confined to the vascular space in the body.

Sirukumab crosses the placenta in studies in monkeys and sirukumab was detected in monkey milk. It is yet unknown whether sirukumab is excreted in human breast milk.

The pharmacokinetic studies performed for this application are generally considered sufficient for the proposed indication.

Toxicology

Repeat-dose toxicology studies conducted in cynomolgus monkeys using doses of up to 50 mg/kg IV weekly or SC twice weekly for 3- and 6-months showed no toxicologically significant findings.

The only treatment related finding (in the 3-month study) was a slight decrease in the T-dependent antibody response to KLH/IFA immunization. There was no dose response, but this is not expected since already at the 10 mg/kg dose, effective blocking of IL-6 is expected and a higher dose will not lead to further blocking. Acknowledging a large individual variation, it is of interest that at the first timepoint (day 22), titers were similar between groups, whereas later on sirukumab-treated animals did not exhibit the normal time-dependent increase in titers seen in the control animals. This could mean that IL-6 blocking does not inhibit the initial B cell response, but it rather inhibits the following B cell expansion and possibly also affinity maturation characteristic of the later stages of an antibody resonse. In line with this reasoning, data on IgM (which does not undergo affinity maturation) showed smaller differences in titers between the groups. Due to the effect on the IgG response, sirukumab treatment could impair vaccine efficacy, where a robust IgG memory response is normally critical. This was addressed in a clinical study showing only a minor decrease in the immune response to the studied vaccines.

Clinical findings on increased serum lipids, hepatotoxicity and neutropenia have not been observed in the animal toxicity studies. Based on available knowledge, it is clear that in all these cases effects are only expected in situations where IL-6 production is increased (such as in chronic inflammation) and that these effects are directly related to inhibition of IL-6 which is playing a homeostatic role in the case of inflammation.

The role of IL-6 for tumour surveillance or tumour growth is unclear and the studies performed by the applicant in mouse tumour models did not provide any further understanding. Whereas immunosuppressive treatment is generally believed to increase the cancer risk, IL-6 is unlikely to be an important player in the tumour immune surveillance. Therefore, from a theoretical point of view, carcinogenicity is not a major concern for this product. However, as for other immunosuppressive and

immunomodulatory treatments, this issue must be addressed in the pharmacovigilance activities. Malignancy is included as an important potential risk in the RMP.

The effects of CNTO 345 (anti-mouse IL-6 mAb), on fertility and early embryonic development was evaluated in in male and female mice. These studies did not reveal any influence of IL-6 inhibition on fertility.

An extended embryofetal development (eEFD) study was conducted in cynomolgus monkeys, with treatment from GD20 through GD118 and caesarean section on GD140. In a second extended pre- and postnatal development (ePPND) study, monkeys were treated from GD 20 to natural delivery (~GD165). Dams and infants were observed and examined for up to approximately 7 months after birth. In the eFFD study, embryofetal losses in the high dose group was 35.7%, exceeding the background values of the laboratory at that time. In the ePPND study, embryofetal losses in the mid dose was 34.8%, only slight outside the background data at that time.

The only toxicological outcome in the developmental toxicity studies of possible relationship to sirukumab treatment is an increase in the incidence of embryo/fetal loss in some of the sirukumab treated groups. There are conflcting data on IL-6 involvement during pregnancy, but there appears to be a role for IL-6 in placental development and embryofoetal development in humans and rodents. The observed increased embryofoetal death in Cynomolgus monkeys remains within historical limits and is in part attributed to the low number of animals used in the ePPND study and the inter-animal variability. Furthermore, because it can be assumed that IL-6 inhibition was complete at all doses, data on embryofoetal death from dams exposed to sirukumab can be pooled. The pooled data also do not show differences compared to control animals. While the risk for an adverse sirukumab related effect on embryofoetal survival is low, it cannot be completely ruled out because the role of IL-6 in pregnancy remains poorly understood. This is now clearly reflected in the SmPC.

In the ePPND study in monkeys, infants to exposed mothers had a high exposure to sirukumab at birth. No effect on the immune response was seen after immunisations at d 120 and d 180, at a time when the sirukumab exposure had decreasd to a low level. It is still uncertain whether in utero exposure to sirukumab could have consequences on immunological development as well as immune responses at early age, such as for some of the childhood vaccinations. This is addressed in section 4.6 of the SmPC.

The nonclinical toxicity studies are not adequate to evaluate an increased risk of infection and complications thereof. For this purpose, challenge studies would be needed. This is not considered a meaningful way forward. Serious infections have been identified in patients, and this is an identified risk in the RMP. It would be of value to consider the experience with other members of this class, where more clinical experience has been collected. It is reasonable to believe that sirukumab will behave similarily as these other agents in this respect.

3.3.5. Conclusion on non-clinical aspects

There are no objections against approval of sirukumab from a non-clinical point of view.

3.4. Clinical aspects

Tabular overview of clinical studies

- Six studies assessed efficacy and safety within the clinical development program for sirukumab in RA, see Table 1. Three, global phase 3 studies were pivotal: ARA3002, ARA3003 and ARA3005. Supporting data were derived from the monotherapy study ARA3001 and the phase 2 proof-of-concept and dose-finding study, C1377T04. Finally, there is an on-going global long-term extension (LTE) of the ARA3002 and ARA3003 studies; ARA3004.

Table 1 Overview of efficacy and safety studies in the clinical development program for sirukumab in RA

Study ID	No. of study centres / locations	Design	Study Posology (Subjs by arm entered)	Primary Objective	Duration	Gender M/F Median Age (range)	Diagnosis Incl. criteria	Primary Endpoints
C1377T04	Part A: 8 sites in 2 countries Part B: 36 sites in 7countries	Phase 2 RCT Parallel group PART A: Proof-of-Concept PART B: Dose-finding	PART A: • Placebo q2w (n=19/17) • Sirukumab 100 mg q2w (n=17/15) PART B: • Placebo (n=30/24) • Sirukumab 100 mg q2w (n=30/27) • Sirukumab 100 mg q4w (n=30/27) • Sirukumab 50 mg q4w (n=30/27) • Sirukumab 25 mg q4w (n=31/31) Crossover: Part A: at Week 12, subjects in placebo group crossed over to sirukumab 100 mg q2w; subjects in sirukumab group crossed over to placebo. Part B: At Week 12, subjects in placebo group crossed over to sirukumab 100 mg q2w.	Evaluate efficacy and safety of sc sirukumab in subjects with active RA despite MTX therapy	76 w (38+38 w)	Gender: PART A: 11M/25F PART B: 23M/128F Median Age: PART A: 49.5 (21,68) PART B: 53.0 (19,78)	18 years (20 years Japanese sites) Active RA: at least 6 swollen and 6 tender joints despite MTX CRP $\geqslant$ 1.0 mg/dL Anti-CCP+ or RF+	ACR 50 response at w12 in Part B

Study ID	No. of study centres / locations	Design	Study Posology (Subjs by arm entered)	Primary Objective	Duration	Gender M/F Median Age (range)	Diagnosis Incl. criteria	Primary Endpoints
ARA3002, SIRROUND D	185 randomizing sites in 18 countries	Phase 3 global RCT Parallel Group	• Placebo q2w (n=556) • Sirukumab 50 mg q4w (n=557) • Sirukumab 100 mg q2w (n=557) Early escape week 18 Late escape week 40: <20% improvement from baseline in both swollen and tender joint counts: Placebo ›sirukumab 50 mg q4w or 100 mg q2w Crossover: At Week 52, all remaining subjects in placebo group crossed over to a sirukumab group	To assess the efficacy of sirukumab as measured by reduction of signs and symptoms of RA and inhibition of radiographic progression in subjects with moderately to severely active RA who were refractory to DMARDs	120w	Gender: 80% F Median age: 54.0 (18,82)	18 years Active RA: at least 6 tender and 6 swollen joints Refractory to single-agent or combination DMARD therapy that included MTX or SSZ. CRP 8.00 mg/L Meet 1 of the following criteria: (a) CCP+ (b) RF+ (c) Erosive RA in hands or feet.	ACR 20 response at w16 Change from baseline in vdH-S score at w52
ARA3003 SIRROUND T	183 randomizing sites in 20 countries	Phase 3 global RCT Parallel group	• Placebo q2w (n=294) • Sirukumab 50 mg q4w(n=292) • Sirukumab 100 mg q2w (n=292) Early escape week 18: <20% improvement from baseline in both swollen and tender joint counts: Placebo ›sirukumab 50 mg q4w or 100 mg q2w Crossover: At Week 24, subjects in placebo group crossed over to a sirukumab group	To assess the efficacy of sirukumab as measured by reduction of signs and symptoms of RA in subjects with moderately to severely active RA who were refractory or intolerant to anti-TNF agents	68w	81.1% F Median age: 57 (18, 84)	18 years Active RA: 4 of 68 tender joints and 4 of 66 swollen joints Refractory to treatment with 1 or more anti-TNF agents or intolerant to 2 or more anti-TNF agents. CRP ⩾8.00 mg/L or ESR ⩾28 mm/hr Meet 1 of the following criteria: (a) CCP+ (b) RF+ (c) Erosive RA in hands	ACR 20 response at w16

Study ID	No. of study centres / locations	Design	Study Posology (Subjs by arm entered)	Primary Objective	Duration	Gender M/F Median Age (range)	Diagnosis Incl. criteria	Primary Endpoints
ARA3005 SIRROUND H	102 randomizing sites in 16 countries	Phase 3 global RCT Parallel group	• Adalimumab 40 mg q2w (n=186) • Sirukumab 50 mg q4w (n=186) • Sirukumab 100 mg q2w (n=187) Early escape week 16: <20% improvement from baseline in both swollen and tender joint counts: adalimumab 40 mg q2w >adalimumab 40 mg q1w or sirukumab 50 mg q4w >sirukumab 100 mg q2w	To demonstrate the superior efficacy of sirukumab monotherapy compared with adalimumab monotherapy in biologic naïve subjects with RA who were intolerant to MTX, who were considered inappropriate for treatment with MTX, or who were inadequate responders to MTX	68w	83.5% F Median age: 53.2(19, 82)	18 years Active RA with at least 8 of 68 tender joints and 6 of 66 swollen joints CRP 10.00 mg/L or ESR 28 mm/hr Biologic-naïve and intolerant to MTX, and/or inappropriate for treatment with MTX, and/or inadequate responders to MTX.	Change from baseline in DAS28 (ESR) at w24 ACR 50 response at w24
ARA3001	21 sites in Japan	Phase 3 RCT Parallel group	• Sirukumab 100 mg q2w (n=61) • Sirukumab 50 mg q4w (n=61)	To assess the safety of sirukumab in long-term administration without DMARDs in Japanese subjects with active RA who were refractory to MTX or SSZ	68w	73.8% F Median age 56.0(29, 76)	Japanese subjects with active RA: at least 6 tender joints out of 68 and 6 swollen joints out of 66 Unresponsive to MTX or SSZ. Subjects had to have 1 of the following: (a) RF+ (b) aCCP+ (c) Erosive RA in hands or feet. (CRP) level ⩾8 mg/L.	None

In ARA3002, at Week 28, subjects in all treatment groups who had <20% improvement from baseline in both swollen and tender joint counts were considered as meeting criteria for adjusting or initiating DMARDs and/or oral corticosteroids from Week 28 onwards. At Week 52, or any time after Week 52, all subjects could adjust or initiate DMARDs and/or oral corticosteroids.

In ARA3003, at or any time after Week 24, subjects could have adjusted or initiated disease modifying antirheumatic drugs (DMARDs) and/or oral corticosteroids at the investigator's discretion.

In ARA3005, subjects with active RA may have required rescue therapy prior to Week 24 based on investigator judgment. Acetaminophen/paracetamol dosed no more than 3.0 gm/day and/or an opioid not exceeding the potency equivalent of 30 mg of orally-administered morphine were allowable as rescue medication for no more than 10 consecutive days.

3.4.1. Pharmacokinetics

Methods

Analytical methods

During clinical development, 2 validated ECLIA methods (on BioVeris and Meso Scale Discovery platform) were used to determine serum sirukumab concentrations. The ECLIA method on the BioVeris platform had a lowest quantifiable concentration of 0.07813 µg/ml, in a sample at a 1:2 dilution. The ECLIA method on the MSD platform had a lowest quantifiable concentration of 0.0977 µg/ml in a sample at a 1:10 dilution. The ECLIA methods were demonstrated to be comparable.

A total of 3 methods were used to detect the antibodies to sirukumab in human serum samples. Cross-validation compared the performance characteristics of the drug target-tolerant ELISA and the drug-tolerant ECLIA methods, the ECLIA method demonstrated slightly better sensitivity and superior drug tolerance than the ELISA method.

A validated competitive ligand binding ECLIA assay was used to detect NAbs to sirukumab in the phase 2 study and in all phase 3 RA studies.

Immunoassays used throughout the program were validated in accordance with the guideline on validation of bioanalytical methods and seems adequate for analysis of sirukumab and antibodies against sirukumab in serum. The ECLIA method developed is considered to have adequate drug-tolerance for the detection of the antibodies to sirukumab in the phase 3 studies.

Population PK analysis

The population PK analysis was performed using integrated data from 4 phase 3 studies (ARA3001, ARA3002, ARA3003 and ARA3005) of sirukumab in RA subjects receiving SC administration of sirukumab 50 mg q4w or 100 mg q2w. The observed concentration-time profiles of sirukumab from RA subjects were adequately described by a one-compartment linear population PK model with first-order absorption and first-order elimination with inter-individual variability on Ka, CL/F and V/F. Among the covariate factors examined, body weight was the primary covariate contributing to the observed PK variability of sirukumab where CL/F and V/F increased non-linearly with body weight with a power exponent of approximately 0.77. In addition, subjects with diabetic comorbidity tend to have higher CL/F and thus lower exposure (13%) after correcting for body weight effect. The effects of diabetic comorbidity and weight on sirukumab exposure may be additive.

All other covariates tested in the full covariate model including age, sex, race, laboratory measures (alkaline phosphatase [ALP], ALT, ALB and WBC), baseline disease characteristics (baseline CRP and IL-6, baseline DAS28 [CRP] score, disease duration [DDUR]), hypertension comorbidity, concurrent alcohol/smoke status, concomitant use of MTX, DMARDs other than MTX, NSAIDs or corticosteroid, study/population effect, and positive antibodies to sirukumab were not found to have significant effect on the exposure of sirukumab.

Absorption

Following sc administration sirukumab was slowly absorbed into the systemic circulation with a median Tmax of 3 to 5 days in healthy subject and RA patients.

The pharmacokinetics of sirukumab was comparable following a single SC administration of sirukumab by prefilled syringe-autoinjector (PFS-AI) or prefilled syringe-passive needle guard. The bioavailability after sc administration of PFS-AI and PFS-passive needle guard was not different and was in the range between 81 to 95%.

During all phase 3 studies the final formulations of sirukumab have been used.

Distribution

Following a single IV administration of 0.3 to 10.0 mg/kg sirukumab (C0136T01), the mean Vz ranged from 121 to 248 mL/kg (i.e., 0.12 to 0.25 L/kg) in healthy subjects. Following a single SC administration of 50 or 100 mg sirukumab in healthy subjects (NAP1001 and NAP1003), the mean Vz/F was estimated to be 154 to 155 mL/kg (i.e., 0.15 to 0.16 L/kg). Following multiple SC administration of sirukumab 25 to 100 mg q4w or 100 mg q2w in subjects with RA (C1377T04), the mean Vz/F ranged from 165 to 286 mL/kg (i.e., 0.17 to 0.29 L/kg).

Elimination

The half-life values after iv administration of sirukumab ranged from 19 to 32 days which is consistent with other IgG antibodies. The half-live after sc was ranged from 15 to 19 days. Mean systemic clearance (CL) was observed over a range of 3.8 to 6.1 ml/day/kg.

Sirukumab is an IgG antibody and as such no mass-balance study was performed. The elimination of sirukumab is expected to occur via degradation into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Dose proportionality and time dependency

Sirukumab exhibited linear PK over a dose range of 25 to 100 mg following single or multiple SC administrations to healthy subjects or subjects with RA (NAP1001, NAP1003, and C1377T04).

Mean accumulation ratios following SC administrations of sirukumab for Cmax and AUC were 1.5 to 1.8 for q4w dosing and 2.6 to 3.0 for q2w dosing. Across the Phase 2 and Phase 3 studies, following multiple dosing of sirukumab at 50 mg q4w and 100 mg q2w SC administration, trough serum sirukumab concentrations reached steady state by approximately Week 12. The trough serum concentrations were maintained at similar levels through Week 52.

Pharmacokinetics in target population

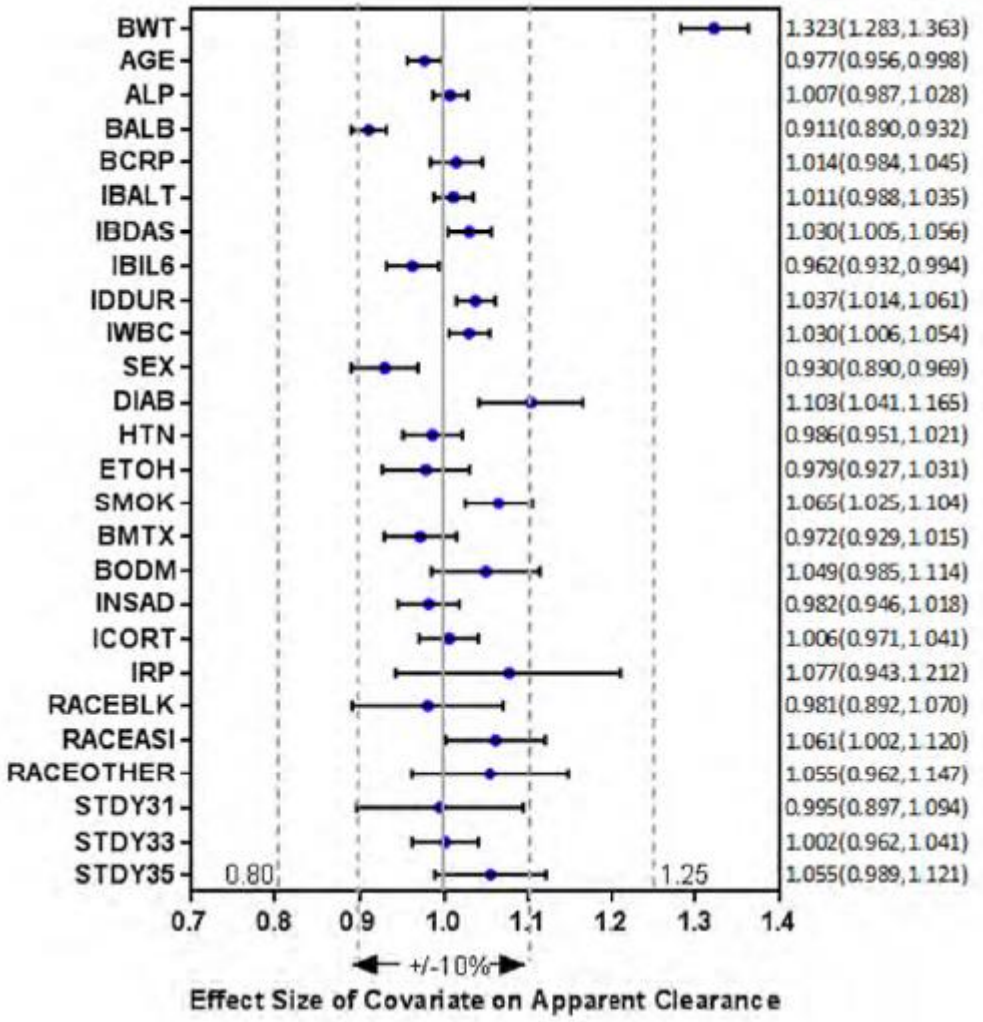
Apparent clearance and apparent volume of distribution appeared to be higher in RA patients, but the half life was estimated to be in the same range. This was confirmed by the population pharmacokinetic modeling performed on the data from the performed phase 3 studies.

The observed concentration-time profiles of sirukumab from RA subjects were adequately described by a one-compartment linear population PK model with first-order absorption and first-order elimination with inter-individual variability (IIV) on Ka, CL/F and V/F. The residual error was best described by a combined additive and proportional error model. No apparent systematic deviations or trends were noticed in any of the goodness-of-fit plots, including stratified Visual Prediction Checks (VPCs) (Figure 2), residual plots and the empirical Bayesian estimates (EBEs) of ETAs versus covariates plots. All parameters of the final PK model were reasonably well estimated with relative standard error (%RSE) less than 15%.

Special population

The effects of covariates on the clearance of sirukumab were investigated using a population pharmacokinetic approach, see Figure 1.

Figure 1 Effects of Covariates on Apparent Clearance From the Full Covariate Model



Effects of covariates were assessed using the stable full covariate model. For discrete covariates, the covariate effects were the parameter estimates for status of 'yes' relative to the reference of 'no'. For continuous covariates, the covariate effect was estimated as the ratio of E75/E25, where E25 and E75 were clearance values with covariate values at 25th percentile and 75th percentile of the population respectively.

Blue points represent model predictions and black line segments are the corresponding 95% confidence intervals. The associated values are shown on the right column. The gray vertical lines are the 80% to 125% bioequivalence intervals and the 90% to 110% significance interval.

Key: BWT= baseline body weight in kilograms; AGE= age; ALP= alkaline phosphatase; BALB= baseline albumin; BCRP= baseline C-reactive protein; IBALT= alanine aminotransferase; IBDAS= baseline disease activity index score 28 using CRP; IBIL6= baseline interleukin 6; IDDUR= disease duration; IWBC= white blood cell count; SEX= sex (female relative to male); DIAB= diabetic comorbidity; HTN= hypertension comorbidity; ETOH= alcohol use; SMOK= smoker; BMTX= baseline methotrexate use; BODM= baseline non-biologic disease modifying antirheumatic drugs (DMARD) other than MTX use; INSAD = baseline nonsteroidal anti-inflammatory drugs (NSAID) use; ICORT= baseline corticosteroids use; IRP= immune response positive; RACEBLK/RACEASI/RACEOTHER= race effects of Black, Asian or Other relative to White; STDY31/STDY33/STDY35= Study effect of CNTO136ARA3001, CNTO136ARA3003 or CNTO136ARA3005 relative to study CNTO136ARA3002

No formal studies were conducted in subjects with renal impairment. The estimated mean baseline levels of CRCL (an indicator of renal function) were 104 mL/min (range: 27.7 to 334 mL/min) for the RA subjects involved in the population PK analysis dataset. The majority of the subjects had normal renal function or mild renal impairment with very few subjects having moderate and severe renal impairment. There were 1367 (69%) subjects with CRCL ≥90 mL/min, 513 (26%) subjects with CRCL ≥

60 and <90 mL/min, 109 (5%) subjects with CRCL ≥30 and <60 mL/min and 2 (0.1%) subjects with CRCL <30 mL/min. The population PK analysis suggested that mild and moderate renal impairment (CRCL <90 mL/min and ≥30 mL/min based on Cockcroft-Gault) had no apparent effect on sirukumab CL/F after taking into account the effect of body weight.

No formal studies were conducted in subjects with hepatic impairment. The majority of the subjects involved in the population PK analysis had normal hepatic function; therefore, there is not enough information to sufficiently assess the effect of hepatic function on PK.

Gender, age, race and the presence of ADAs had no impact on sirukumab pharmacokinetics.

Body weight was a significant covariate identified for both CL/F and V/F of sirukumab. Among subjects with RA, the change in CL/F attributable to body weight ranged from −12.6% to +15.0% relative to the median CL/F estimate when body weight increased from the 25th percentile (58.7 kg) to the 75th percentile (84.0 kg); the change in V/F attributable to body weight ranged from −11.4% to +13.4% relative to the median V/F estimate when body weight increased from the 25th to the 75th percentile. The model-predicted median steady-state trough concentration and area under the curve during doing interval (AUC_{τ}) of sirukumab in RA subjects with a body weight ≥100 kg were about 37% and 34% lower than in subjects <100 kg, respectively, at 50 mg q4w and 100 mg q2w.

Diabetic comorbidity was a significant covariate identified for CL/F of sirukumab. Among subjects with RA, the change in CL/F attributable to diabetic comorbidity was 13% relative to the median CL/F. Simulation show that the trough concentration and AUC0-4w were decreased with almost 50% in patients with diabetes and body weight ≥100 kg, compared to patients without diabetes and body weight <100 kg.

Interactions

The potential effects of concomitant medications including MTX, DMARDs other than MTX, NSAIDs and corticosteroids on the PK of sirukumab were investigated through population PK analysis. Concomitant use of MTX was not identified as a significant covariate in the population PK analysis. Population PK analysis also indicated that concomitant use of DMARDs (other than MTX), NSAIDs and corticosteroids did not have an apparent impact on sirukumab CL/F.

The effects of sirukumab on the PK of CYP probe substrates midazolam (CYP3A4), omeprazole (CYP2C19), S-warfarin (CYP2C9), and caffeine (CYP1A2) in subjects with active RA was evaluated.

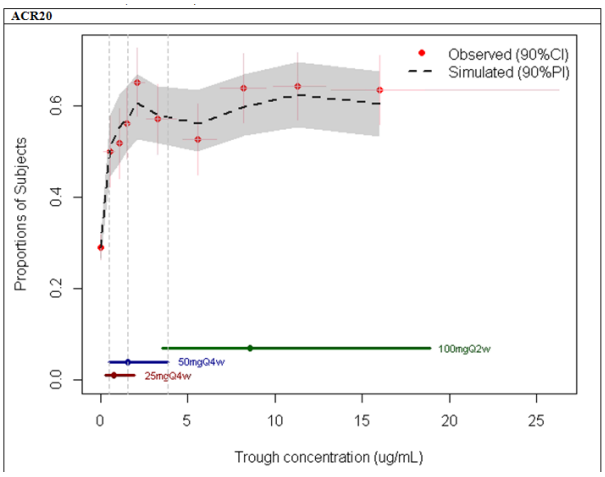
One week following a single SC administration of 300 mg sirukumab, AUC for midazolam, omeprazole, and S-warfarin were reduced by 30%, 45% and 18%, respectively, while caffeine AUCinf was increased by 20%. Similar results were also observed at 3 weeks and 6 weeks after sirukumab SC administration, which indicate the effect of sirukumab on CYP substrates was sustained for at least 6 weeks.

Exposure –Response

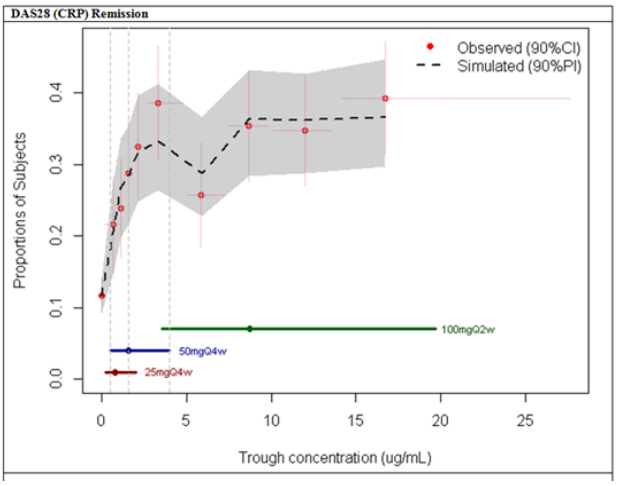
Two exposure-response modelling approaches were applied; Landmark analysis and Longitudinal analysis for ACR and DAS28 endpoints. The Landmark analysis investigates the exposure-response relationship at a fixed time point (Week 16 and Week 24 for ACR and DAS28, respectively) in contrast to the Longitudinal analysis where the exposure-response relationship over time is investigated. Both analyses methods describe data adequately and exposure-response relationships were detected for all investigated endpoints. It is evident from the analyses that higher exposure gives higher response and that the exposure given by the 50 mg q4w dose is not on the Emax part of the curves.

Figure 2 Observed versus predicted Week 16 ACR response (A) and Observed versus predicted week 24 DAS28 (CRP) (B) using through concentration as exposure metric (pooled data)

A)



B)



3.4.2. Pharmacodynamics

Sirukumab inhibits IL-6 mediated signalling by binding to IL-6 in contrast to the currently approved IL-6 inhibitor Tocilizumab which binds to the IL-6 receptors.

Across the clinical studies, the proportion of subjects that developed antibodies to sirukumab was low and included only a few percent of the subjects randomized in the trials.

A number of biomarkers were measured but, most importantly, the levels of the acute phase reactants CRP and ESR were studied at different time points. A pronounced CRP suppression was apparent already at Day 5 and ESR suppression was evident 2 weeks after the start of sirukumab treatment. The suppression appeared to be maintained as sirukumab treatment continued. The mean values of these two acute phase reactants following sirukumab treatments seemed to rather rapidly fall within, or close to, the normal range.

In subjects with RA who were anemic at baseline, decreases in levels of hepcidin associated with increases in hemoglobin levels were observed with sirukumab treatment compared with placebo.

In the initial application, the Applicant stated that the potency of sirukumab is 50-90 fold greater compared to tocilizumab, based on in-vitro assays. No head-to-head comparison with tocilizumab was made in this study, therefore the greater potency of sirukumab had not been confirmed. In contrast, in the non-clinical part a 6-22 fold more potency is reported. It was explained that the different estimates of the potency of sirukumab to reduce the expression of chemokine MCP-1 were actually due to variations of the functional assays that were used. Sirukumab was more potent to reduce IL-6 stimulated MCP-1 production than the registered product tocilizumab.

3.4.3. Discussion on clinical pharmacology

Sirukumab inhibits IL-6 mediated signalling by binding to IL-6 in contrast to the currently approved IL-6 inhibitor tocilizumab which binds to the IL-6 receptors. The pharmacokinetic and pharmacodynamical properties of sirukumab have been characterized in four Phase 1 studies, one Phase 2 study, and five Phase 3 RA studies.

Across the clinical studies, the proportion of subjects that developed antibodies to sirukumab was low and included only a few percent of the subjects randomized in the trials.

Levels of the acute phase reactants CRP and ESR were studied at different time points. A pronounced CRP suppression was apparent already at Day 5 and ESR suppression was evident 2 weeks after the start of sirukumab treatment. The suppression appeared to be maintained as sirukumab treatment continued. The mean values of these two acute phase reactants following sirukumab treatments seemed to rather rapidly fall within, or close to, the normal range.

Clinical pharmacokinetic properties of sirukumab were investigated to a limited extent, which is acceptable for a human IgG monoclonal antibody. Over the whole clinical pharmacology program, sirukumab displayed pharmacokinetic properties typical of a human IgG.

The population pharmacokinetic model plays a central role in the assessment of the pharmacokinetic properties of sirukumab.

The effects of different intrinsic factors on the sirukumab pharmacokinetics have been evaluated with adequate popPK analysis using phase III data.

No study was performed in renal and hepatic impaired subjects, this is acceptable considering that sirukumab is a large antibody and as such is not expected to be influenced.

Neither mass-balance nor in vitro studies has been performed. As sirukumab is an antibody this is acceptable. The elimination is expected to occur via degradation into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG but not metabolized by any CYP enzymes.

As sirukumab is a cytokine modulator the treatment may potentially reverse IL-6 modulation of CYP enzyme activities and possible also co-regulated transporter activities in patients with RA which could lead to altered metabolism and distribution of drugs that are CYP substrates. This was investigated using a cocktail approach with selective CYP probe substrates after one single sc dose of sirukumab. The data shows that sirukumab single dose SC administration of 300 mg decreased the activities of CYP3A4, CYP2C9, CYP2C19 and increased CYP1A2 activities. . The changes were maintained at least 6 weeks after a single dose of sirukumab. Although the changes are not large, especially narrow therapeutic drugs that are titrated may need to be adjusted during treatment of Plivensia.

Although some special populations, such as diabetic comorbidity and high body weight, display lower sirukumab exposure there was no clear indication that an increased exposure would lead to a higher response.

It is evident from the exposure-response analyses that higher exposure give higher response and that the exposure given by the 50 mg q4w dose is not on the Emax part of the curves. No subgroups that could benefit from a higher dose were identified, although it is still possible that individual patients could benefit from a higher dose.

3.4.4. Conclusions on clinical pharmacology

The clinical pharmacology package for sirukumab that inhibits IL-6 mediated signalling by binding to IL-6 has overall been adequately characterized. A pronounced effect on acute phase reactants is noted, with a distinct CRP suppression recorded already at Day 5.

In the initial application, the Applicant stated that the potency of sirukumab is 50-90 fold greater compared to tocilizumab, based on in-vitro assays. No head-to-head comparison with tocilizumab was made in this study, therefore the greater potency of sirukumab had not been confirmed. In contrast, in

the non-clinical part a 6-22 fold more potency is reported. The Applicant explained that the different estimates of the potency of sirukumab to reduce the expression of chemokine MCP-1 were actually due to variations of the functional assays that were used. Sirukumab was more potent to reduce IL-6 stimulated MCP-1 production than the registered product tocilizumab. The clinical relevance of these in-vitro outcomes is not clear, as there are no head-to-head comparative clinical trials available.

3.4.5. Clinical efficacy

Dose-response studies and main clinical studies

Six studies assessed efficacy within the clinical development program for sirukumab in RA. There were three pivotal phase 3 RCT: ARA3002, ARA3003, and ARA3005. A Japanese monotherapy study ARA3001 and the Phase 2 proof-of-concept and dose-finding study, C1377T04 provided supportive data. Finally, there is an on-going global long-term extension (LTE) of the ARA3002 and ARA3003 studies; ARA3004 for which no efficacy data are currently available.

For an overview of the study methodology, see Table 1 (*Overview of efficacy and safety studies in the clinical development program for sirukumab in RA*) above. For a summary of the main efficacy results in the three pivotal trials, see Table 2 (*Summary of main efficacy results in the three pivotal trials ARA3002, 3003 and 3005*) below.

For *details* on study methodology and results, see Clinical Assessment Report; however, the most important aspects are presented below.

Dose-response study C1377T04

C1377T04 included subjects with RA refractory to MTX. The study had 2 parts; Part A was the initial proof-of-concept portion and Part B the dose-finding portion. In Part A sirukumab 100 mg q2w (n=17) was compared against placebo (n=19). In Part B four different sirukumab dose groups; sirukumab 100 mg q2w (n=30), sirukumab 100 mg q4w (n=30), sirukumab 50 mg q4w (n=30) and sirukumab 25 mg q4w (n=31) were compared against placebo (n=30).

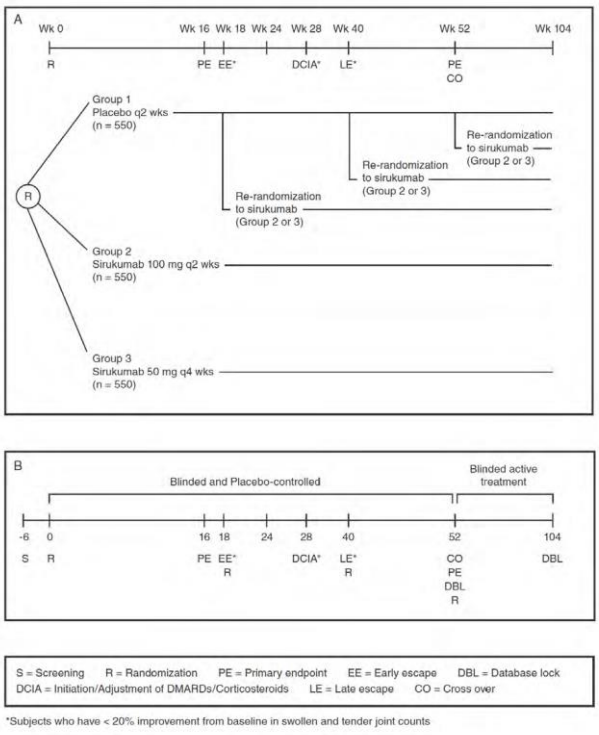
Main results C1377T04

In Part A, proof-of-concept (in terms of DAS28 (CRP), ACR 50 response and CRP suppression) was considered to be demonstrated for Sirukumab 100 mg q2w vs placebo. In Part B, the outcome for the primary efficacy outcome ACR 50 response at week 12 was 3.3% in the placebo group vs 26.7%, 23.3%, 26.7% and 19.4% in the sirukumab 100 mg q2w, 100 mg q4w, 50 mg q4w and 25 mg q4w respectively. Neither the effect as measured by the major secondary efficacy outcome, change in DAS28 (CRP) from baseline at week 12, was substantially different across dose groups. However, taking into account the outcome all efficacy analysis of this trial, it is noted that the best response was generally found in the highest dose group (100 mg q2w) while the most modest response was generally found in the lowest dose group (25 mg q4w).

Pivotal phase 3 study ARA3002

ARA3002 included subjects with active RA with at least one poor prognostic factor who were refractory to conventional first line treatment (see inclusion and exclusion criteria below). Sirukumab 100 mg q2w (n=557) and Sirukumab 50 mg q4w (n=557) were compared against placebo (n=556). The study included 18 weeks that were pure placebo-controlled. From week 18 onwards, there were two opportunities for placebo non-responders, i.e., subjects that had <20% improvement from baseline in both swollen and tender joint counts, to escape to sirukumab. In total, the placebo controlled period lasted 52 weeks.

Figure 3 Overview of study design ARA3002



Main inclusion criteria ARA3002: ≥18 years, active RA with at least 6 tender joints and 6 swollen joints, refractory to single-agent or combination DMARD therapy that included MTX or SSZ due to lack of benefit after at least 12 weeks of DMARD, CRP ≥8.00 mg/L and meet 1 of the following 3 criteria: (a) CCP antibody-positive at screening, (b) RF-positive at screening (c) Radiographic evidence of erosive RA in hands or feet.

Main exclusion criteria ARA3002:

- Intolerance to at least 2 or inadequate response to at least 1 anti-TNFαagent
- Exclusion criteria pertaining to certain concomitant medications (including other biologics) within pre-specified time ranges
- Abnormal laboratory test results (regarding Hb, WBC, neutrophils, platelets, liver tests, serum creatinine) with in pre-specified ranges
- Current signs or symptoms of severe, progressive, or uncontrolled active inflammatory arthritis other than RA, renal, hepatic, dermatologic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, or neurologic disease
- Hospitalization for a cardiovascular event (myocardial infarction, unstable angina, stroke, TIA within 3 months prior to the first administration of study agent
- Marked baseline prolongation of the QTc interval ≥ 450 msec, a history of risk factors for Torsade de Pointes or a history of second- or third-degree heart block
- History of severe infection within 2 months, chronic or ongoing/recurrent infectious
- History of known demyelinating diseases or gastrointestinal perforation, currently active diverticulitis

- Known malignancy or has a history of malignancy within the previous 5 years (with the exception of a non-melanoma skin cancer that has been treated with no evidence of recurrence for at least 3 months before the first study agent administration or cervical neoplasia that has been surgically cured)
- Received, or is expected to receive, any live virus or bacterial vaccination within 3 months before the first administration of study agent, during the study, or within 4 months after the last administration of study agent, have had a BCG vaccination within 12 months

Main efficacy results ARA3002:

The proportion of ACR 20 response rate at week 16, co-primary endpoint 1, was 54.8% in the Sirukumab 50 mg group and 53.5% in the Sirukumab 100 mg group compared to 26.4% in the placebo group ($p<0.001$ for both comparisons, difference between groups [95% CI] for Sirukumab 50 mg vs placebo 0.283 [0.228 to 0.338] and for Sirukumab 100 mg vs placebo 0.271 [0.216 to 0.326]). Also in the small subgroups not using any DMARD at baseline, the odds for a subject to achieve an ACR 20 response at Week 16 was higher in both sirukumab groups relative to the placebo group.

The mean change (SD) from Baseline in vdH-S Score, co-primary endpoint 2, was 0.50 (2.961) in the Sirukumab 50 mg group, 0.46 (3.258) in the Sirukumab 100 mg group and 3.69 (9.245) in the placebo group ($p<0.001$ both comparisons). Also in the subgroup of subjects not receiving DMARDs, the median change from baseline in vdH-S was lower in subjects treated with sirukumab 50 mg or 100 mg compared with placebo. The median difference (95% CI) for comparing change from baseline in vdH-S Score at Week 52 in the Sirukumab 50 mg q4w group versus the placebo group, for patients not taking DMARD at baseline, was 0.50 (0.0-2.8). The median difference (95% CI) for comparing change from baseline in vdH-S Score at Week 52 in the Sirukumab 100 mg q2w group versus the placebo group, for patients not taking DMARD at baseline, was 1.18 (0.0-3.0).

For all 4 major secondary endpoints; change in HAQ-DI score, ACR 50 response, DAS 28 (CRP) remission at week 24 and major clinical response at week 52, a statistical difference vs placebo was demonstrated for both sirukumab doses. Finally, mean change at week 16 from baseline in CDAI, which is a CRP-independent outcome, was numerically larger in the two Sirukumab groups compared to placebo.

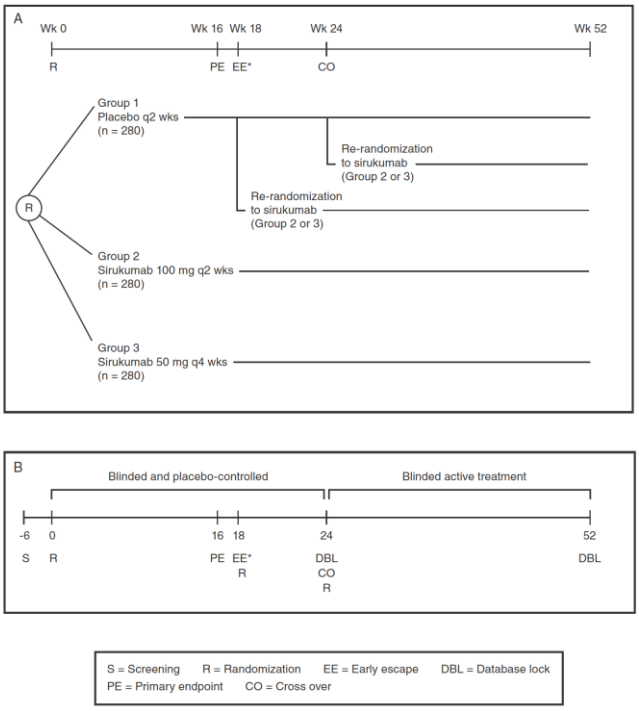
Mean (SD) change from baseline in CRP at week 16 was -0.4890 (3.17554) in the placebo group compared to -2.2841 (2.43707) in Sirukumab 50 mg group and -2.3166 (2.65115) in the Sirukumab 100 mg group ($p <0.001$ for both comparisons). At week 16, also the mean percent improvements from baseline for the other individual ACR components (mean number of swollen joints, number of tender joints, patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, HAQ-DI score) were numerically higher in both sirukumab groups compared to placebo with no large differences between the two dose groups of sirukumab.

Overall, no large differences with regards to efficacy were noted between the two sirukumab doses studied in ARA3002 for the primary or the major secondary endpoints.

Pivotal phase 3 study ARA3003

ARA3003 included subjects with moderately to severely active RA who were refractory or intolerant to anti-TNF agents (see inclusion and exclusion criteria below). Sirukumab 100 mg q2w (n=292) and Sirukumab 50 mg q4w (n=292) were compared against placebo (n=294). The study included 18 weeks that were pure placebo-controlled. At week 18, placebo subjects that had <20% improvement from baseline in both swollen and tender joint counts escaped to sirukumab. There were no escape possibilities for patients initially randomized to sirukumab. Week 24-52, all subjects were treated with sirukumab.

Figure 4 Overview study design ARA3003



Main inclusion criteria ARA3003: ≥18 years, active RA with at least 4 of 68 tender joints and 4 of 66 swollen joints, refractory to treatment with 1 or more anti-TNF agents or intolerant to 2 or more anti-TNF agents, CRP ≥8.00 mg/L or ESR ≥28 mm/hr, and meet 1 of the following 3 criteria: (a) CCP - positive (b) RF-positive or (c) Radiographic evidence of erosive RA in hands or feet.

Main exclusion criteria ARA3003: see study ARA3002, the exclusion criteria were essentially the same for the two studies except for "Intolerance to at least 2 or inadequate response to at least 1 anti-TNFαagent" which was not an exclusion criterion in ARA3003.

Main efficacy results ARA3003:

The primary endpoint ACR 20 response at week 16 was achieved by a greater proportion of subjects in both the sirukumab 50 mg q4w (40.1%) and sirukumab 100 mg q2w (45.2%) groups compared with the placebo group (24.1%, both p<0.001). Regarding the subgroup analysis based on baseline DMARD; there were only 7 subjects in the placebo group, 15 in the Sirukumab 50 mg group and 22 in the Sirukumab 100 mg group that did not take a DMARD at baseline and achieved an ACR 20 response. Accordingly, OR was >1 for both subgroups for both sirukumab doses, but the confidence

interval of the OR for the Sirukumab 50 mg dose for the subgroup not taking DMARDs at baseline, includes 1.

Mean improvement in HAQ-DI score from baseline at Week 24 (major secondary endpoint) was 0.31 in the sirukumab 50 mg q4w group and 0.33 in the sirukumab 100 mg q2w group vs 0.12 in the placebo group (both p<0.001). ACR 50 response at Week 24 (major secondary endpoint) was 20.9% in the sirukumab 50 mg q4w and 21.6% in the sirukumab 100 mg q2w groups compared to 8.8% in the placebo group (both p<0.001). Proportion of subjects in DAS28 (CRP) remission at Week 24 (major secondary endpoint) was 19.2% in the sirukumab 50 mg q4w and 21.6% in the sirukumab 100 mg q2w groups compared to 8.2% in the placebo group (both p<0.001).

Change from baseline in CRP (mg/dl) at week 16 was -0.08 (2.277) in the placebo group compared to -1.89 (2.302) in the sirukumab 50 mg group and -2.08 (2.423) in the sirukumab 100 mg group. The mean percent improvement from baseline for the other individual (non-CRP) ACR components (mean number of swollen joints, number of tender joints, patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, HAQ-DI score) were generally numerically higher in both sirukumab groups even though the difference between placebo and active treatment were not as pronounced for these outcomes as for CRP. Generally, a greater improvement was seen for the Sirukumab 100 mg q2w compared to the Sirukumab 50 mg q4w dose. The difference between the dose groups was most apparent for the swollen joint count for which the mean percent difference from baseline was 43% for the sirukumab 100 mg q2w dose and 30% for the sirukumab 50 mg q4w dose vs 28% for placebo.

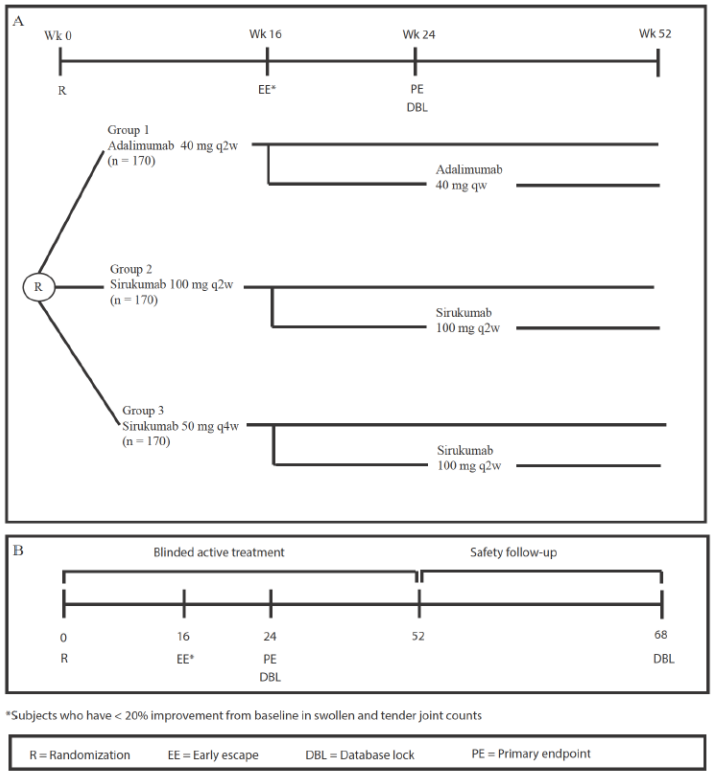
Mean change from baseline in CDAI at week 16 was larger in the two Sirukumab groups compared to placebo.

Overall it is noted that there was no clear difference in terms of efficacy between the sirukumab 50 mg q4w and 100 mg q2w dosing regimens in study ARA3003. For some endpoints, there was a numerically better clinical response for the sirukumab 100 mg q2w dose group than the 50 mg q4w group but this finding was not consistent throughout the endpoints.

Pivotal phase 3 study ARA3005

ARA3005 included biologically naïve patients with active RA for whom their physicians have judged that MTX therapy would not be of benefit (see inclusion and exclusion criteria below). Randomization was stratified by two groups based on the reason for which subjects failed MTX: either for efficacy alone or for any safety/tolerability reason. Sirukumab 100 mg q2w (n=187) and Sirukumab 50 mg q4w (n=186) as monotherapy were compared against an active comparator, the TNF-blocker adalimumab as monotherapy (n=186). At Week 16, subjects in all treatment groups who had <20% improvement from baseline in both swollen and tender joint counts qualified for early escape; subjects receiving adalimumab 40 mg q2w would change to every week (q1w) dosing, subjects on sirukumab 50 mg q4w would change to 100 mg q2w dosing, while subjects on sirukumab 100 mg q2w would remain on their randomized dose at EE. This study was still ongoing at the date of submission.

Figure 5 Overview study design ARA3005



Main inclusion criteria 3005: 18 years, active RA with at least 8 of 68 tender joints and 6 of 66 swollen joints, CRP ≥10.00 mg/L or ESR ≥28mm/hr at screening, intolerant to MTX, and/or inappropriate for treatment with MTX (including MTX-naïve subjects for whom it is inappropriate to administer MTX), and/or inadequate responders to MTX.

Main exclusion criteria ARA3005: see study ARA3002, the exclusion criteria were very similar for the two studies except for prior biologic DMARD use, which was an exclusion criterion in ARA3005, whereas in ARA3002, "Intolerance to at least 2 or inadequate response to at least 1 anti-TNFα agent" was an exclusion criterion.

Main efficacy results ARA3005:

For the co-primary efficacy endpoint 1, mean change from baseline in DAS 28 (ESR) at week 24, both treatment arms of sirukumab monotherapy were considered superior to the comparator adalimumab monotherapy. Mean change (SD) in DAS28 (ESR) at week 24 was -2.19 (1.437) in the adalimumab arm and -2.58 (1.524) and -2.96 (1.580) in the sirukumab 50 mg q4w and sirukumab 100 mg q2w respectively ($p<0.001$ for the 100mg q2w comparison, $p=0.013$ for the 50mg q4w comparison). In the stratum of subjects who failed MTX at baseline for safety reasons (i.e., the population that the current monotherapy claim includes), mean (SD) change from baseline in DAS28 (ESR) at week 24 was -2.84 (1.521) in the Sirukumab 50 mg q4w group and -2.89 (1.557) in the Sirukumab 100 mg q2w compared to -2.20 (1.564) in the adalimumab group. For the co-primary endpoint 2, ACR 50 Response at Week 24, sirukumab was not demonstrated to be superior to the comparator adalimumab. The proportion of responders in the adalimumab arm was 31.7% vs 26.9% in the sirukumab 50 mg q4w (% difference from the comparator with 95% CI=-4.8 [-14.1; 4.4]) and 35.3% in the sirukumab 100

mg q2w (% difference from the comparator with 95% CI=3.6 [-6.0; 13.1]). The results in the stratum that failed MTX due to safety reasons were consistent with the result in the overall population.

In the whole study population, proportion of subject that achieved DAS 28 (ESR) remission at week 24 (major secondary endpoint) was 7.5% in the comparator arm, 12.9% in the sirukumab 50 mg q4w arm and 20.3% in the sirukumab 100 mg q2w arm (nominal p=0.086 and p<0.001 respectively). In the stratum that failed MTX for safety reasons, the proportion of subject that achieved DAS 28 (ESR) remission at week 24 was 7.5% in the comparator arm, 20.0% in the sirukumab 50 mg q4w arm and 23.8% in the sirukumab 100 mg q2w arm (no p-value from hypothesis testing provided). For ACR 20 response at week 24 (major secondary endpoint) sirukumab was not demonstrated to be superior to the comparator adalimumab.

Mean change from baseline in HAQ-DI at week 16 was for the whole population -0.4397 for Sirukumab 50 mg q4w and -0.4550 for Sirukumab 100 mg q2w (LS Mean Difference [95% CI] Sirukumab 50 mg q4w vs the comparator 0.06 (-0.06; 0.18) and LS Mean Difference [95% CI] Sirukumab 100 mg 2qw vs the comparator -0.00 [-0.12; 0.11]).

Proportion of subjects who achieved DAS28 (ESR) Low Disease Activity was numerically higher in the sirukumab groups compared to the comparator both at week 16 (i.e. before subjects were given the early escape possibilities) and at week 24. At week 16, the proportion of subjects with Low Disease Activity was 16.1% in the comparator group vs 24.7% (% Difference [95% CI] = 8.6 [0.5; 16.7]) in the sirukumab 50 mg q4w group and 34.2% (% Difference [95% CI] = 18.1 [9.5; 26.7]) in the sirukumab 100 mg q2w group.

Mean CRP reductions at Week 24 were -0.85 mg/dL for adalimumab 40 mg q2w, -1.78 mg/dL for sirukumab 50 mg q4w (nominal p-value 0.001) and -1.72 mg/dL for sirukumab 100 mg q2w (nominal p-value 0.003). Mean reduction in ESR at week 24 was -13.7 for adalimumab 40 mg q2w, -34.1 for sirukumab 50 mg q4w and -34.7 for sirukumab 100 mg q2w (nominal p<0.001 for both analyses). When examining the mean percent change from baseline in the other individual (non-CRP) ACR components at week 24, the numerically lowest percent change was consistently found in the sirukumab 50 mg q4w except for change in CRP, for which the percent change was numerically lowest in the comparator group.

Mean change from baseline in CDAI at week 16 was -21.80 for Sirukumab 50 mg q4w (LS Mean Difference [95% CI] Sirukumab 50 mg q4w vs the comparator 2.13 [-0.91; 5.17] and -25.51 for Sirukumab 100 mg q2w (LS Mean Difference [95% CI] Sirukumab 100 mg q2w vs the comparator -1.58 [-4.62; 1.46]).

As monotherapy, there were numerical differences for several endpoints that favoured sirukumab 100 mg q2w over sirukumab 50 mg q4w.

Supporting phase 3 study ARA3001

ARA3001 included subjects with moderately to severely active RA, refractory to MTX or SSZ. The study had a safety focus (see section Clinical Safety). With this study, the requirement from the Japanese authorities of at least 100 Japanese subjects being exposed to the recommended doses of sirukumab, for a minimum of 1 year were to be met. Two different dose regimens of sirukumab in monotherapy: Sirukumab 100 mg q2w (n=61) and Sirukumab 50 mg q4w (n=61) were to be compared without placebo or active comparator as a control.

Main efficacy results ARA3001: ACR response rates as well as the proportion of subjects in DAS 28 remission were generally higher in this monotherapy study than in the other phase 3 studies included

in this application. The proportion of subjects that achieved DAS28 remission was higher in the sirukumab 100 mg q2w group than in the sirukumab 50 mg q4w group.

Summary of main efficacy results table

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

Table 2 Summary of main efficacy results in the three pivotal trials

Title: ARA3002			
Study identifier	EudraCT Number: 2010-022242-24		
Design	RCT		
	Duration of main phase:		120 weeks, including a blinded treatment phase of approximately 2 years (i.e., a placebo-controlled period from Week 0 to Week 52 and an active-controlled period from Week 52 to Week 104)
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		Unless subjects elected to enter the long-term extension study, there was a safety follow-up phase of 16 weeks after the last administration of study agent
Hypothesis	Superiority		
Treatments groups	Sirukumab 50 mg q4w		n=557
	Sirukumab 100 mg q2w		n=557
	Placebo		n=556
Endpoints and definitions	Co-Primary endpoint 1	ACR 20 Response week 16	
	Co-Primary endpoint 2	Change from baseline in vdH-S score week 52	
Database lock	12 November 2015 (Week 52 database lock)		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population	The non-radiographic efficacy endpoints were analyzed based on the efficacy full analysis set which included all subjects who were randomized i.e. ITT population. In total of 1,670 subjects (placebo [n=556], sirukumab 50 mg q4w [n=557], and sirukumab 100 mg q2w [n=557]) were included in the efficacy full analyses, The radiographic efficacy endpoints were analyzed based on the efficacy full analysis set for radiographic assessment which included all randomized subjects who received at least 1 (partial or complete) dose of study agent and who had non-missing baseline vdH-S score. The efficacy full analysis set for radiographic assessment included 1,654 subjects (placebo [n=550], sirukumab 50 mg q4w [n=553], and sirukumab 100 mg q2w [n=551])			
Descriptive statistics and estimate variability	Treatment group	Sirukumab 50 mg q4w	Sirukumab 100 mg q2w	Placebo
	ACR 20 Response at week 16 (%)[a]	54.8%	53.5%	26.4%
	95% CI	***50.7%, 58.9%***	***49.4%, 57.6%***	***22.7%, 30.1%***
	Change from baseline in vdH-S score week 52 (mean)[d]	0.50	0.46	3.69
	SD	2.961	3.258	9.245

Effect estimate per comparison	ACR 20 Response at week 16 (%)	Comparison groups	Sirukumab 50 mg q4w vs placebo	Sirukumab 100 mg 2qw vs placebo
		Difference between groups	0.283	0.271
		95% CI[b] difference	0.228 to 0.338	0.216 to 0.326
		P-value[c]	<0.001	<0.001
	Change from baseline in vdH-S score week 52 (mean)	Comparison groups	Sirukumab 50 mg q4w vs placebo	Sirukumab 100 mg 2qw vs placebo
		Difference between groups	**-3.19**	**-3.23**
		95% CI for difference	***-4.03, -2.41***	***-4.08, -2.44***
		P-value[e]	<0.001	<0.001

Title: ARA3003	
Study identifier	EudraCT Number: 2010-022243-38
Design	RCT

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks, including a blinded treatment phase of 1 year (i.e., 52 weeks) and a placebo controlled period from Week 0 to Week 24 Not applicable Unless subjects elected to enter the long-term extension study, there was a safety follow-up phase of 16 weeks after the last administration of study agent		
Hypothesis	Superiority				
Treatments groups	Sirukumab 50 mg q4w		n=292		
	Sirukumab 100 mg q2w		n=292		
	Placebo		n=294		
Endpoints and definitions	Primary endpoint	ACR 20 Response week 16			
Database lock	05 February 2016 (Week 52 database lock)				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population	The efficacy analyses for the placebo-controlled period were based on the Efficacy Analysis Set which includes all randomized subjects The efficacy full analysis set included 878 subjects (placebo [n=294], sirukumab 50 mg q4w [n=292], and sirukumab 100 mg q2w [n=292])				
Descriptive statistics and estimate variability	Treatment group	Sirukumab 50 mg q4w	Sirukumab 100 mg q2w	Placebo	
	ACR 20 Response at week 16 (%)[f]	40.1%	45.2%	24.1%	
	95% CI	***34.5%, 45.7%***	***39.5%, 50.9%***	***19.2%, 29.0%***	
Effect estimate per comparison	ACR 20 Response at week 16 (%)	Comparison groups	Sirukumab 50 mg q4w vs placebo	Sirukumab 100 mg 2qw vs placebo	
		Difference between groups	0.159	0.210	
		95% CI[g] Difference	0.085 to 0.232	0.136 to 0.285	
		P-value[h]	<0.001	<0.001	
Title: ARA3005					
Study identifier	EudraCT NUMBER: 2013-001417-32				
Design	RCT, active control				
	Duration of main phase:	Duration of the study is 68 weeks which includes 52 weeks of treatment with study agent			

	Duration of Run-in phase: Duration of Extension phase:		Not applicable There was a 16 weeks of safety follow-up after the last study agent administration
Hypothesis	Superiority		
Treatments groups	Sirukumab 50 mg q4w		n=186
	Sirukumab 100 mg q2w		n=187
	Adalimumab		n=186
Endpoints and definitions	Primary endpoint 1	Change from baseline in DAS28 (ESR) at week 24	
	Primary endpoint 2	ACR 50 response at Week 24	
Database lock	***12 November 2015***		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population	The efficacy full analysis set included all randomized subjects who received at least 1 (partial or complete) dose of study agent, i.e., the modified Intent-to-Treat (mITT) population A total of 559 subjects (adalimumab 40 mg q2w [n=186], sirukumab 50 mg q4w [n=186], and sirukumab 100 mg q2w [n=187]) were included in the efficacy analyses			
Descriptive statistics and estimate variability	Treatment group	Sirukumab 50 mg q4w	Sirukumab 100 mg q2w	Adalimumab
	Change from baseline in DAS28 (ESR) at week 24 (mean)[i]	-2.58	-2.96	-2.19
	SD	1.524	1.580	1.437
	ACR 50 response at Week 24[k]	26.9%	35.3%	31.7%
	95% CI	***20.5%, 33.3%***	***28.5%, 42.2%***	***25.0%, 38.4%***

Effect estimate per comparison	Change from baseline in DAS28 (ESR) at week 24 (mean	Comparison groups	Sirukumab 50 mg q4w vs adalimumab	Sirukumab 100 mg q2w vs adalimumab
		LS Mean Difference between groups	- 0.39	-0.76

		95% CI[j] LS Mean Difference	-0.69 to -0.08	-1.07 to -0.46
		P-value[j]	0.013	<0.001
	ACR 50 response at Week 24	Comparison groups	Sirukumab 50 mg q4w vs adalimumab	Sirukumab 100 mg q2w vs adalimumab
		% Difference between groups	-4.8	3.6
		95% CI[l] for % Difference	-14.1 to 4.4	-6.0 to 13.1
		P-value[m]	0.306	0.464

[a] The ACR response was based on imputed value by Missing Data (NR)/TF(NR), [b] The confidence intervals were based on Wald statistic, [c] The p-values were based on CMH test, [d] The vdH-S score was based on imputed value by EE Rules and then Missing Data Rules,[e] The p-values were based on van der waerden ANOVA,[f] The ACR20 response is based on imputed values (non-responder) after TF and imputed values (non-responder) for missing data, [g] The confidence intervals are based on the Wald statistic, [h] The p-values are based on the CMH test, [i] Subjects with missing DAS28 (ESR) at baseline were excluded from the analysis; For subjects with DAS28 (ESR) not missing at baseline but missing at Week 24, change from baseline was set to 0, that is, imputed as no change from baseline at Week 24, [j] The confidence intervals and p-values were based on ANCOVA,[k] The ACR response was based on imputed value by Missing Data(NR)/TF(NR)/EE(NR), [l] The confidence intervals were based on Wald statistic, [m] The p-values were based on CMH test.

Clinical studies in special populations

The three pivotal studies included subgroup analysis according to age. The main findings of these subgroup analyses are discussed in section 3.4.6 (for details see clinical AR).

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

The applicant performed integrated analyses of results from ARA3002 and ARA3003. The integrated data analysis from ARA3002 and 3003 demonstrate that approximately half of the sirukumab treated patients that had previously failed first and second line treatment respectively, achieved ACR 20 Response at week 16 while 1/4 achieve DAS 28 remission at week 24.

The applicant also performed post hoc analysis of the efficacy of sirukumab as monotherapy in ARA3002 and ARA3003. The outcomes of these analyses were summarized together with data from the pre-specified monotherapy subgroup analysis of the primary endpoints in ARA3002 and ARA3003 to support the proposed monotherapy wording (see further discussion in section 3.4.6 and 5.7.3)

Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development program for sirukumab in RA included the three RCTs ARA3002, ARA3003, and ARA3005. A Japanese monotherapy study ARA3001 and the Phase 2 proof-of-concept and dose-finding study, C1377T04, provided supportive data.

C1377T04 included subjects with RA refractory to MTX. The study had 2 parts; Part A was the initial proof-of-concept portion and Part B the dose-finding portion. In Part A sirukumab 100 mg q2w (n=17) was compared against placebo (n=19). In Part B four different sirukumab dose groups; sirukumab 100 mg q2w (n=30), sirukumab 100 mg q4w (n=30), sirukumab 50 mg q4w (n=30) and sirukumab 25 mg q4w (n=31) were compared against placebo (n=30). The design and conduct of this study were overall acceptable.

ARA3002 included subjects with active RA with at least one poor prognostic factor who were refractory to conventional first line treatment. Sirukumab 100 mg q2w (n=557) and Sirukumab 50 mg q4w (n=557) were compared against placebo (n=556). The study included 18 weeks that were pure placebo-controlled. After week 18 there were two opportunities for placebo non-responders i.e. subjects that had <20% improvement from baseline in both swollen and tender joint counts, to escape to sirukumab. In total, the placebo controlled period lasted 52 weeks.

ARA3003 included subjects with moderately to severely active RA who were refractory or intolerant to anti-TNF agents. Sirukumab 100 mg q2w (n=292) and Sirukumab 50 mg q4w (n=292) were compared against placebo (n=294). The study included 18 weeks that were pure placebo-controlled. At week 18, placebo subjects that had <20% improvement from baseline in both swollen and tender joint counts escaped to sirukumab. There were no escape possibilities for patients initially randomized to sirukumab. Week 24-52, all subjects were treated with sirukumab.

The assessment of the endpoints evaluated beyond week 18 is somewhat complicated by the study design with early escape only in the placebo arm. For the primary endpoint, this is not a concern since it was evaluated before week 18 but for the secondary endpoints it is. However, the primary analyses for the secondary endpoints all exclude data post early escape for patients in all treatment groups imputing failure for binary variables and using LOCF for continuous variables and this is endorsed.

ARA3005 included biologically naïve patients with active RA for whom their physicians have judged that MTX therapy would not be of benefit. Randomization was stratified by two groups based on the reason for which subjects failed MTX: either for efficacy alone or for any safety/tolerability reason. Sirukumab 100 mg q2w (n=187) and Sirukumab 50 mg q4w (n=186) as monotherapy were compared against an active comparator, the TNF-blocker adalimumab as monotherapy (n=186). Study agent was administered during 52 weeks. As stated in EMA *"Points to consider on clinical investigation of medical products other than NSAIDs for the treatment of rheumatoid arthritis"*, comparative studies against an established comparator should be undertaken. The choice of adalimumab is adequate given the target population and indication that is aimed for. It is noted that the currently approved monotherapy indication for adalimumab as well as the proposed SmPC 4.1-wording for Plivensia, essentially only covers the randomized subjects that did not take MTX because of safety issues. The population of MTX inadequate responders is not covered by the two 4.1-wordings. However, randomization was stratified by the two reasons for MTX failure, the subjects that did not take MTX for safety issues constituted almost half of the study population and the primary endpoints were analysed according to stratum. Thus, the study is likely to yield information specific to the group of patients that failed MTX for safety/tolerability issues (i.e. were treated according to the approved comparator indication and the proposed Plivensia indication respectively).

At Week 16, subjects in all treatment groups who had <20% improvement from baseline in both swollen and tender joint counts qualified for early escape; subjects receiving adalimumab 40 mg q2w would change to every week (q1w) dosing, subjects on sirukumab 50 mg q4w would change to 100 mg q2w dosing, while subjects on sirukumab 100 mg q2w would remain on their randomized dose. For the adalimumab group, this is in accordance with the SmPC, however, for the sirukumab group this was not according to the ***initially proposed*** SmPC. Hence, a sensitivity analysis allowing for this dose increase in the adalimumab group but not in the sirukumab group for the primary endpoints was requested (for information on the outcome of this analysis, see below).

ARA3001 included Japanese subjects with moderately to severely active RA, refractory to MTX or SSZ. The study had a safety focus (see section Clinical Safety). With this study, the requirement from the Japanese authorities of at least 100 Japanese subjects being exposed to the recommended doses of sirukumab, for a minimum of 1 year were to be met. Two different dose regimens of sirukumab in

monotherapy: Sirukumab 100 mg q2w (n=61) and Sirukumab 50 mg q4w (n=61) were to be compared without placebo or active comparator as a control. Given that this study only included subject that had discontinued MTX or SSZ for efficacy reason, it does not fully appear to support the current Plivensia 4.1-wording which does only include monotherapy for safety reasons.

Efficacy data in the phase 2 and phase 3 studies

In **C1377T04,** in Part A, a relevant effect in terms of DAS28 (CRP), ACR 50 response and CRP suppression was demonstrated for Sirukumab 100 mg q2w compared to placebo even though the small number of subjects affects the p-values for the analysis. Thus, it is agreed that proof-of-concept was shown.

In Part B of the study, the outcome for the primary efficacy outcome ACR 50 response at week 12 was 3.3% in the placebo group vs 26.7%, 23.3%, 26.7% and 19.4% in the sirukumab 100 mg 2q, 100 mg q4, 50 mg q4 and 25 mg q4 groups, respectively. The magnitude of effect appeared to be rather similar across the dose groups. Neither the effect as measured by the major secondary efficacy outcome, change in DAS28 (CRP) from baseline at week 12, was substantially different across dose groups. However, taking into account the outcome all efficacy analysis of this trial, it is noted that the best response was generally found in the highest dose group (100 mg q2w) while the most modest response was generally found in the lowest dose group (25 mg q4w). This could be interpreted as at least a slight tendency for a dose response and it could also be questioned whether the plateau in such dose response has been reached i.e. whether an even higher dose would confer incremental benefit to patients. This finding, together with pharmacokinetic data (see separate section) and some of the efficacy data from the phase 3 studies, lead to a question on whether the posology that is currently proposed by the applicant needs revision in order to allow dose escalation (see also discussion below). ***In the response to the second LoQ, the applicant has now revised the posology so that for those patients being treated with Plivensia 50 mg every 4 weeks monotherapy who are not responding adequately by weeks 12 to 16 (after 3 to 4 doses), the dosage of Plivensia can be escalated to 100 mg every two weeks monotherapy.***

In **ARA3002**, the proportion of ACR 20 responders at week 16 was one of the co-primary endpoints. The proportion of ACR 20 response rate was 54.8% in the Sirukumab 50 mg group and 53.5% in the Sirukumab 100 mg group compared to 26.4% in the placebo group ($p<0.001$ for both comparisons. The difference between groups [95% CI] was 0.283 [0.228 to 0.338] for Sirukumab 50 mg vs placebo and 0.271 [0.216 to 0.326] for Sirukumab 100 mg vs placebo. Also in the small subgroups not using any DMARD at baseline, the odds for a subject to achieve an ACR 20 response at Week 16 was higher in both sirukumab groups relative to the placebo group. The magnitude of effect for this endpoint overall appeared comparable to data presented for the already approved IL-6 inhibitor tocilizumab.

The other co-primary endpoint was mean change (SD) from Baseline in vdH-S Score at Week 52. The mean change (SD) from Baseline in vdH-S Score was 0.50 (2.961) in the Sirukumab 50 mg group, 0.46 (3.258) in the Sirukumab 100 mg group and 3.69 (9.245) in the placebo group ($p<0.001$ both comparisons). Also in the subgroup of subjects not receiving DMARDs, the median change from baseline in vdH-S was lower in subjects treated with sirukumab 50 mg or 100 mg compared with placebo. The median difference (95% CI) for comparing change from baseline in vdH-S Score at Week 52 in the Sirukumab 50 mg q4w group versus the placebo group, for patients not taking DMARD at baseline, was 0.50 (0.0-2.8). The median difference (95% CI) for comparing change from baseline in vdH-S Score at Week 52 in the Sirukumab 100 mg q2w group versus the placebo group, for patients not taking DMARD at baseline, was 1.18 (0.0-3.0).

Initially, there were some concerns regarding imputation in study ARA3002. These concerns have now been satisfactory addressed by the applicant.

For all 4 major secondary endpoints a statistical difference vs placebo was demonstrated for both sirukumab doses. The major secondary endpoints were: change in HAQ-DI score, ACR 50 response, DAS 28 (CRP) remission at week 24 and major clinical response at week 52.

Mean (SD) change from baseline in CRP at week 16 was -0.4890 (3.17554) in the placebo group compared to -2.2841 (2.43707) in Sirukumab 50 mg group and -2.3166 (2.65115) in the Sirukumab 100 mg group ($p < 0.001$ for both comparisons). At week 16, also the mean percent improvements from baseline for the other individual ACR components (mean number of swollen joints, number of tender joints, patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, HAQ-DI score) were numerically higher in both sirukumab groups compared to placebo with no large differences between the two dose groups of sirukumab.

No large differences with regards to efficacy were noted between the two sirukumab doses studied in ARA3002 for the primary or the major secondary endpoints.

In general, the assessments of the endpoints that were evaluated after week 18 were somewhat complicated by the study design with the two escape-possibilities in the placebo arm. However, the result of relevant sensitivity analysis supports the result of the primary analyses. Moreover, many of the variables of interest were measured also before escape-time points. Most clinical efficacy variables, including the remission variables and the CRP-independent CDAI-variable, were evaluated before week 16 and there were generally differences in outcome in favour of the active treatment arms compared to placebo.

A small group of patients in ARA3002 were not concomitantly treated with DMARDs during the study. Out of the 1670 patients included in ARA3002, 132 were not taking MTX at baseline. Out of these 132 patients, only 61 were not taking MTX because of intolerance to MTX or MTX being inappropriate i.e. would actually support the monotherapy claim in section 4.1 of the SmPC.

It is relevant to the prescriber whether the improvements in clinical disease activity and function are maintained through a year's treatment with sirukumab. However, the data initially provided by the applicant were not sufficient to judge whether this is the case or not and additional analysis were requested. ***Judging from the totality of data that can be derived from the multiple analyses that have now been conducted, the response to treatment appears to be largely sustained over time and this presented in the product information in an acceptable way provided that a small addendum is made to increase clarity.***

In **ARA3003,** at Week 16, the primary endpoint ACR 20 response was achieved by a greater proportion of subjects in both the sirukumab 50 mg q4w (40.1%) and sirukumab 100 mg q2w (45.2%) groups compared with the placebo group (24.1%, both $p<0.001$). For the subgroup analysis based on baseline DMARD, which is of importance for the 4.1-wording proposed by the applicant, there were only 7 subjects in the placebo group, 15 in the Sirukumab 50 mg-group and 22 in the Sirukumab 100 mg-group that did not take DMARD at baseline and achieved an ACR 20 response. Accordingly, OR was >1 for both subgroups for both sirukumab doses, but the confidence interval of the OR for the Sirukumab 50 mg dose for the subgroup not taking DMARDs at baseline, includes 1.

Though the number of subjects with prior use of tocilizumab was low in ARA3003, the subgroup analyses indicate that sirukumab could be efficacious in patients previously treated with tocilizumab, another biologic DMARD that target the IL-6 pathway. This information is now included in section 5.1 of the SmPC, see separate document for details.

The outcome of the primary analysis of ARA3003 for sirukumab appeared roughly comparable to, but somewhat less favorable than the results in the RADIATE study that concerned the currently approved IL-6 blocker tocilizumab. Overall, similarly designed studies were performed for sirukumab as for tocilizumab, also targeting the IL-6 pathway. Although the treatment effects of sirukumab were comparable to those reported for tocilizumab before for the main target population of RA patients irresponsive to MTX, the treatment effect of sirukumab were relatively small in other, more difficult-to-treat study populations such as patients irresponsive to TNF-I (placebo-controlled study), or patients requiring monotherapy without MTX (adalimumab controlled study, see below). It is noted that there was a more limited contrast in the sirukumab studies as compared to the original tocilizumab trials, since the response to either placebo or active-control was relatively high in the sirukumab trials. However, given the limitations of historic controls, no conclusions regarding the relative efficacy between sirukumab and tocilizumab can be made.

The outcome of the analysis of the secondary endpoints was generally in line with the outcome for the primary endpoint i.e. sirukumab was superior to placebo but no large differences between the two different sirukumab dose regimens were observed. Mean improvement in HAQ-DI score from baseline at Week 24 was 0.31 in the sirukumab 50 mg q4w group and 0.33 in the sirukumab 100 mg q2w group vs 0.12 in the placebo group (both $p<0.001$). ACR 50 response at Week 24 was 20.9% in the sirukumab 50 mg q4w and 21.6% in the sirukumab 100 mg q2w groups compared to 8.8% in the placebo group (both $p<0.001$). Proportion of DAS28 (CRP) remission at Week 24 was 19.2% in the sirukumab 50 mg q4w and 21.6% in sirukumab 100 mg q2w groups compared to 8.2% in the placebo group (both $p<0.001$).

The assessment of the secondary endpoints that were to be evaluated beyond week 18 is somewhat complicated by the study design with early escape at that time point only in the placebo arm. However, all observations after early escape in all treatment groups have been excluded in the analyses and replaced with LOCF/failure imputation which is considered acceptable. Moreover, ACR response, mean changes from baseline in DAS28 (CRP), the remission measures, HAQ, SDAI, CDAI and CRP were all assessed at week 16 and the outcome generally favoured sirukumab over placebo. Among these variables, the remission scores are judged to be the most clinically relevant.

Demonstration of efficacy in terms of CDAI is of great importance as it is a CRP-independent endpoint. In this regard, it is further noted that, as expected for a DMARD targeting IL-6, there was a clear numerical difference in mean (SD) change from baseline in CRP at week 16 in favour of active treatment vs placebo: -0.08 (2.277) in the placebo group compared to -1.89 (2.302) in the sirukumab 50 mg group and -2.08 (2.423) in the sirukumab 100 mg group. However, also the mean percent improvement from baseline for the other individual ACR components (mean number of swollen joints, number of tender joints, patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, HAQ-DI score) were generally numerically higher in both sirukumab groups even though the difference between placebo and active treatment were not as pronounced for these outcomes as for CRP. Generally, a greater improvement was seen for the sirukumab 100 mg q2w compared to the sirukumab 50 mg q4w dose. The difference between the dose groups was most apparent for the swollen joint count for which the mean percent difference from baseline was 43% for the sirukumab 100 mg q2w dose and 30% for the sirukumab 50 mg q4w dose vs 28% for placebo.

Overall it is noted that there was no clear difference in terms of efficacy between the sirukumab 50 mg q4w and 100 mg q2w dosing regimens in study ARA3003. For some endpoints, there seem to be a better clinical response for the sirukumab 100 mg q2w group than the 50 mg q4w group but this finding was not consistent throughout the endpoints.

It is noted that approximately ¼ of the total number of the included patients were not taking MTX at baseline. The reasons for why these patients were not taking MTX were requested. According to the response to the LoQ, approximately half of the subjects that were not taking MTX at baseline and for which the reasons for why these patients were not taking MTX at baseline was available, were not treated with MTX because of intolerance to MTX or MTX being inappropriate. However, these data were lacking for many of the included patients.

The applicant claims that for subjects initially randomized to sirukumab, the improvements observed at Week 24 were maintained through Week 52. In order to assess whether the claim is justified, additional analyses were requested. ***Judging from the totality of data that can be derived from the multiple analyses that have now been conducted, the response to treatment appears to be largely sustained over time and this is presented in the product information in an acceptable way provided that a small addendum is made to increase clarity.***

In **ARA3005,** for the co-primary efficacy endpoint 1, mean change from baseline in DAS 28 (ESR) at week 24, both treatment arms of sirukumab monotherapy were considered superior to the comparator adalimumab monotherapy. Mean change (SD) in DAS28 (ESR) at week 24 was -2.19 (1.437) in the adalimumab arm and -2.58 (1.524) and -2.96 (1.580) in the sirukumab 50 mg q4w and sirukumab 100 mg q2w, respectively (LS Mean Difference [95% CI] = -0.39 [-0.69; -0.08] and -0.76 [-1.07; -0.46], respectively). In the stratum of subjects who failed MTX at baseline for safety reasons, mean (SD) change from baseline in DAS28 (ESR) at week 24 was -2.84 (1.521) in the Sirukumab 50 mg q4w group and -2.89 (1.557) in the Sirukumab 100 mg q2w group, compared to -2.20 (1.564) in the adalimumab group. Thus, the change from baseline in DAS28 (ESR) was numerically higher in the two sirukumab groups compared to in the adalimumab group also in the stratum that failed MTX due to safety reasons, i.e. the population that the current monotherapy claim pertains to, but no formal hypothesis testing was conducted. There were 256 subjects (46%) that had failed prior MTX for safety /tolerability reasons.

A sensitivity analysis based on data where the DAS 28 (ESR) value after TF/EE, whether missing or not missing, as well as any missing post-baseline observation, is set to the baseline value (sensitivity analysis 3) was conducted and is likely to be conservative. The outcome of this analysis is in line with the outcome of the primary analysis and supports the conclusion that sirukumab was indeed superior to adalimumab in terms of DAS28 (ESR) change from baseline to week 24. This conclusion is also supported by the fact that for this variable, a difference between sirukumab and the comparator in favour of the former was noted already at week 16, i.e. before the EE possibility.

For the co-primary endpoint 2, ACR 50 Response at Week 24, sirukumab was not demonstrated to be superior to the comparator adalimumab. The proportion of responders in the adalimumab arm was 31.7% vs 26.9% in the sirukumab 50 mg q4w (% difference vs the comparator with 95% CI=-4.8 [-14.1; 4.4]) and 35.3% in the sirukumab 100 mg q2w (% difference vs the comparator with [95% CI] =3.6 [-6.0; 13.1]). The results in the stratum that failed MTX due to safety reasons i.e. the population that the current monotherapy claim includes were consistent with the result in the overall population. The outcome of the sensitivity analyses was in line with the primary analysis.

The ACR 50 response rate for adalimumab monotherapy observed in ARA3005 appears to be roughly consistent with what has been found in previous studies. The response rates for sirukumab in ARA3005 are slightly lower than what might be expected for IL-6 inhibitor monotherapy in the studied population (see discussion above).

Of the two major secondary endpoints, DAS 28 (ESR) remission at week 24 appears to be the most clinically relevant. In the whole study population, the proportion of subject that achieved DAS 28 (ESR)

remission at week 24 was 7.5% in the comparator arm, 12.9% in the sirukumab 50 mg q4w arm and 20.3% in the sirukumab 100 mg q2w arm (% difference vs the comparator with [95% CI] = 5.4 [-0.7; 11.4] and 12.8 [5.9; 19.7], respectively). In the stratum that failed MTX for safety reasons, the proportion of subject that achieved DAS 28 (ESR) remission at week 24 was 7.5% in the comparator arm, 20.0% in the sirukumab 50 mg q4w arm and 23.8% in the sirukumab 100 mg q2w arm (no p-value or 95% CI provided). For the second major efficacy endpoint, ACR 20 response at week 24 sirukumab did not appear superior to the comparator adalimumab.

The proportion of subjects who achieved the clinically relevant outcomes DAS28 (ESR) Low Disease Activity and DAS28 Remission was numerically higher in the sirukumab groups compared to the comparator both at week 16 (i.e. before subjects were given the early escape possibilities) and at week 24. At week 16, the proportion of subjects with Low Disease Activity was 16.1% in the comparator group vs 24.7% (% Difference [95% CI] = 8.6 [0.5; 16.7]) in the sirukumab 50 mg q4w group and 34.2% (% Difference [95% CI] = 18.1 [9.5; 26.7]) in the sirukumab 100 mg q2w group. Almost identical figures for Low Disease Activity in the three different groups were found at week 24. The proportion of subjects in DAS28 (ESR) Remission at week 16 was 7.0% in the comparator group vs 15.1% in the sirukumab 50 mg q4w group (% Difference [95% CI] =8.1 [1.8; 14.4]) and 20.3% in the sirukumab 100 mg q2w group (% Difference [95% CI] =13.3 [6.5; 20.2]). There is a numerical difference between the comparator and sirukumab in the proportion of subjects with Low Disease Activity and remission for both doses of sirukumab. However, the difference relative the comparator was numerically higher for the 100 mg q2w dose. There are thus indications of a dose response relationship for this endpoint which is an endpoint that is hard to achieve. Sirukumab was not superior to the comparator in terms of number of subjects achieving the SDAI- and Boolean-based ACR/Remission criteria. It should however be noted that only a few individuals in each treatment group achieved remission based on these criteria which can have implications for the conclusions that can be drawn regarding this comparison.

The results for the ACR Response outcomes included among the "other efficacy endpoints" were generally in line with the ACR Response endpoints included in the primary efficacy endpoints and major secondary endpoints. Thus, sirukumab was not demonstrated to be superior to the comparator adalimumab for these endpoints. Neither was sirukumab superior to the comparator in terms of CDAI-change from baseline.

As expected for a DMARD targeting IL-6, sirukumab appeared to have a more pronounced effect on acute phase reactants (CRP, ESR) than the comparator which was observed already at week 2 and was sustained until week 24 (see section 2 of this report). Mean CRP reductions at Week 24 were -0.85 mg/dL for adalimumab 40 mg q2w, -1.78 mg/dL for sirukumab 50 mg q4w (nominal p-value 0.001) and -1.72 mg/dL for sirukumab 100 mg q2w (nominal p-value 0.003). Mean reduction in ESR (mm/hr) at week 24 was -13.7 for adalimumab 40 mg q2w, -34.1 for sirukumab 50 mg q4w and -34.7 for sirukumab 100 mg q2w (nominal p<0.001 for both analyses). When examining the mean percent change from baseline in the individual non-CRP ACR components at week 24, the numerically lowest percent change was consistently found in the sirukumab 50 mg q4w except for change in CRP, for which the percent change was numerically lowest in the comparator group. Even though the differences between the groups with regards to percent change from baseline for the individual non-CRP ACR components were not large, the outcomes for these variables stand in contrast to the outcome for the CRP variable. In other words, as expected, sirukumab has an effect on all the ACR components (which is more pronounced for the sirukumab 100 mg q2w dose) that is largely comparable to adalimumab's effect. However, sirukumab' s effect on the acute phase reactants, in this case CRP, appears greater than the effect that adalimumab has. This could explain why superiority for sirukumab vs the comparator was not noted for the CDAI change from baseline since CDAI is a

composite score that excludes acute phase reactants. It could perhaps also explain why superiority for sirukumab vs the comparator was seen for the primary endpoint based on DAS28 (ESR) and not for the primary endpoint based on ACR 50. While the formula used to calculate DAS28 (ESR) includes ESR in an additive manner for which it has been argued that excess weighting is provided to acute phase reactants (Smolen et al, ARD 2016) so that a large effect on ESR will thus always have an effect on the overall DAS28 (ESR) outcome, ACR 50 response will not be affected by a large effect on the acute phase reactant CRP, unless other components (especially swollen and tender joints) are affected as well.

As monotherapy, there were generally numerical differences that favoured sirukumab 100 mg q2w over sirukumab 50 mg q4w. This pattern was relatively consistent for all study endpoints including the clinically relevant endpoints disease remission and low disease activity. Thus, the applicant was asked to discuss whether a posology that allows a dose escalation if needed, especially when monotherapy is indicated, is warranted. ***In the response to the second LoQ, the applicant has now revised the posology so that for those patients being treated with Plivensia 50 mg every 4 weeks monotherapy who are not responding adequately by weeks 12 to 16 (after 3 to 4 doses), the dosage of Plivensia can be escalated to 100 mg every two weeks monotherapy.***

It is noted that <10% of the randomized patients in each treatment arm in ARA3005 qualified for the early escape, rendering this aspect of the study design somewhat less important for the outcome. However, there were reasons for why the issue ***initially*** needed further consideration. In ARA3005, at Early Escape patients in adalimumab and sirukumab low dose groups (the two groups of relevance for this application) were allowed to increase their doses. For the adalimumab group, this is in accordance with the SmPC, however, for the sirukumab group this is not according to the ***initially*** proposed SmPC. Hence, a sensitivity analysis allowing for this dose increase in the adalimumab group but not in the sirukumab group for both primary endpoints was requested. Thus, a sensitivity analysis was performed for the co-primary endpoints of study ARA3005 at Week 24 allowing for dose escalation in adalimumab EE subjects (using observed data), and not allowing for dose escalation in sirukumab 50 mg q4w EE subjects (using imputed data). The co-primary endpoints in study ARA3005 were change from baseline in DAS28 (ESR) and ACR 50 response at Week 24; with EE at Week 16. ACR 50 response rates were unchanged from the original analysis as no adalimumab EE subjects achieved an ACR 50 response at Week 24. Mean improvement in DAS28 (ESR) from baseline remained numerically higher for the sirukumab 50 mg group compared with the adalimumab group, with a Least-squares means difference of -0.20. However, compared with the primary efficacy analysis, the difference between the sirukumab 50 mg group and the adalimumab group was numerically smaller and no longer statistically significant. The applicant states that this approach is considered conservative and does not fully reflect the true efficacy that subjects experienced on sirukumab 50 mg up to the time of early escape. It is agreed with the applicant that the requested analysis is conservative. However, it is consistent with the ***initially*** proposed dosing of sirukumab and of interest to the prescriber as a sort of worst-case scenario. That being said, demonstrating better (or equal effect) as an established comparator, is not a prerequisite for approval which has to be acknowledged when these findings are evaluated. ***The issue is now considered resolved as the proposed posology has been revised by the Applicant as well as the 5.1-wording, see separate SmPC document.***

In conclusion, taking into account all efficacy outcomes of importance in the ARA3005 study, including the primary endpoints change from baseline in DAS 28 (ESR) and ACR 50 Response), remission (which is clinically relevant) and CDAI (which is relevant in terms of its CRP-independence), changes in CRP as well as in non-CRP ACR components, the efficacy of sirukumab as monotherapy appears roughly similar to adalimumab monotherapy. As expected for an IL-6 blocker, relative to the anti-TNF

comparator, sirukumab appeared to have a greater effect on acute phase reactants but an effect on acute phase-independent outcomes was also seen.

In **ARA3001,** there was no placebo or active comparator as a control. It is thus agreed with the applicant that it is difficult to draw any firm conclusions about the degree of efficacy of sirukumab from this study. It is however noted that the ACR response rates as well as the proportion of subjects in DAS 28 remission were generally higher in this monotherapy study than in the other phase 3 studies included in this application. It is further noted that the proportion of subjects that achieved DAS28 remission was higher in the sirukumab 100 mg q2w group than in the sirukumab 50 mg q4w group.

The proportion of subjects with antibodies towards sirukumab was low and no neutralizing antibodies were found. This is a reassuring finding.

Efficacy analysis in the elderly subpopulation across the three pivotal studies

In Study ARA3002, the odds ratio for subjects >65 years to achieve an ACR 20 response at week 16 were consistently higher in the sirukumab groups than in the placebo group even though the odds ratio in the oldest category that included only a small number of patients were wide and included 1. For the radiographic endpoint, there appeared to be an effect relative placebo for all age categories even though less pronounced in the category of patients≥65 years.

In study ARA3003, the odds ratio for subjects 65-75 years to achieve an ACR 20 response at Week 16 was not higher in the 50 mg q4w sirukumab than in the placebo group. Post-hoc analyses of the major secondary efficacy endpoints (DAS28 remission at Week 24, ACR 50 response at week 24, change from baseline in HAQ-DI score) showed the same pattern. The applicant states that change from baseline in DAS28 results in the 50 mg group was still consistent with the overall study population. However, also the outcome of this variable appears less convincing in the age group 65-75 years than the in the other age categories. The applicant argues that the results of the 65-75 year group in the ARA3003 are likely to be incidental, given the lack of correlation with the result in subjects 75 years and older, as well as the high placebo response rate in this group and relatively small number of subjects in the subgroup. These arguments are partially endorsed; it is agreed that a high placebo rate and small number of subjects in the subgroup could to some extent explain the findings. However, it is noted that neither the results in the >75 year subgroup for the 50 mg-regimen is as strong as for the younger subgroups. Could the longer disease duration in the older patients (mean disease duration 14.72 in patients >65 years compared to 9.38 in patients >45 years) be of some importance? The longer the disease duration, the greater risk of structural damage (especially in this group of patients with a high frequency of poor prognostic factors), which could in turn blur the picture when it comes to assessing some of the efficacy endpoints such as ACR Response and HAQ. Moreover, a more advanced disease could be more difficult to treat and require a higher dose. In any case a more thorough analysis of the reasons for these findings appeared necessary.

In study ARA3005, for the sirukumab 100 mg-arm the outcome of the two co-primary endpoints was generally similar in the subgroup >65 years compared to the whole population and comparable to the outcome in the comparator arm. However, for the sirukumab 50 mg-arm, the outcome of the two co-primary endpoints appeared weaker in the subgroup >65 years compared to the overall population and moreover the treatment effects were lower than for the comparator.

Overall, many of the subgroup analyses according to age include a rather low number of subjects and confidence intervals are overlapping. Accordingly, these analyses should be interpreted with caution. However, even though sirukumab appears to have an effect in all studied age categories, the effect seems somehow less pronounced in the elder categories. A thorough analysis of this finding was

requested from the applicant. In response to the LoQ, the applicant performed a statistical analysis to model the treatment by age interaction, using age as a continuous variable and concluded that there was no consistent impact of age on the treatment effect across studies (ARA3002, ARA3003, and ARA3005), endpoints (ACR 20, ACR 50 or change in DAS28), visits (Week 16, Week 24, or Week 52 [ARA3002 only]) or dose of sirukumab. In the light of the outcome of the additional analysis conducted by the applicant, it appears possible that the previously noted trend of lower treatment effect in the elderly could be a chance finding and the issue will not be further pursued.

A summary of the total number of individuals in the three different age categories; 65-74, 75-84 and 85+ in the development program for sirukumab is presented in tabulated form below.

Summary of Ages at Baseline; Randomized Subjects in CNTO136ARA3002, CNTO136ARA3003 and CNTO136ARA3005

		Sirukumab[b]				
	Placebo[a]	50 mg q4w	100 mg q2w	Combined	Adalimumab 40 mg q2w[c]	Total
Analysis Set: Randomized Subjects	850	1035	1036	2071	186	3107
Age(years)						
N	850	1035	1036	2071	186	3107
Mean (SD)	53.8 (12.06)	53.6 (12.02)	52.9 (11.91)	53.2 (11.97)	52.0 (12.15)	53.3 (12.01)
Median	55.0	54.0	54.0	54.0	54.0	54.0
Range	(18; 84)	(18; 82)	(20; 81)	(18; 82)	(20; 82)	(18; 84)
IQ range	(46.0; 62.0)	(46.0; 62.0)	(45.0; 61.0)	(46.0; 62.0)	(45.0; 60.0)	(46.0; 62.0)
<45	183 (21.5%)	222 (21.4%)	246 (23.7%)	468 (22.6%)	45 (24.2%)	696 (22.4%)
≥45 and <65	511 (60.1%)	640 (61.8%)	626 (60.4%)	1266 (61.1%)	118 (63.4%)	1895 (61.0%)
≥65 and <75	133 (15.6%)	142 (13.7%)	142 (13.7%)	284 (13.7%)	18 (9.7%)	435 (14.0%)
≥75 and <85	23 (2.7%)	31 (3.0%)	22 (2.1%)	53 (2.6%)	5 (2.7%)	81 (2.6%)
≥85	0	0	0	0	0	0

[a] Subjects randomized to placebo group in studies CNTO136ARA3002 and CNTO136ARA3003.
[b] Subjects randomized to sirukumab (50 mg q4w or 100 mg q2w) groups in studies CNTO136ARA3002, CNTO136ARA3003 and CNTO136ARA3005.
[c] Subjects randomized to adalimumab 40 mg q2w group in study CNTO136ARA3005.

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Efficacy analysis in the diabetic subpopulation across the three pivotal studies

As the pharmacokinetic data indicate that there are differences in exposure between the diabetic and the non-diabetic population (see separate AR), the primary efficacy outcomes in the three pivotal trials ARA3002, ARA3003 and ARA3005 according to whether subjects had diabetes at baseline or not were requested. In the response to the LoQ, the applicant stated that for both doses of sirukumab, there was a trend across all 3 studies for a numerically lower clinical response in subjects with diabetes compared with subjects without diabetes, however, 95% CIs overlapped and similar observations were made for placebo and adalimumab comparator arms. Moreover, the applicant states that despite the higher PK exposure with the sirukumab 100mg q2w dose compared with the 50 mg q4w dose, a clinically meaningful difference in response between sirukumab doses in diabetic subjects was not apparent. And thus, dose escalation to sirukumab 100 mg q2w would not provide a meaningful incremental benefit despite the approximate 6-fold increase in sirukumab serum trough levels. The requested data has been provided. As the numbers of diabetics in the different treatment groups in the three studies were small it is difficult to draw any firm conclusions on the benefit of dose escalation in this patient group. The data presented are suggestive of a slightly better effect in the sirukumab 100 mg q2w dose group compared to the 50 mg q4w group but the applicant has made it clear that they are not in favor of dose escalation. The data provided are considered too limited to justify any other SmPC changes pertaining to this patient group and the issue is not critical enough to call for mandatory additional studies. Thus, the issue will not be further pursued.

Efficacy analysis in the subpopulation with weight>100 kg across the three pivotal studies

When the results for the primary outcome in the three pivotal studies were examined according to weight quartiles, a clear pattern was difficult to discern even though there seem to be a tendency for lower response for some endpoints in the higher weight quartiles. As the pharmacokinetic data indicate that there are distinct differences in exposure between subjects with weight<100 kg vs subjects with weight>100 kg, the results for the primary efficacy variables in the three pivotal trials ARA3002, ARA3003 and ARA3005, in subjects with weight<100 kg vs subjects with weight>100 kg should be presented. Moreover, data in subjects with diabetes and >100 kg as well as non-diabetic subjects with weight<100 kg, and subjects that are either diabetic or have a body weight>100 kg was requested. In response to the LoQ, the applicant stated that despite the higher pharmacokinetic (PK) exposure with the sirukumab 100 mg q2w dose compared with the 50 mg q4w dose, a clinically meaningful difference in response between sirukumab doses in subjects with diabetes or ≥100 kg was not apparent and thus dose escalation to sirukumab 100 mg q2w would not provide a meaningful incremental benefit. The requested data has been provided. As the numbers of subjects that weighed ≥100 kg in the different treatment groups in the three studies were small, it is difficult to draw any firm conclusions on the benefit of dose escalation in this patient group. ***The data presented are suggestive of a slightly better effect in the sirukumab 100 mg q2w dose group compared to the 50 mg q4w group but the data provided are considered too limited to justify any other SmPC changes pertaining specifically to this patient group.***

Efficacy analysis in the monotherapy subpopulation in ARA3002 and ARA3003

The applicant performed post hoc analysis of the efficacy of sirukumab as monotherapy in ARA3002 and ARA3003. The outcomes of these analyses were summarized together with data from the pre-specified monotherapy subgroup analysis of the primary endpoints in ARA3002 and ARA3003 to support the proposed monotherapy wording. Judging from the outcome of these analyses, sirukumab was efficient also as monotherapy in these studies. However, the analyses have several limitations which limit the inference that can be made upon the findings. More comprehensive data from sirukumab monotherapy was derived from ARA 3005.

The applicant is requested to include the 100 mg q2w monotherapy regimen in the posology, e.g. for patients failing on the regular 50 mg q4w dose. Several efficacy outcomes were favorable for the 100 mg q2w dose, whereas the risk of infections or serious events appeared similar for each dosage. As treatment options are limited for patients requiring monotherapy due to intolerance to MTX, it may be relevant to titrate in case of insufficient response to Low Dose sirukumab. ***In the response to the second LoQ, the applicant has now revised the posology so that for those patients being treated with Plivensia 50 mg every 4 weeks monotherapy who are not responding adequately by weeks 12 to 16 (after 3 to 4 doses), the dosage of Plivensia can be escalated to 100 mg every two weeks monotherapy.***

For a complete discussion on the wording of the indication, including the wording regarding monotherapy, see section 5.7.3.

3.4.6. Conclusions on clinical efficacy

Sirukumab has a relevant effect on clinical measures of disease activity, including ACR response and the two clinically important outcomes low disease activity and remission. As expected, a clear effect is seen on acute phase reactants and acute phase reactant-dependent outcomes. However numerical differences vs placebo are seen also for acute phase reactant-independent outcomes such as the composite CDAI-score and non-CRP components of the ACR score, including HAQ which is a measure

of function. Finally, there seems to be an effect on radiographic progression. Effect has been demonstrated both in populations that are refractory to/ intolerant to conventional DMARD and anti-TNF, respectively. Efficacy has been shown also as monotherapy.

The development programme included a study where the TNF-blocker adalimumab was used as an active comparator. Overall, the efficacy of sirukumab appeared comparable to this comparator.

The way that the efficacy data from the development program of sirukumab is reflected in the SmPC is now acceptable provided that a small addendum to section 5.1 is made to increase clarity, see separate SmPC document.

3.4.7. Clinical safety

Patient exposure

The safety database from the 7 studies in the RA clinical development program includes 3,120 sirukumab-treated subjects with a median duration of treatment of 1.38 years. In the Phase 3 studies, subjects have received treatment for up to 3.4 years with a median duration of 1.46 years. By dose regimen, 1,363 and 1,372 subjects who received sirukumab 50 mg q4w and 100 mg q2w, respectively, were exposed for at least 6 months; 1,041 were exposed for at least 1 year in each sirukumab group.

In the placebo-controlled analysis set (ie, ARA3002 and ARA3003), approximately equal numbers of subjects received placebo (n=850), sirukumab 50 mg (n=848), or sirukumab 100 mg (n=850); most were exposed for ≥18 weeks: 93.2% in the placebo group and 96.1% in the combined sirukumab group (Table 3). The mean duration of exposure was 0.61 years in the placebo group and 0.78 years in the combined sirukumab group.

Table 3 Number of subjects with duration of exposure by category; placebo controlled analysis set

		Sirukumab		
	Placebo	50 mg	100 mg	Combined
Placebo controlled subjects	850	848	850	1698
Duration of exposure				
0-<18 Weeks	58 (6.8%)	35 (4.1%)	31 (3.6%)	66 (3.9%)
≥18 Weeks	792 (93.2%)	813 (95.9%)	819 (96.4%)	1632 (96.1%)
≥24 Weeks	485 (57.1%)	772 (91.0%)	760 (89.4%)	1532 (90.2%)
≥52 Weeks	261 (30.7%)	444 (52.4%)	442 (52.0%)	886 (52.2%)

Exposure=first dose to last dose + 16 weeks (at least 5 half-lives).
Placebo controlled analysis set= all subjects who received at least 1 (partial or complete) dose of study agent in ARA3002 and ARA3003.

Similarly, in the sirukumab-controlled analysis set (ie, ARA3001, ARA3002, ARA3003, and ARA3005), approximately equal numbers of subjects received sirukumab 50 mg (n=1461) and sirukumab 100 mg (n=1465), with 93.3% and 93.7% of subjects, respectively, exposed for ≥24 weeks. Subjects were treated for up to 3.4 years, with a median duration of exposure of 1.46 years in the sirukumab 50 mg group and 1.46 years in the sirukumab 100 mg group.

Table 4 Number of subjects with duration of exposure by category; sirukumab controlled analysis set

	Sirukumab		
	50 mg	100 mg	Combined
Sirukumab controlled subjects	1461	1465	2926
Duration of exposure			
≥24 Weeks	1363 (93.3%)	1372 (93.7%)	2735 (93.5%)
≥52 Weeks	1041 (71.3%)	1041 (71.1%)	2082 (71.2%)
≥104 Weeks	392 (26.8%)	406 (27.7%)	798 (27.3%)
≥156 Weeks	23 (1.6%)	22 (1.5%)	45 (1.5%)

Exposure=first dose to last dose + 16 weeks (at least 5 half-lives).

In the all-subjects analysis population (ie, ARA3001, ARA3002, ARA3003, and ARA3005 plus C1377T04 and ARA1001), the mean duration of exposure was 0.59 years for the placebo group, 1.45 years for the combined sirukumab group, and 0.88 years for the adalimumab group.

Table 5 Summary of subject years of exposure; all subjects analysis

	Placebo	Sirukumab Combined	Adalimumab	Total
All subjects analysis set	899	3120	186	4205
Duration of exposure (first dose to last dose + up to 5 half-lives)				
N	899	3120	186	4205
Mean(SD)	0.59 (0.306)	1.45 (0.727)	0.88 (0.206)	1.24 (0.736)
Median	0.46	1.38	0.89	1.01
IQ Range	(0.3, 1.0)	(0.8, 2.0)	(0.8, 1.0)	(0.7, 1.8)
Range	(0.0, 1.3)	(0.0, 3.4)	(0.1, 1.3)	(0.0, 3.4)
Duration of treatment (first dose to last dose)				
N	899	3120	186	4205
Mean(SD)	0.56 (0.321)	1.36 (0.795)	0.82 (0.240)	1.16 (0.777)
Median	0.46	1.33	0.88	1.00
IQ Range	(0.3, 1.0)	(0.8, 2.0)	(0.8, 1.0)	(0.5, 1.7)
Range	(0.0, 1.3)	(0.0, 3.4)	(0.0, 1.0)	(0.0, 3.4)

Exposure=first dose to last dose + 16 weeks (at least 5 half-lives).

Across the Phase 3 studies, demographic characteristics at baseline of the primary study were similar to those in the placebo-controlled population and between the sirukumab 50 mg and 100 mg groups.

Adverse events

Sirukumab leads to immunosuppression by inhibiting IL-6-mediated signalling and the biological effects of IL-6. Based upon the safety profile of IL-6 pathway inhibition and other targeted DMARDs, the following adverse events of special interest (AEI) were identified in the sirukumab RA clinical program:

Serious infections, Gastrointestinal perforations Hypersensitivity reactions, Malignancies, Major Adverse Cardiovascular Events (MACE), Hepatobiliary abnormalities, Laboratory abnormalities, Demyelination.

The primary integrated analyses for discussion are as follows:

- Comparisons of sirukumab vs placebo during the true placebo-controlled period for ARA3002 and ARA3003, ie, through 18 weeks of exposure before those subjects were allowed to enter EE;
- Comparisons of the originally randomized sirukumab and placebo groups in ARA3002 and ARA3003 through the end of the last placebo-controlled period (for ARA3002), ie, through 52 weeks of exposure; and
- Comparisons of the sirukumab 50 mg q4w and sirukumab 100 mg q2w dose regimens across the Phase 3 studies through the SCS cutoff date, representing all Phase 3 exposure to sirukumab (ie, in ARA3001, ARA3002, ARA3003, and ARA3005, as well as ARA3002 and ARA3003 subjects in the LTE, ARA3004).

Table 6 provides an overall summary of AEs by type of event in the 18-week placebo-controlled period of ARA3002 and ARA3003. The following differences were noted between the placebo and sirukumab 50 mg q4w and sirukumab 100 mg q2w groups or between the 2 sirukumab groups:

- AEs overall and AEs leading to discontinuation of study agent were reported in more subjects in the sirukumab groups compared with the placebo group.
- At 18 weeks, no major differences were seen in mortality, MACE, or malignancy.
- Serious infections were reported with higher frequency in the sirukumab groups compared with the placebo group.
- Four GI perforations occurred in subjects receiving sirukumab, none in the placebo group.
- Hepatobiliary abnormalities were more frequent in the sirukumab groups compared with the placebo group.
- No dose relationship was apparent between the sirukumab dose regimens, with the exception of hypersensitivity reactions and injection-site reactions, which occurred more frequently in the 100 mg group.

Table 6 Overall summary of adverse events through 18 weeks of exposure

	Randomized Subjects in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set	850	848	850
Average duration of exposure (weeks)	17.94	17.99	18.01
Average number of study agent administrations	8.4	8.4	8.3
Subjects who died on study	1 (0.1%)	1 (0.1%)	1 (0.1%)
Subjects with 1 or more:			
AEs	444 (52.2%)	515 (60.7%)	548 (64.5%)
AEs leading to discontinuation of study agent	22 (2.6%)	34 (4.0%)	45 (5.3%)
SAEs	27 (3.2%)	41 (4.8%)	46 (5.4%)
Serious infections:	7 (0.8%)	16 (1.9%)	14 (1.6%)
Pneumonia[a]	2 (0.2%)	5 (0.6%)	4 (0.5%)
Cellulitis[b]	1 (0.1%)	3 (0.4%)	0
Sepsis[c]	1 (0.1%)	1 (0.1%)	1 (0.1%)
Opportunistic infection	0	0	0
GI perforation	0	1 (0.1%)	3 (0.4%)
MACE	2 (0.2%)	3 (0.4%)	2 (0.2%)
Malignancy	2 (0.2%)	1 (0.1%)	1 (0.1%)
Hepatobiliary abnormalities	2 (0.2%)	7 (0.8%)	7 (0.8%)
Serious or moderate/severe systemic hypersensitivity reaction or serum sickness AE	1 (0.1%)	0	4 (0.5%)
Injection site reactions	18 (2.1%)	69 (8.1%)	136 (16.0%)
SAE of demyelination	0	0	0

Exposure=first dose to last dose + 16 weeks (at least 5 half-lives).
a: Includes preferred terms (PTs) of pneumonia and pneumonia bacterial.
b: Includes PTs of cellulitis and erysipelas.
c: Includes PTs of sepsis, septic shock, and urosepsis.

Table 7 provides an overall summary of AEs by type of event through 52 weeks of exposure in ARA3002 and ARA3003, by randomized group. Placebo group subjects were censored once they transitioned to sirukumab at the Week 18 EE or Week 40 LE rescue time points (or crossed over to sirukumab at Week 24 in ARA3003), hence, the shorter average duration of exposure in the placebo group compared with the sirukumab 50 mg and 100 mg groups.

Table 7 Overall summary of adverse events through 52 weeks of exposure

	Randomized subjects in ARA3002 and ARA3003		
		Sirukumab	
	Placebo[a]	50 mg q4w	100 mg q2w
Exposure time controlled analysis set	850	848	850
Average duration of exposure (weeks)	31.89	48.42	48.15
Average number of study agent administrations	14.83	22.38	22.24
Subjects who died on study	1 (0.1%)	4 (0.5%)	6 (0.7%)
Subjects with 1 or more:			
AEs	545 (64.1%)	703 (82.9%)	695 (81.8%)
AEs leading to discontinuation of study agent	31 (3.6%)	76 (9.0%)	80 (9.4%)
Serious adverse events	56 (6.6%)	112 (13.2%)	95 (11.2%)
Serious infections	14 (1.6%)	41 (4.8%)	36 (4.2%)
Pneumonia AEs	3 (0.4%)	18 (2.1%)	17 (2.0%)
Cellulitis AEs	5 (0.6%)	20 (2.4%)	18 (2.1%)
Sepsis AEs	2 (0.2%)	4 (0.5%)	6 (0.7%)
Opportunistic infection	0	0	1 (0.1%)
GI perforations	1 (0.1%)	2 (0.2%)	4 (0.5%)
MACE	4 (0.5%)	10 (1.2%)	4 (0.5%)
Malignancies	3 (0.4%)	8 (0.9%)	6 (0.7%)
Hepatobiliary abnormalities	3 (0.4%)	7 (0.8%)	8 (0.9%)
Hypersensitivity reaction or serum sickness AE	2 (0.2%)	1 (0.1%)	6 (0.7%)
Injection site reaction	25 (2.9%)	103 (12.1%)	164 (19.3%)
Demyelination AE	0	0	0

Exposure=first dose to last dose + 16 weeks (at least 5 half-lives).
a: Subjects in the placebo group were censored after EE/LE/CO to sirukumab.

Table 8 provides an overall summary of AEs by type of event through the SCS cutoff date in all subjects exposed to sirukumab across the Phase 3 RA studies. In this longer-term integrated analysis, dose effect was observed between the two sirukumab dose regimens, for injection-site reactions and hypersensitivity reactions. Serious infections were reported in 7% of subjects receiving sirukumab 50 mg and 100 mg alike, whereas opportunistic infections were few in number (ophthalmic herpes zoster [2 subjects], Candida esophagitis [2 subjects]) and reported as nonserious). As of the SCS cutoff, no events of demyelinating disease have been reported in the sirukumab RA development program.

Table 8 Overall summary of adverse events during the sirukumab controlled period

	Combined Sirukumab	
	50 mg q4w	**100 mg q2w**
Sirukumab controlled analysis set	1461	1465
Average duration of exposure (weeks)	78.33	78.73
Average number of study agent administrations	37.11	37.18
Subjects who died on study	15 (1.0%)	14 (1.0%)
Subjects with 1 or more:		
Adverse events	1207 (82.6%)	1237 (84.4%)
Serious adverse events	265 (18.1%)	267 (18.2%)
AEs leading to discontinuation of study agent	174 (11.9%)	196 (13.4%)
Serious infections	102 (7.0%)	101 (6.9%)
Pneumonia AEs	37 (2.5%)	44 (3.0%)
Cellulitis AEs	45 (3.1%)	51 (3.5%)
Sepsis	7 (0.5%)	12 (0.8%)
Opportunistic infections	1 (0.1%)	3 (0.2%)
GI perforations	5 (0.3%)	9 (0.6%)
MACE	20 (1.4%)	9 (0.6%)
Malignancies	23 (1.6%)	19 (1.3%)
Hepatobiliary abnormalities	8 (0.5%)	17 (1.2%)
Hypersensitivity reaction or serum sickness AEs	3 (0.2%)	16 (1.1%)
Injection site reactions	182 (12.5%)	314 (21.4%)
AEs of demyelination	0	0

Exposure=first dose to last dose + 16 weeks (at least 5 half-lives).

Common adverse events

Integrated Placebo-Controlled Period

Table 9 Number of subjects with ≥1 treatment-emergent AEs by MedDRA SOC through 18 weeks of exposure in ≥5% of subjects by PT (any treatment group)

	Randomized Treatment Groups in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set	850	848	850
Average duration of exposure (weeks)	17.94	17.99	18.01
Average number of study agent administrations	8.4	8.4	8.3
Subjects with 1 or more AEs	444 (52.2%)	515 (60.7%)	548 (64.5%)
MedDRA SOC/ PT			
Infections and infestations	220 (25.9%)	219 (25.8%)	200 (23.5%)
Upper respiratory tract infection	56 (6.6%)	38 (4.5%)	35 (4.1%)
Nasopharyngitis	46 (5.4%)	46 (5.4%)	30 (3.5%)
Investigations	43 (5.1%)	159 (18.8%)	165 (19.4%)
Alanine aminotransferase increased	16 (1.9%)	82 (9.7%)	95 (11.2%)
Aspartate aminotransferase increased	9 (1.1%)	53 (6.3%)	66 (7.8%)
General disorders and administration site conditions	51 (6.0%)	92 (10.8%)	161 (18.9%)
Injection site erythema	11 (1.3%)	48 (5.7%)	88 (10.4%)
Injection site pruritus	2 (0.2%)	10 (1.2%)	48 (5.6%)
Musculoskeletal and connective tissue disorders	110 (12.9%)	68 (8.0%)	81 (9.5%)
Rheumatoid arthritis	49 (5.8%)	20 (2.4%)	19 (2.2%)

MedDRA= Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class.
Exposure=first dose to last dose + 16 weeks (at least 5 half-lives).

The difference in overall AE rates between placebo and sirukumab was primarily driven by AEs in the Investigations SOC and the General disorders and administration site conditions SOC.

The specific PTs that were reported most often (ie, in ≥5% of subjects in the placebo, sirukumab 50 mg, or sirukumab 100 groups) through 18 weeks of exposure were Alanine aminotransferase increased, Aspartate aminotransferase increased, Injection site erythema, Nasopharyngitis, Upper respiratory tract infection, and Rheumatoid arthritis.

Adalimumab Controlled Period

In ARA3005, with similar average durations of exposure through the SCS cutoff date (~44 to ~46 weeks), treatment-emergent AEs were reported in similar proportions of subjects in the adalimumab (67.2%), sirukumab 50 mg q4w (68.8%), and sirukumab 100 mg q2w (68.4%) groups. The SOC with the most frequently reported AEs was Infections and infestations (in 28.5%, 30.6%, and 29.4% of subjects, respectively); Nasopharyngitis, Bronchitis, and Upper respiratory tract infection were the most frequently reported PTs. In the General disorders SOC, the proportions of AEs were similar in the adalimumab and sirukumab 50 mg groups but higher in the sirukumab 100 mg group (14.0%, 14.5%, and 25.7%, respectively), driven primarily by ISRs in that group. The proportions of subjects with events in the Investigations SOC were higher in the sirukumab 50 mg and 100 mg groups (18.8% and

18.2%) compared with the adalimumab group (12.9%), driven primarily by events of Alanine aminotransferase increased and Aspartate aminotransferase increased in the sirukumab groups.

Long-Term Integrated Safety Data

Through 52 weeks of exposure, the sirukumab treatment groups had approximately equal average durations of exposure (~48 weeks) and numbers of study agent administrations (~22), whereas these decreased in the placebo group (~32 weeks and ~15 administrations, respectively), due to EE in both studies, LE in ARA3002, and protocol-required CO of placebo-treated subjects to sirukumab at Week 24 in ARA3003 (subjects in ARA3002 could continue on placebo through Week 52).

Table 10 Number of subjects with ≥1 treatment-emergent AEs in ≥5% of subjects by PT (any treatment group) through 52 weeks of exposure by MedDRA SOC

	Randomized Subjects in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set	850	848	850
Average duration of exposure (weeks)	31.89	48.42	48.15
Average number of study agent administrations	14.8	22.4	22.2
Subjects with 1 or more AEs	545 (64.1%)	703 (82.9%)	695 (81.8%)
MedDRA system organ class/ Preferred term			
Infections and infestations	300 (35.3%)	398 (46.9%)	387 (45.5%)
Upper respiratory tract infection	82 (9.6%)	80 (9.4%)	86 (10.1%)
Nasopharyngitis	64 (7.5%)	88 (10.4%)	77 (9.1%)
Bronchitis	34 (4.0%)	46 (5.4%)	51 (6.0%)
Investigations	72 (8.5%)	243 (28.7%)	239 (28.1%)
Alanine aminotransferase increased	29 (3.4%)	120 (14.2%)	133 (15.6%)
Aspartate aminotransferase increased	20 (2.4%)	72 (8.5%)	88 (10.4%)
General disorders and administration site conditions	73 (8.6%)	151 (17.8%)	214 (25.2%)
Injection site erythema	13 (1.5%)	71 (8.4%)	110 (12.9%)
Injection site pruritus	3 (0.4%)	18 (2.1%)	63 (7.4%)
Injection site swelling	0	17 (2.0%)	48 (5.6%)
Musculoskeletal and connective tissue disorders	166 (19.5%)	175 (20.6%)	173 (20.4%)
Rheumatoid arthritis	72 (8.5%)	56 (6.6%)	53 (6.2%)
Blood and lymphatic system disorders	53 (6.2%)	92 (10.8%)	95 (11.2%)
Neutropenia	5 (0.6%)	46 (5.4%)	31 (3.6%)
Vascular disorders	41 (4.8%)	55 (6.5%)	73 (8.6%)
Hypertension	30 (3.5%)	40 (4.7%)	45 (5.3%)

Exposure=first dose to last dose + 16 weeks (at least 5 half-lives).

Effect of DMARDs on Frequency of AEs

Across the Phase 3 studies through the SCS cutoff, the proportion of sirukumab-treated subjects reporting AEs was slightly higher in the group that was using DMARDs at baseline (85.1%) than in the group that was not using DMARDs (79.0%), but no dose effect was seen between the 50 mg and 100 mg groups in either DMARD subgroup. Subjects who were receiving DMARDs at baseline had a higher

average duration of exposure (~86 weeks) and number of administrations (41) compared with the group that was not receiving DMARDs at baseline (~58 weeks of exposure and ~26 administrations).

All subjects in Sirukumab RA Studies

In the all-subjects population (ie, subjects with RA in all of the Phase 3 studies) through the SCS cutoff date, 83.6% of sirukumab-treated subjects reported AEs, with an average duration of exposure of ~76 weeks, and 64.7% of placebo-treated subjects reported AEs, with an average duration of exposure of ~31 weeks .

Serious adverse events and deaths

Deaths

Through the SCS cutoff date of 02 February 2016, a total of 35 deaths have been reported for subjects who participated in the sirukumab RA development program. In the true placebo-controlled period, ie, through Week 18, one subject each in the placebo, sirukumab 50 mg, and sirukumab 100 mg groups died. After Week 18, there was substantially greater exposure to sirukumab than placebo (4,548 compared with 534 subject-years of follow up, respectively), as well as loss of randomization due to the switch to active treatment of placebo subjects who were failing. This makes direct comparisons among the treatment groups difficult to interpret. The mortality rate of sirukumab-treated subjects across the Phase 3 studies (ie, ARA3001, ARA3002, ARA3003, and ARA3005, as well as ARA3002 and ARA3003 subjects in ARA3004) was generally constant over time and cumulatively through the SCS cutoff date, the rate of deaths was 0.66 per 100 subject-years of exposure, which the Applicant claims is comparable to mortality rates in other RA development programs. The causes of the deaths for sirukumab-treated subjects were the same causes of death that are seen in the general RA population and in other RA development programs of immunosuppressant DMARDs. In most cases, subjects who died had additional risk factors associated with their cause of death.

Table 11 Timing of deaths in the sirukumab RA development program by study

	Timing of death relative to last dose of study agent		
Study	≤16 weeks	>16 weeks	Total
C1377T04	1	0	1
ARA3001	0	0	0
ARA3002	20[a]	2	22
ARA3002 during LTE (ARA3004)	3	0	3
ARA3003	5	1	6
ARA3003 during LTE (ARA3004)	1	0	1
ARA3005	1	1	2
Total	31	4	35

a: One death occurred in a placebo-treated subject.

Controlled Period Analyses

Integrated Placebo-Controlled Period (Week 18)

In the Phase 3 RA studies ARA3002 and ARA3003, 3 deaths were reported through the placebo-controlled period of 18 weeks resulting in exposure-adjusted mortality rates of 0.34 per 100 subject-years of exposure for each of the 3 treatment groups through 18 weeks. The causes of death were acute respiratory distress syndrome (ARDS) in 1 subject in the placebo group, sudden cardiac death in 1 subject in the sirukumab 50 mg q4w group, and myocardial infarction (MI) in 1 subject in the

sirukumab 100 mg q2w group. All 3 subjects were in ARA3002, and all 3 were using DMARDs at baseline.

Adalimumab-Controlled Study (ARA3005)

As of the 02 February 2016 SCS cut-off date, 1 subject in ARA3005, in the sirukumab 100 mg q2w group, died of haemorrhagic stroke. A second subject, in the sirukumab 50 mg q4w group, reported an adenocarcinoma on Study Day 106, 7 days after the Week 14 study agent administration, and died on Study Day 247, more than 16 weeks after the last dose of sirukumab and therefore was not included in the incidence rate calculations. No deaths occurred in the adalimumab group. Since the SCS cutoff date, 2 other ARA3005 deaths have been reported, 1 in the sirukumab 50 mg q4w group and 1 in the sirukumab 100 mg q2w group.

Long-Term Integrated Safety Data

Multiple cuts of long-term integrated safety data were examined to assess the rates of deaths over time and to assess for dose dependency in the rates. In long-term analyses beyond Week 18, comparisons of mortality rates are potentially confounded because of transitions from the placebo group to sirukumab treatment due to EE/LE/CO. The placebo group is therefore depleted of subjects who EE/LE due to active disease or who reached the CO time points (Week 24 in ARA3003, Week 52 in ARA3002), moving these same subjects to sirukumab treatment groups. Treatment switch may therefore be related to patient factors associated with mortality risk, thus introducing confounding in comparisons of mortality rates.

In the pooled placebo-controlled studies through Week 52, a total of 16 subjects in ARA3002 (n=12) and ARA3003 (n=4) died. By randomized treatment group, 1 subject in the placebo group, 4 subjects in the sirukumab 50 mg group, and 6 subjects in the sirukumab 100 mg group died (

Table 12). The other 5 deaths through Week 52 were subjects in the placebo group who transitioned to sirukumab 50 mg or 100 mg via EE (n=3), LE (n=1), or CO (n=1) time points.

Table 12 Incidence rate (subject based per 100 subject years of follow-up) of deaths through 52 weeks of exposure

	ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis	850	848	850
Number of subjects who died	1 (0.1%)	4 (0.5%)	6 (0.7%)
Total subject-years (SY) of exposure[a]	519.5	786.9	784.4
Incidence per 100 SY of exposure (95%CI)	0.19 (0.00, 1.07)	0.51 (0.14, 1.30)	0.76 (0.28, 1.66)
Difference of incidence rates (95%CI) with respect to placebo, per 100 SY of exposure		0.32 (-0.64, 1.13)	0.57 (-0.43, 1.49)

Exposure=first dose to last dose + 16 weeks (at least 5 half-lives).
a: For subjects who have an event, the duration of exposure is only until the occurrence of the first event.

Across the Phase 3 trials cumulatively through the SCS cut-off date (ie, ARA3001, ARA3002, ARA3003, and ARA3005, as well as ARA3002 and ARA3003 subjects in ARA3004), 29 deaths occurred in sirukumab-treated subjects. The incidence rates of deaths per 100 subject-years of exposure were 0.68 in the combined sirukumab 50 mg q4w group, 0.63 in the combined sirukumab 100 mg q2w

group, and 0.66 for the 2 groups combined. There was no notable dose-effect relation in rates of death.

Deaths by age subgroups across the Phase 3 studies through the SCS cut-off date confirm the association of older age with mortality in RA. Nine of 424 (2.1%) subjects aged ≥65 to <75 years, and 8 of 74 (10.8%) 74 subjects aged ≥75 to <85 years, died. The increased mortality with increasing age in sirukumab-treated subjects is consistent with observations in the general RA population.

Placebo Group Subjects Who Transitioned to Sirukumab

Fourteen of 29 deaths in subjects who participated in ARA3002 and ARA3003 were in placebo group subjects who had transitioned to sirukumab via EE, LE, or CO. The higher incidence rate of death in these EE/LE/CO subjects compared with the randomized sirukumab groups is evident in multiple analyses of the long-term integrated data.

Table 13 Incidence Rate (Subject Based per 100 Subject Years of Exposure) of Deaths During the Study; All subjects in CNTO136ARA3002 and CNTO136ARA3003 (Study CNTO136ISS)

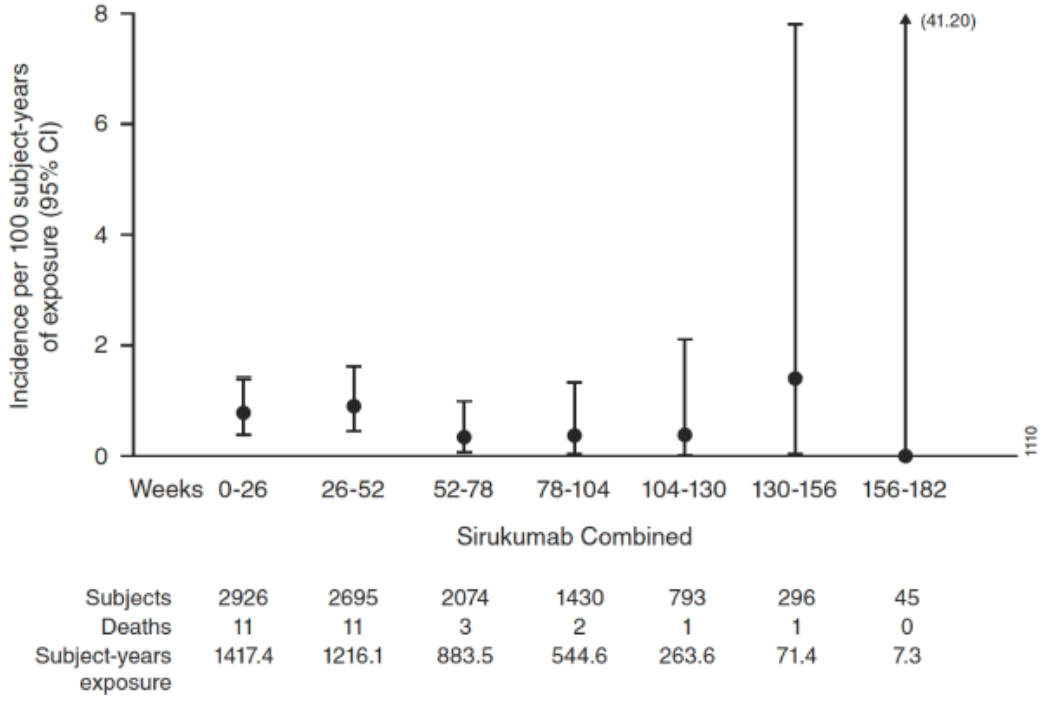
	All Subjects in CNTO136ARA3002 and CNTO136ARA3003						
	Placebo	Pbo → 50 mg q4w due to EE/LE/CO	Pbo → 100 mg q2w due to EE/LE/CO	Start 50 mg q4w	Start 100 mg q2w	Combined 50 mg q4w	Combined 100 mg q2w
All subjects in CNTO136ARA3002 and CNTO136ARA3003	850	366	367	848	850	1214	1217
Number of Deaths	1 (0.1%)	7 (1.9%)	7 (1.9%)	8 (0.9%)	6 (0.7%)	15 (1.2%)	13 (1.1%)
Total subject-years of exposure (first dose to last dose + up to 5 half lives) [a]	520.6	475.2	473.2	1488.6	1501.4	1963.8	1974.6
Incidence per 100 subject-years of exposure (95%CI)	0.19 (0.00, 1.07)	1.47 (0.59, 3.03)	1.48 (0.59, 3.05)	0.54 (0.23, 1.06)	0.40 (0.15, 0.87)	0.76 (0.43, 1.26)	0.66 (0.35, 1.13)
Difference of incidence rates (95%CI) with respect to the respective placebo → sirukumab treatment group, per 100 subject-years of exposure				-0.94 (-2.53, 0.09)	-1.08 (-2.67, -0.08)		

The EE/LE/CO subjects who switched from placebo to active therapy had a higher risk of death. A clear explanation for this was not evident despite several exploratory analyses performed. EE/LE subjects who transition to sirukumab because of more active disease may have a different risk for AEs compared with subjects originally randomized to sirukumab. One risk factor for all-cause mortality and cardiovascular disease-related death in RA patients that the EE/LE subjects shared in common was persistent inflammatory disease activity for an additional 18 to 52 weeks while they received only placebo and background therapy to which they had inadequate response in order to be eligible for the studies.

Assessment of Mortality Incidence Rates Over Time

To evaluate whether rates of death increased over time with longer exposure to sirukumab, incidence rates of deaths across the Phase 3 studies were evaluated by 6-month intervals of exposure. Although this analysis is limited by the low numbers of events in each interval, especially in the 156- to 182-week interval, the data does not show that mortality rates increased over the study period (Fig. 6 below).

Figure 6 Incidence rate (subject based per 100 subject years of follow-up) of deaths in 6-month incremental periods with sirukumab treatment exposure time aligned to Week 0 for EE, LE, and CO subjects; all subjects in Phase 3 studies



Analyses of Time to Death

Risk of death and time to death were analysed in subjects receiving sirukumab 100 mg q2w compared with sirukumab 50 mg q4w. In Kaplan-Meier analyses of all-cause deaths in long-term integrated data across the Phase 3 studies (ARA3001, ARA3002, ARA3003, and ARA3005, as well as ARA3002 and ARA3003 subjects in ARA3004), the sirukumab 50 mg and 100 mg curves overlap, again suggesting a relatively constant rate of deaths over time, with similar slopes, suggesting no dose relation in time to death (Figure 7 below). Interpretation of the curves beyond 120 weeks of exposure is limited by the relatively small numbers of subjects at risk.

Figure 7 Kaplan-Meier analysis of the time to death during the sirukumab controlled period; sirukumab controlled analysis set

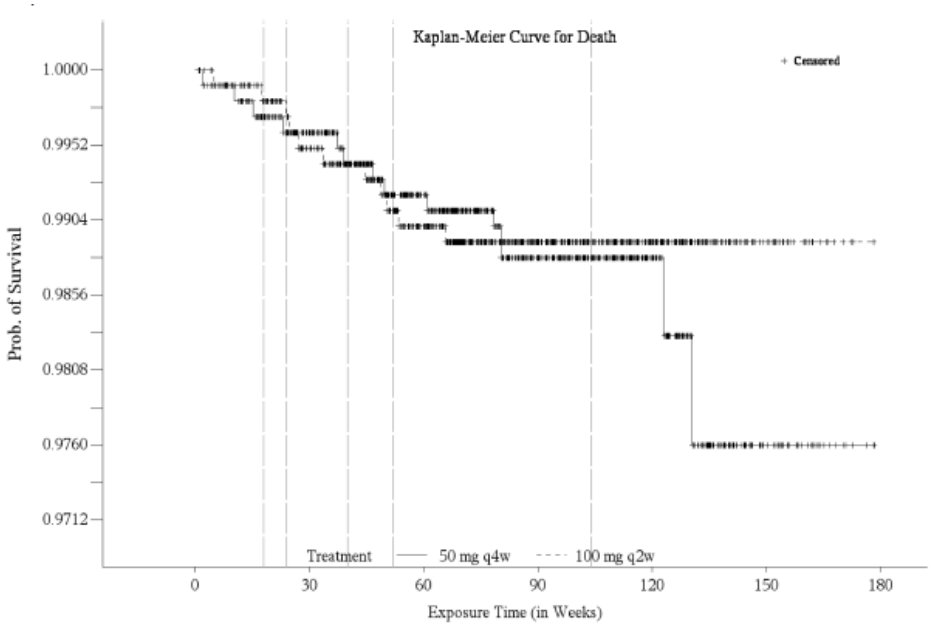
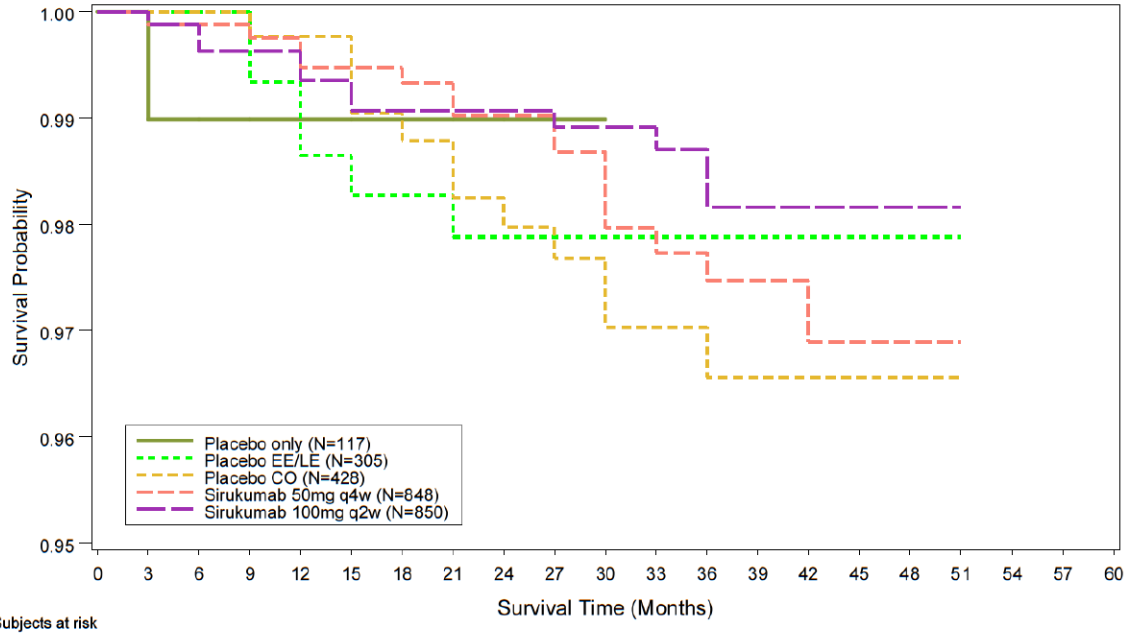


Figure 7b: Kaplan Meier Plots for Time to Death Through 28 February 2017



Number of Subjects at risk

Placebo Only	117	94	47	24	13	6	1	1	1	1	1							
Placebo EE/LE	305	305	305	296	270	261	253	248	237	225	206	170	122	84	54	27	10	1
Placebo CO	428	428	428	424	417	403	383	366	345	319	288	228	169	130	78	32	11	5
Sirukumab 50mg q4w	848	829	788	747	709	677	651	623	603	574	525	415	306	215	129	69	26	6
Sirukumab 100mg q4w	850	830	785	742	711	684	655	640	616	594	533	428	324	235	135	67	29	5

The date of the latest safety follow-up is used for censoring.
Survival times for subjects in the Placebo EE/LE and Placebo CO groups includes exposure to placebo prior to EE/LE or CO to Sirukumab.
One subject in the Placebo only group has a safety follow up of 970 days but has no record for crossing over to sirukumab (as of the 28th February 2017 cut-off date).
For this reason the placebo only survival curve extends beyond the expected duration of approximately 16 months (i.e., 12 months treatment plus 4 months follow-up).
ss693934: /arenv/arprod/gsk2973327/mid207163/iss_03/drivers/f_kmplots_150.sas 07AUG2017 09:24

Causes of Death

CHMP's comment: This section needs to be updated since a readjudication has been performed, see JRAR Q 14. However, since some uncertainty regarding recalculation persists, this has not yet been done

In the sirukumab development program, the main causes of death (defined as SAEs with a fatal outcome) were cardiovascular events, serious infections, and malignancies, regardless of whether the subjects had been originally randomized to sirukumab or were EE/LE/CO subjects. Of 34 deaths in sirukumab-treated subjects in the RA development program, 11 were adjudicated as MACE. Each subject with fatal MACE had 2 or more traditional risk factors (eg, age, hyperlipidemia, hypertension, known atherosclerotic disease, smoking, obesity) in addition to RA.

Table 14 displays incidence rates per 100 subject-years of follow-up for deaths overall and cause-specific deaths in the RA development program. Of note, in this integrated dataset, ~90% of the exposure is to sirukumab (4,548 subject-years, compared with 534 subject-years for placebo), which makes comparisons of AE rates difficult to interpret. When examining cause of mortality, 68% (23/34) of deaths on sirukumab were attributable to MACE, malignancy, or serious infection; more than one of these reasons was recorded for 2 subjects. These events will be monitored as part of the risk management program for sirukumab.

Table 14 Incidence rate (subject based per 100 subject years of follow-up) of deaths overall and by cause in the sirukumab RA development program; all subjects analysis set

	Sirukumab (n=3,120)	
	Number of deaths	Incidence per 100SY, 95% CI
All causes of death	34[a]	0.75 (0.52, 1.04)
MACE	11	0.24 (0.12, 0.43)
Malignancy	6	0.13 (0.05, 0.29)
Serious infection	8	0.18 (0.08, 0.35)
Other causes	11	0.24 (0.12, 0.43)

MACE=major adverse cardiovascular event; RA=rheumatoid arthritis; SY=subject-years.
a: One subject had death attributable to serious infection and MACE and another subject had death attributable to malignancy and serious infection.

Standardized Mortality Ratios

Patients with RA have an excess mortality of 40% to 50% over the general population. Predictors of mortality in RA include age, RA disease severity, extra-articular manifestation, the presence of rheumatoid factor positivity and/or anti-cyclic citrullinated peptide, and the presence of comorbidities (especially cardiovascular disease and interstitial lung disease). The mortality rate in subjects randomized to sirukumab treatment in the Phase 3 development program was compared with published mortality data in the general RA population, recognizing that clinical trial populations are selectively screened against eligibility criteria. In terms of published mortality rates, a study of RA patients from 1965 to 2005 in Olmstead County, Minnesota, yielded a rate of 2.4 to 2.5 deaths per 100 patient years (Gonzales et al Arthritis Rheum 2007). A recent study using a large health administration database in Ontario, Canada, determined the age- and sex standardized mortality rates in RA patients to range in a decreasing fashion from 1.3 to 0.9 per 100 patient-years over the year range of 1996 to 2009 (Widdifield J et al Arthritis Care Res. 2015)

Computation of standardized mortality ratios (SMRs) using the sirukumab Phase 3 mortality data and the reference RA population of the Ontario study resulted in an overall SMR (95% CI) of 0.87 (0.53, 1.34). The SMR of 0.87 is below 1 (0.5, 1.3), which indicates that sirukumab-exposed patients in the sirukumab Phase 3 studies have a death rate similar to that of the general RA population.

The study populations in the different Phase 3 trials represent differences in the spectrum of RA. To explore differences by trial population, SMRs were also calculated for each trial separately:

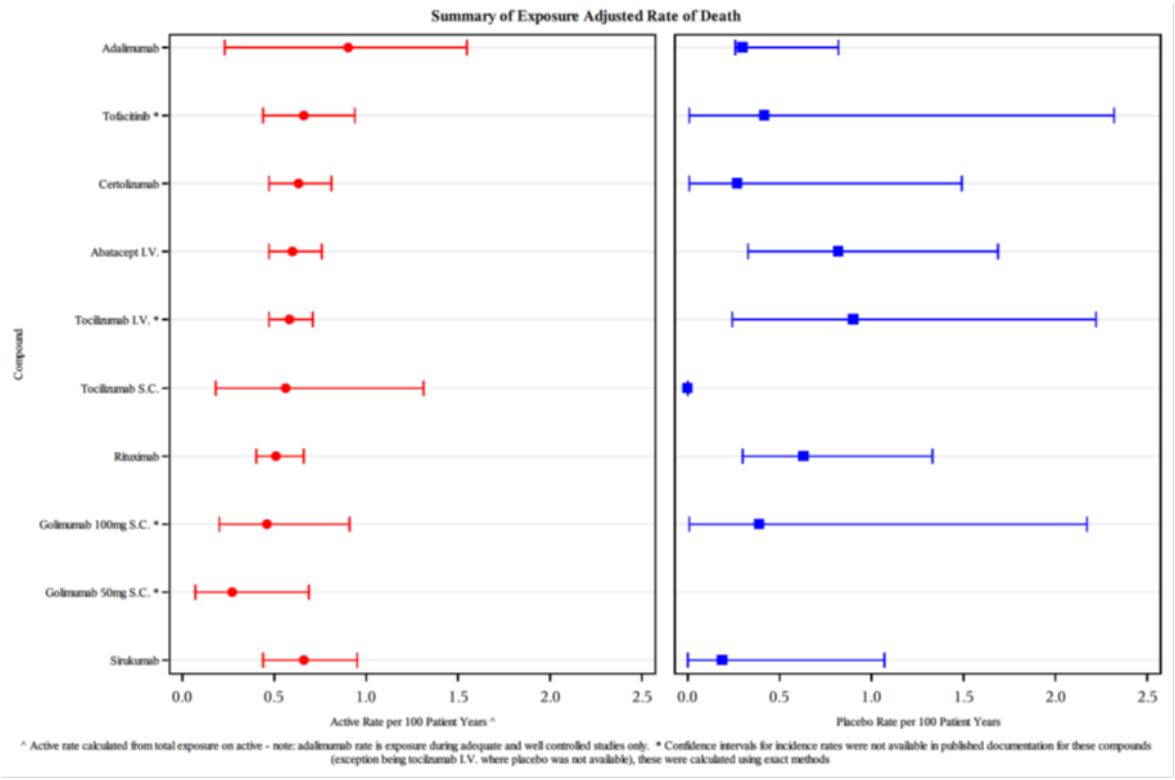
Table 15

	ARA3002	ARA3003	ARA3005
SMR (95% CI)	1.23 (0.68-2.04)	0.44 (0.11-1.19)	0.61 (0.10-2.01)

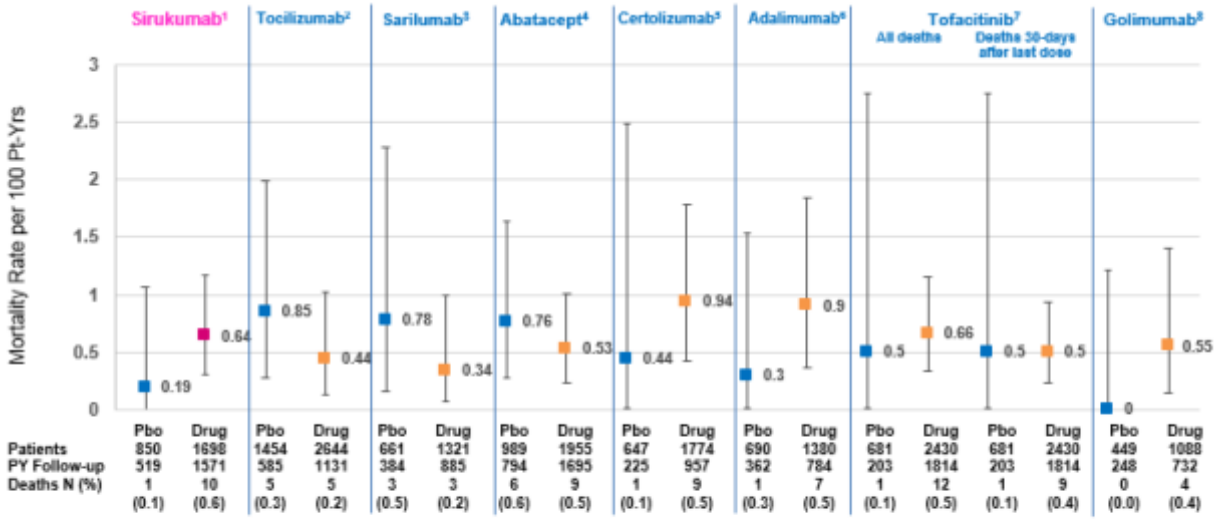
Comparator Clinical Trial Mortality Rates

Death rates in the sirukumab program were compared indirectly against publicly reported, exposure-adjusted mortality rates from development programs or large, randomized, controlled clinical trials of approved RA therapies. The combined sirukumab mortality rate per 100 subject-years of exposure (95% CI) of 0.66 (0.44, 0.95) in the long-term Phase 3 studies (ie, ARA3001, ARA3002, ARA3003, and ARA3005, as well as ARA3002 and ARA3003 subjects in ARA3004) and the placebo mortality rate of 0.19 (0.00, 1.07) for the placebo-controlled studies (ARA3002, ARA3003) were plotted beside the exposure-adjusted mortality rates from the comparator programs and trials (Figure 8). The mortality rate for both placebo- and sirukumab-treated patients falls within the range for the mortality rates of other randomized clinical trial populations. The point estimate of the placebo rate is on the lower end of the range of mortality rates reported for placebo groups in various clinical trials, albeit with wide 95% confidence intervals.

Figure 8 Exposure-adjusted mortality rates from the sirukumab RCT program and published rates from comparator RCT programs



Mortality rates in controlled data across RA programs

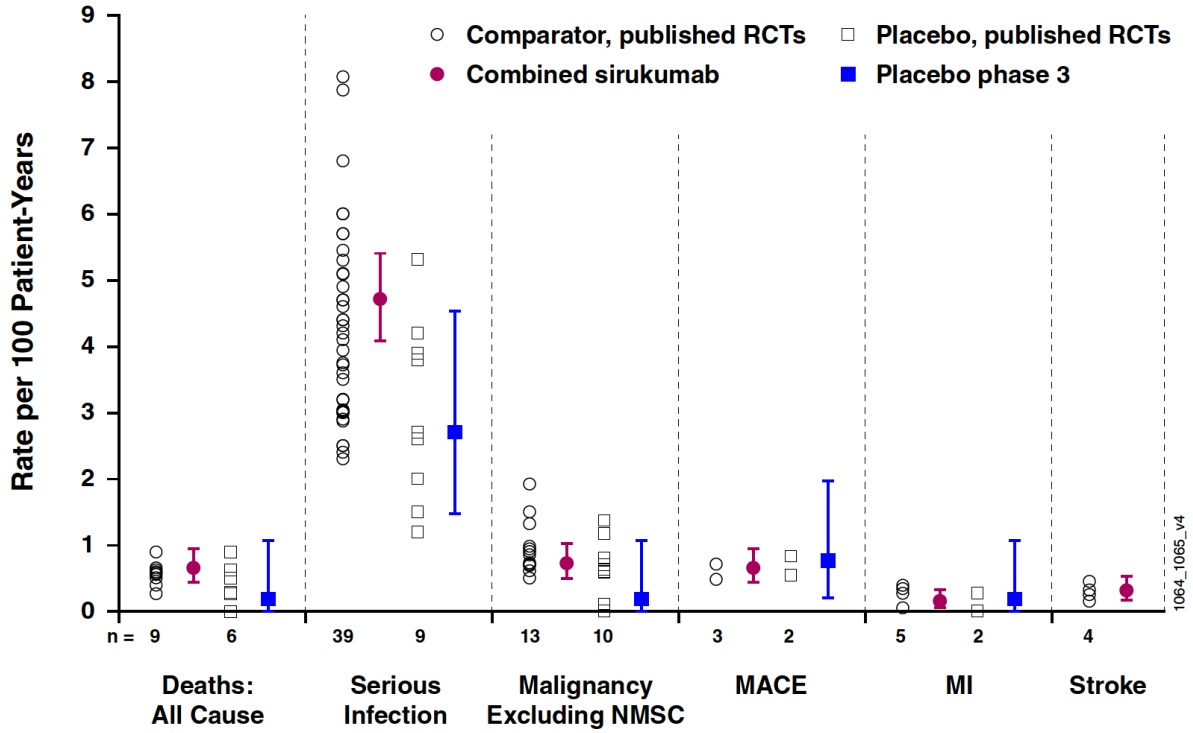


[1]as randomized Sirukumab groups through Week 52
[2]https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125276s000MedR.pdf
[3]http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004254/WC500230070.pdf
[4]https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/125118_S0000_MedR.pdf
[5]https://www.accessdata.fda.gov/drugsatfda_docs/bla/2009/125160Orig1s080.pdf
[6]https://www.fda.gov/ohrms/dockets/ac/03/briefing/3930B1_01_C--HUMIRA.Med.Review.pdf; Derived based on data available in https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/125118_S0000_MedR.pdf
[7]https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203214Orig1s000MedR.pdf
[8] Data on file, Janssen

The exposure-adjusted incidence rates of serious infections, malignancies, MACE, MI, and stroke in the combined sirukumab and placebo groups in the integrated sirukumab dataset were similar to respective rates reported in comparator RA development programs and trials (Figure 9). Thus for these

events of interest, the sirukumab Phase 3 study populations appeared to be similar to the populations in other comparator randomized controlled trials.

Figure 9 Rates of mortality and SAEs of interest in patients with RA: Summary of data from RCTs/ RA development programs



Data includes sirukumab and published incidence rates from RCTs/RA development programs for anti TNFs (golimumab, certolizumab, adalimumab, etanercept), rituximab, abatacept, tocilizumab, and tofacitinib.

Deaths Across All Sirukumab RA Studies

The mortality incidence rate adjusted for follow-up time was 0.75 deaths per 100 subject-years (95% CI 0.52, 1.04) for all deaths reported in sirukumab-treated subjects in the RA studies, regardless of the death occurring within 16 weeks of the last dose.

To benchmark the mortality rates observed in the sirukumab studies at this time, the sirukumab study eligibility criteria were operationalized and applied (to the extent possible) in RA patients captured in 3 observational databases: (1) Swedish ARTIS registry, (2) Hungarian National Health Insurance Fund and Administration (NHIFA) database, and (3) Optum Extended Data Mart (Date of Death) database from the US, hereafter referred to as Optum DOD. All 3 databases have reliable capture of mortality, which allowed for estimation of mortality rates in each of the 3 databases separately among non-TNFα biologic users (in ARTIS database) and specifically among IL-6 (tocilizumab) users in NHIFA and Optum databases to obtain a patient group eligible for non-TNFα biologics. All three analyses also included recent data (up to mid-2016) to ensure representation of recent treatment advances and currently available clinical choices.

The Swedish Biologics Register, ARTIS is an existing observational RA research project from the Karolinska Institutet, Stockholm. A descriptive analysis was conducted by investigators at the

Karolinska Institutet to estimate age- and sex-standardized mortality rates among RA patients that are new users of TNFα and non-TNFα biologics in the Swedish database during 2006-2015, both before and after applying sirukumab trial eligibility criteria.

A total of 16,932 patients (11,023 starting TNFα biologics and 5,909 starting non-TNFα biologics) were identified in the ARTIS database, of which around 36% remained after sirukumab RCT criteria were applied, corresponding to 3,889 TNFα biologic new users and 2,157 non-TNFα biologic new users.

A descriptive analysis using coded insurance claims data from Hungarian National Health Insurance Fund and Administration (NHIFA) database was conducted to estimate mortality rates in patients with RA (who were new users of TNFα or IL-6 class of biologic therapies) that met the sirukumab trial eligibility criteria, during the years 2006-2016. The analyses were conducted through collaboration with the payer (NHIFA), the pharmaceutical industry (Janssen) and an independent consulting company (Healthware Ltd.) based in Hungary. A substantial minority (~43%) of the clinical trial sites (and subjects) in the sirukumab clinical development program were from Eastern Europe (including Hungary), and the NHIFA has direct linkage to mortality indices for the population with little lag, thus allowing complete capture of deaths. A total of 5,512 TNFα biologic new users and 1,597 IL-6 biologic (tocilizumab) new users were identified in the NHIFA, during the years 2006-2016. After applying sirukumab RCT eligibility criteria, less than 20% of RA patients remained, resulting in 963 TNFα users and 246 tocilizumab biologic users.

Although not all RCT criteria could be operationalized due to the nature of claims data (eg, clinical severity scores are not available), distributions of factors such as age, gender, and disease duration seemed to be generally similar, especially among tocilizumab users in the NHIFA database and those observed among sirukumab trial subjects.

The Optum Extended DataMart (Date of Death), US administrative claims database is a US administrative claims database, considered broadly representative of the US population enrolled in commercial health plans. The Optum DOD dataset includes linkage to the social security death index. The study period for the Optum DOD analysis was restricted to years 2001-2012, as states were no longer required to report deaths nationally post-2012. As mortality data for the study relied on availability of patient death records, for the purpose of this analysis, the observation time ended on December 31, 2012. Similar to the other studies, RA patients who were new users of TNFα biologics (n=15,670) or tocilizumab (n=824) were first identified. After applying the sirukumab study selection criteria, 8,901 TNFα users and 364 tocilizumab users remained.

Table: Mortality rates estimated in descriptive analyses from ARTIS registry (Sweden), NHIFA (Hungary), and Optum DOD (US) in RA patients AFTER applying sirukumab trial selection criteria

Table 16: Mortality rates estimated in descriptive analyses from ARTIS registry (Sweden), NHIFA (Hungary), and Optum DOD (US) in RA patients AFTER applying sirukumab trial selection criteria

	ARTIS‡		NHIFA†		Optum DOD†	
	TNFα	**Non-TNFα Biologics[b]**	**TNFα**	**Tocilizumab[a]**	**TNFα**	**Tocilizumab[c]**
Number of patients	3889	2157	963	246	8901	364
Number of deaths	NA	NA	64	<10	200	3
Person-years (PY)	7054	3824	4852.48	761.16	21279.35	375.27
Mortality rate/100 PY	NA	NA	1.32	*<1.18*	0.94	0.80
95% CI	NA	NA	1.00-1.64	*<0.41-<1.96*	0.81-1.07	0-1.70

‡rates are age-and sex standardized
† rates are unadjusted
[a]Due to the NHIFA's inner data protection policy, data cannot be provided for third parties when the number of patients or cases is less than 10. In these cases, the missing value (italic) was replaced by its upper estimate.
[b]Rituximab, Abatacept, Tocilizumab
[c]Lower 95% CI limit for tocilizumab mortality rate is 0 due to low number of deaths

These analyses suggest mortality rates in the external cohorts are in the range of estimates observed in the sirukumab trials.

Deaths Not Included in the SCS Analyses

Deaths Occurring More than 16 Weeks After the Last Dose

In the exposure-adjusted analyses summarized above, 3 deaths in the sirukumab 50 mg q4w group (breast cancer; adenocarcinoma; malignant neoplasm of renal pelvis) and 1 death in the sirukumab 100 mg group (bladder cancer) were excluded because the date of death occurred more than 16 weeks after the subject's last dose (eg, Subject 20426 died from renal pelvis cancer that occurred >1 year after discontinuation of study participation for a nonserious AE of liver disorder).

Deaths Since SCS Cutoff Date

Through 29 July 2016, 8 additional deaths have been reported in sirukumab-treated subjects in the Phase 3 studies: in ARA3002, 1 sirukumab-treated subject (sepsis; dose blinded); in ARA3004, 1 sirukumab-treated subject (death due to unknown cause; dose blinded) and 4 subjects on sirukumab 100 mg (sudden cardiac death, sepsis/pneumonia, acute pneumococcal meningitis, hemorrhagic cerebrovascular accident); and in ARA3005, 1 subject on sirukumab 50 mg (worsening of respiratory insufficiency) and 1 subject on sirukumab 100 mg (erysipelas with severe respiratory and cardiovascular failure). With the exception of the death due to unknown cause in ARA3004, these deaths occurred within 16 weeks after the last dose of study agent. Additional details will be included in the next safety update.

Serious adverse events

Integrated Placebo-Controlled Period

Through 18 weeks of exposure, the proportions of subjects with 1 or more SAEs in ARA3002 and ARA3003 were low and similar between the sirukumab treatment groups: 3.2%, 4.8%, and 5.4% of subjects in the placebo, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups, respectively (Table 17). Infections and Infestations was the SOC in which SAEs were most frequently reported, in 0.7%, 1.9%, and 1.8% of subjects, respectively, and accounted for most of the difference between the placebo group and the sirukumab groups. Pneumonia and cellulitis were the most commonly reported SAEs.

Table 17 Number of subjects with 1 or more treatment-emergent SAEs by MedDRA SOC through 18 weeks of exposure

	Randomized Treatment Groups in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set	850	848	850
Average duration of exposure (weeks)	17.94	17.99	18.01
Average number of study agent administrations	8.4	8.4	8.3
Subjects with 1 or more SAEs	27 (3.2%)	41 (4.8%)	46 (5.4%)
MedDRA SOC			
Infections and infestations	6 (0.7%)	16 (1.9%)	15 (1.8%)
Investigations	2 (0.2%)	2 (0.2%)	5 (0.6%)
Musculoskeletal and connective tissue disorders	6 (0.7%)	8 (0.9%)	6 (0.7%)
Injury, poisoning and procedural complications	3 (0.4%)	4 (0.5%)	6 (0.7%)
Gastrointestinal disorders	3 (0.4%)	3 (0.4%)	5 (0.6%)
Respiratory, thoracic and mediastinal disorders	2 (0.2%)	0	2 (0.2%)
Hepatobiliary disorders	0	0	3 (0.4%)
Cardiac disorders	4 (0.5%)	3 (0.4%)	2 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.1%)	0	2 (0.2%)
Nervous system disorders	1 (0.1%)	1 (0.1%)	2 (0.2%)
Skin and subcutaneous tissue disorders	1 (0.1%)	0	3 (0.4%)
Vascular disorders	1 (0.1%)	0	3 (0.4%)
Blood and lymphatic system disorders	1 (0.1%)	1 (0.1%)	2 (0.2%)
Eye disorders	0	1 (0.1%)	1 (0.1%)
General disorders and administration site conditions	1 (0.1%)	4 (0.5%)	2 (0.2%)
Metabolism and nutrition disorders	0	0	1 (0.1%)
Renal and urinary disorders	1 (0.1%)	0	1 (0.1%)
Pregnancy, puerperium and perinatal conditions	0	0	1 (0.1%)
Psychiatric disorders	1 (0.1%)	1 (0.1%)	0
Reproductive system and breast disorders	1 (0.1%)	0	0

Exposure=first dose to last dose + 16 weeks (at least 5 half-lives).

Adalimumab Controlled Period

In ARA3005, the proportions of subjects with 1 or more SAEs were 7.0% (n=13), 12.4% (n=23), and 8.0% (n=15) in the adalimumab, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups through the SCS cutoff date. As with the placebo-controlled studies, Infections and Infestations was the SOC in which SAEs were most frequently reported, in 2.2%, 5.9%, and 2.1% of subjects, respectively.

Long-Term Integrated Safety Data

Through 52 weeks of exposure, the proportions of subjects with 1 or more SAEs in ARA3002 and ARA3003 were 6.6%, 13.2%, and 11.2% in the placebo, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups, respectively, with exposure-adjusted incidence rates of 11.07, 15.05, and 12.69, respectively (Table 18). Infections and Infestations remained the SOC in which SAEs were most frequently reported.

Table 18 Incidence rate and number of subjects with 1 or more SAEs in ⩾1% of subjects (any treatment group) by SOC and PT through 52 weeks of exposure

	Randomized Subjects in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set	850	848	850
Average duration of exposure (weeks)	31.89	48.42	48.15
Average number of study agent administrations	14.8	22.4	22.2
Subjects with 1 or more SAEs	56 (6.6%)	112 (13.2%)	95 (11.2%)
Number of SAEs	94	173	171
Total subject-years of exposure[a]	505.9	744.1	748.6
Incidence per 100 subject-years of exposure (95%CI)	11.07 (8.36, 14.37)	15.05 (12.39, 18.11)	12.69 (10.27, 15.51)
Difference of incidence rates (95%CI) with respect to placebo, per 100 subject-years of exposure		3.98 (-0.26, 8.07)	1.62 (-2.48, 5.53)
MedDRA SOC/ PT			
Infections and infestations	**14 (1.6%)**	**38 (4.5%)**	**35 (4.1%)**
Pneumonia	1 (0.1%)	12 (1.4%)	10 (1.2%)
Injury, poisoning and procedural complications	**8 (0.9%)**	**8 (0.9%)**	**13 (1.5%)**
Musculoskeletal and connective tissue disorders	**14 (1.6%)**	**16 (1.9%)**	**14 (1.6%)**
Rheumatoid arthritis	9 (1.1%)	5 (0.6%)	4 (0.5%)
Gastrointestinal disorders	**4 (0.5%)**	**10 (1.2%)**	**8 (0.9%)**
Nervous system disorders	**4 (0.5%)**	**10 (1.2%)**	**5 (0.6%)**
Cardiac disorders	**4 (0.5%)**	**10 (1.2%)**	**4 (0.5%)**

Exposure=first dose to last dose + 16 weeks (at least 5 half-lives).

Across the Phase 3 studies through the SCS cutoff date, the proportions of subjects with SAEs and incidence rates were virtually identical between the sirukumab 50 mg q4w and 100 mg q2w combined groups.

Table 19 Incidence rate and number of subjects with 1 or more SAEs in ⩾1% of subjects (any treatment group) by SOC or PT during the sirukumab controlled period; sirukumab controlled analysis set

	Combined Sirukumab Groups		All
	50 mg q4w	100 mg q2w	Sirukumab
Sirukumab controlled analysis set	1461	1465	2926
Subjects with 1 or more SAEs	265 (18.1%)	268 (18.3%)	533 (18.2%)
Number of SAEs	420	443	863
Total subject-years of exposure	2020.5	2042.7	4063.2
Incidence per 100 subject-years of exposure (95%CI)	13.12 (11.58, 14.79)	13.12 (11.60, 14.79)	13.12 (12.03, 14.28)
Difference of incidence rates (95%CI) with respect to the 50 mg q4w group, per 100 subject-years of exposure		0.00 (-2.26, 2.27)	
MedDRA SOC/PT			
Infections and infestations	97 (6.6%)	98 (6.7%)	195 (6.7%)
Pneumonia	17 (1.2%)	25 (1.7%)	42 (1.4%)
Cellulitis	12 (0.8%)	19 (1.3%)	31 (1.1%)
Musculoskeletal and connective tissue disorders	37 (2.5%)	41 (2.8%)	78 (2.7%)
Injury, poisoning and procedural complications	26 (1.8%)	35 (2.4%)	61 (2.1%)
Gastrointestinal disorders	28 (1.9%)	26 (1.8%)	54 (1.8%)
Respiratory, thoracic and mediastinal disorders	18 (1.2%)	25 (1.7%)	43 (1.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	20 (1.4%)	21 (1.4%)	41 (1.4%)
Nervous system disorders	24 (1.6%)	16 (1.1%)	40 (1.4%)
Vascular disorders	13 (0.9%)	21 (1.4%)	34 (1.2%)
Cardiac disorders	18 (1.2%)	10 (0.7%)	28 (1.0%)
General disorders and administration site conditions	14 (1.0%)	11 (0.8%)	25 (0.9%)

Exposure=first dose to last dose + up to 16 weeks (at least 5 half-lives).

Incidence rates (subject- and event-based) for SAEs at multiple other timepoints also showed a lack of dose effect, including through 18 weeks, 24 weeks, and 52 weeks of exposure; in ARA3002 and ARA3003 through the SCS cutoff date and across the Phase 3 studies.

Effect of DMARDs on SAEs

The occurrence of SAEs was slightly higher in the sirukumab groups receiving baseline DMARDs (19.5% and 20.1% in the 50 mg and 100 mg groups, respectively) than in the groups not receiving baseline DMARDs (14.4% and 13.3%, respectively), but incidence rates per 100 subject-years of exposure were comparable between the treatment groups regardless of DMARD use: 12.92 and 13.28 in the DMARDs group and 13.97 and 12.49 in the no DMARDs group, indicating that there was no meaningful difference between the subjects who were or were not taking DMARDs at baseline.

All Subjects in Sirukumab RA Studies

In the all-subjects population (ie, subjects with RA in ARA3001, ARA3002, ARA3003, and ARA3005 plus C1377T04 and ARA1001) through the SCS cutoff date, 17.6% of sirukumab-treated subjects and 6.7% of placebo-treated subjects reported SAEs.

Infections

IL-6 is a mediator of inflammation and cellular immune responses in the defense against some intracellular pathogens. Blockage of IL-6 could affect B-cell proliferation and antibody production, as well as T-cell differentiation and cytotoxicity needed for adaptive immunity and immune surveillance, (Lang VR et al, ePub 2011) and may blunt the acute-phase pyretic response so that fever may be masked in patients receiving an IL-6 pathway inhibitor. Serious and sometimes fatal infections have been reported in patients with RA receiving tocilizumab, the first-in-class IL-6R signaling inhibitor.

Integrated Placebo-Controlled Period

Table 20 Number of subjects with 1 or more treatment-emergent infections in ≥1% of subjects (any treatment group) by MedDRA SOC and PT through 18 weeks of exposure

	Randomized Treatment Groups in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set	850	848	850
Average duration of exposure (weeks)	17.94	17.99	18.01
Average number of study agent administrations	8.4	8.4	8.3
Subjects with 1 or more infections	205 (24.1%)	209 (24.6%)	186 (21.9%)
MedDRA SOC/PT			
Infections and infestations	196 (23.1%)	195 (23.0%)	174 (20.5%)
Upper respiratory tract infection	52 (6.1%)	36 (4.2%)	35 (4.1%)
Nasopharyngitis	45 (5.3%)	46 (5.4%)	27 (3.2%)
Urinary tract infection	15 (1.8%)	11 (1.3%)	22 (2.6%)
Bronchitis	15 (1.8%)	19 (2.2%)	14 (1.6%)
Pharyngitis	15 (1.8%)	14 (1.7%)	11 (1.3%)
Herpes zoster	4 (0.5%)	9 (1.1%)	4 (0.5%)
Sinusitis	7 (0.8%)	10 (1.2%)	4 (0.5%)

Exposure=first dose to last dose + 16 weeks (at least 5 half-lives).

Through the 18-week placebo-controlled period of exposure in ARA3002 and ARA3003, infections were reported in similar proportions of subjects in the placebo, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups: 24.1%, 24.6%, and 21.9%, respectively. Similar rates were seen in event-based data. The most frequently reported infections included upper respiratory tract infection, nasopharyngitis, and urinary tract infection.

Adalimumab Controlled Period

In ARA3005, infections were reported in similar proportions of subjects in the adalimumab, sirukumab 50 mg q4w, sirukumab 100 mg q2w groups: 29.6%, 31.7%, and 29.9% of subjects, respectively. The most frequently reported infections included nasopharyngitis, bronchitis, and upper respiratory tract infection.

Long-Term Integrated Safety Data

Through 52 weeks of exposure in ARA3002 and ARA3003, the proportions of subjects with 1 or more infections were 32.9%, 46.1%, and 42.9% in the placebo, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups, respectively, with exposure-adjusted incidence rates of 67.9, 68.7, and 62.9 per 100 subject-years, respectively

Through the SCS cutoff date, a dose effect on the frequency of infections was not apparent, with similar frequencies of infections and exposure adjusted incidence rates in the sirukumab 50 mg q4w (50.3%; 53.1) and sirukumab 100 mg q2w (49.4%; 51.8) groups in the combined Phase 3 studies, as well as between the dose groups in each study. Similar results were seen for ARA3002 data alone through 52 weeks of exposure and in the Phase 3 studies before Week 52 and with event-based incidence rates.

Effect of DMARDs on Infection Frequency

Through the SCS cutoff, the frequency of infection was higher in subjects taking DMARDs at baseline than those who were not (51.8% vs 45.7% for sirukumab 50 mg q4w and 51.4% vs 43.9% for sirukumab 100 mg q2w). On average, subjects on baseline DMARDs received 86 weeks of sirukumab while subjects not on baseline DMARDs received 58 weeks of sirukumab, which the Appplicant claims likely accounts for the difference in infection frequency. This pattern was not evident at 18 or 52 weeks of exposure.

Serious Infections

Table 21 Number of subjects with 1 or more serious infections in >1 subject in any treatment group by MedDRA SOC or PT through 18 weeks of exposure

	Randomized Treatment Groups in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set	850	848	850
Subjects with 1 or more serious infections	7 (0.8%)	16 (1.9%)	14 (1.6%)
MedDRA SOC/PT			
Infections and infestations	6 (0.7%)	16 (1.9%)	12 (1.4%)
Pneumonia	1 (0.1%)	5 (0.6%)	4 (0.5%)
Cellulitis	1 (0.1%)	3 (0.4%)	0
Urinary tract infection	1 (0.1%)	0	2 (0.2%)
Osteomyelitis	0	2 (0.2%)	1 (0.1%)
Gastrointestinal disorders	0	0	2 (0.2%)

Exposure=first dose to last dose + 16 weeks (at least 5 half-lives).

Two subjects in the sirukumab 100 mg group had multiple infections. One subject developed a perirectal abscess of the buttock area following trauma to that area; this subject also developed septic shock and a urinary tract infection. The other subject initially presented with acute perforated diverticulitis with an abdominal abscess, which was complicated by cholecystitis and pancreatitis, and subsequent pneumonia. Both subjects recovered.

Adalimumab Controlled Period

In ARA3005, the number of subjects with serious infections was 4 (2.2%), 12 (6.5%), and 4 (2.1%) in the adalimumab, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups, respectively. Incidence rates per 100 subject-years of exposure (95% CI) were similar in the adalimumab (2.46 [0.67, 6.30]) and sirukumab 100 mg q2w (2.51 [0.68, 6.43]) groups and higher in the sirukumab 50 mg q4w (7.80 [4.03, 13.63]) group; however, the 95% CIs were overlapping.

Long-Term Integrated Safety Data

Through 52 weeks of exposure, the proportions of subjects with 1 or more serious infections in ARA3002 and ARA3003 were 1.6%, 4.8%, and 4.2% in the placebo, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups, respectively, with exposure-adjusted incidence rates of 2.71, 5.29, and 4.65, respectively.

Across the Phase 3 studies through the SCS cutoff date, a dose effect was not seen (7.0% and 6.9% in the combined sirukumab 50 mg q4w and combined sirukumab 100 mg q2w groups). Additional analyses of longer-term integrated safety also did not demonstrate a consistent dose effect on rates of serious infections.

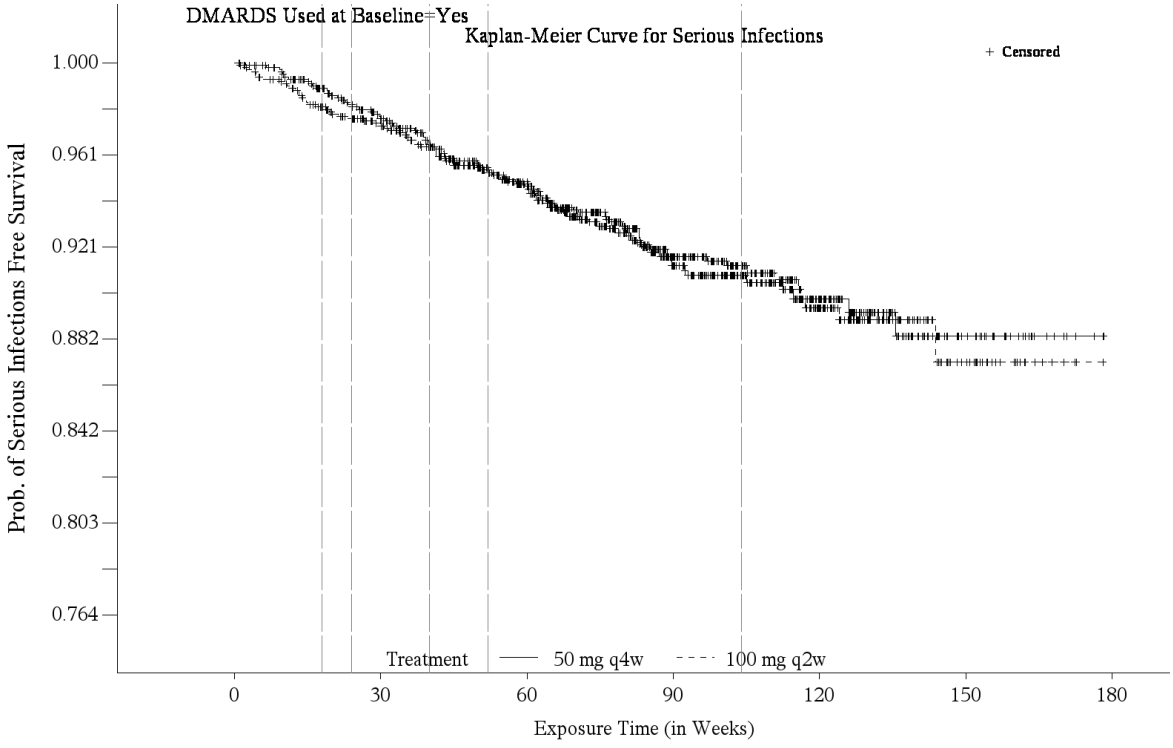
Effect of DMARDs on Serious Infection Frequency

Subject-based incidence rates of serious infections per 100 subject-years of exposure were similar when comparing subjects who were or were not on baseline DMARDs across the Phase 3 studies through the SCS cutoff date. These results were generally similar to those seen at other time periods, ie, through 18, 24, and 52 weeks, and through the SCS cutoff date for both subject-based and event-based incidence rates. The lack of an association between DMARD use and serious infection incidence suggests that there is not a cumulative immunosuppressive effect.

Rates of Serious Infections over Time

To evaluate whether the risk of serious infections increased over time with continued exposure to sirukumab, a Kaplan-Meier plot of the time to onset of serious infections was generated for subjects through the SCS cutoff date in the integrated Phase 3 data.

Figure 10 Kaplan-Meier Analysis of the Time to Onset of Serious Infections During the Sirukumab Controlled Period; Sirukumab Controlled Analysis Set



Kaplan-Meier plots among subjects exposed to placebo, as well as subjects who either started on sirukumab or switched to sirukumab (either through EE/LE or CO) are generally linear, demonstrating that the rates of serious infections do not increase over time with continued exposure to sirukumab. Similar results were seen for subjects who were or were not taking DMARDs at baseline.

In study ARA3005, the hazard ratios (95% CIs) for the sirukumab 50 mg q4w and sirukumab 100 mg q2w groups were 3.524 (1.049, 10.909) and 1.045 (0.261, 4.179), respectively, suggesting an increased risk for the sirukumab 50 mg q4w group compared with the adalimumab group. The number of subjects and events is relatively small in this single study, however, and it would be expected that if there was a truly higher risk compared with adalimumab, it would also be observed in the higher sirukumab dose group.

Across the Phase 3 studies through the SCS cutoff date, the incidence rates of serious infection were 4.76 subjects per 100 subject-years of exposure for sirukumab 50 mg q4w, and 4.67 subjects per 100 subject-years of exposure for sirukumab 100 mg q2w. Incidence rates per 100 subject-years were generally stable at other time periods, indicating a constant rate of serious infections over time.

Serious Infections of Interest

Table 22 summarizes the number of subjects with serious infections of interest (pneumonia, cellulitis and sepsis) through 52 weeks of exposure in ARA3002 and ARA3003.

Table 22 Number of subjects with 1 or more serious infections of interest through 52 weeks of exposure

	Randomized Subjects in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set	850	848	850
Average duration of exposure (weeks)	31.89	48.42	48.15
Average number of study agent administrations	14.8	22.4	22.2
Subjects with 1 or more:			
Pneumonia SAE	3 (0.4%)	12 (1.4%)	10 (1.2%)
Cellulitis SAE	1 (0.1%)	6 (0.7%)	5 (0.6%)
Sepsis SAE	2 (0.2%)	4 (0.5%)	5 (0.6%)
Opportunistic infection SAE	0	0	0

Exposure=first dose to last dose + 16 weeks (at least 5 half-lives).

Effect of DMARDs on Serious Infections of Interest

The occurrence of pneumonia and cellulitis SAEs were similar when comparing subjects who were or were not taking DMARDs at baseline. Although the number of events was small (<1% of subjects in any treatment group), all sepsis SAEs occurred in subjects who were taking DMARDs at baseline.

Opportunistic Infections

No infections that were assessed by the Sponsor as serious opportunistic infections were reported through the SCS cutoff date. The Sponsor is aware of 1 serious opportunistic infection that was identified as such after the SCS cutoff date, a case of retro-orbital Aspergillus infection in a subject in the sirukumab 100 mg q2w group.

Across the Phase 3 studies through the SCS cutoff date, 2 cases of latent TB were reported in the 100 mg group and 2 SAEs of pulmonary TB were reported, 1 each in the sirukumab 50 mg and100 mg groups. An SAE of pulmonary TB was also reported in the adalimumab group in ARA3005. No TB cases were reported in the placebo group.

Through 18 weeks of exposure in ARA3002 and ARA3003, nonserious events of herpes zoster were reported in 4 (0.5%), 9 (1.1%), and 4 (0.5%) subjects in the placebo, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups, respectively. Through 52 weeks of exposure, herpes zoster was reported in 7 (0.8%), 20 (2.4%), and 12 (1.4%) subjects in the placebo, 50 mg, and 100 mg groups, respectively.

Through 18 weeks of exposure in ARA3002 and ARA3003, an event of DNA positive hepatitis B was reported in a subject in the sirukumab 50 mg q4w group. Through 52 weeks of exposure, a nonserious AE of hepatitis B (100 mg group) was reported in ARA3002 The subject became hepatitis B core IgM positive and was felt to have acute infection; this subject was withdrawn from study treatment. There are no known instances of symptomatic hepatitis virus reactivation during the sirukumab development program.

Gastrointestinal Perforations

CHMP's comment: The numbers in the below section needs to be updated, since a readjudication has been provided, see JRAR Q 14. However, since some uncertainty regarding recalculation persists, this has not yet been performed

Historically, patients with RA have had low rates of predominantly upper gastrointestinal (GI) perforations [1.12 per 1000 person-years (95% CI: 0.50-2.49)] related to peptic ulcerations associated with nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticosteroid use. Recently, however, lower GI perforations have been increasingly identified as a risk for RA populations, specifically associated with diverticula and anti-IL-6R therapy (ie, tocilizumab) (Gout et al, Clinical Rheumatol. 2011). As a result, GI perforations were closely monitored during the sirukumab clinical development program, including adjudication of all perforation events by an independent gastroenterologist. Subjects with acute diverticulitis requiring antibiotic treatment or with a history of GI perforation were excluded from the clinical trials.

Integrated Placebo-Controlled Period

Through 18 weeks of exposure, the numbers of subjects with GI perforations were low: no subjects in the placebo group, 1 subject in the sirukumab 50 mg q4w group, and 3 subjects in the sirukumab 100 mg q2w group. Through Week 24, 1 additional subject in the sirukumab 50 mg group had a GI perforation.

Adalimumab Controlled Period

In ARA3005 through the SCS cutoff, GI perforations were reported as follows: 0 in the adalimumab group, 1 in the sirukumab 50 mg q4w group, and 1 in the sirukumab 100 mg q2w group.

Long-Term Integrated Safety Data

Table 23 Incidence rate and number of subjects with 1 or more GI perforations by SOC and PT through 52 weeks of exposure

	Randomized Subjects in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set	850	848	850
Subjects with 1 or more GI perforations	1 (0.1%)	2 (0.2%)	4 (0.5%)
Number GI perforations	1	2	6
Total subject-years of exposure[a]	519.3	786.3	783.2
Incidence per 100 subject-years of exposure (95%CI)	0.19 (0.00, 1.07)	0.25 (0.03, 0.92)	0.51 (0.14, 1.31)
Difference of incidence rates (95%CI) with respect to placebo, per 100 subject-years of exposure		0.06 (-0.85, 0.75)	0.32 (-0.64, 1.14)
MedDRA SOC/ PT			
Gastrointestinal disorders	1 (0.1%)	2 (0.2%)	3 (0.4%)
Diverticular perforation	0	1 (0.1%)	1 (0.1%)
Duodenal ulcer perforation	0	0	1 (0.1%)
Gastric ulcer perforation	0	1 (0.1%)	1 (0.1%)
Gastric perforation	1 (0.1%)	0	0
Infections and infestations	0	0	2 (0.2%)
Abdominal abscess	0	0	1 (0.1%)
Diverticulitis	0	0	1 (0.1%)
Peritonitis	0	0	1 (0.1%)

a: Exposure=first dose to last dose + 16 weeks (at least 5 half-lives).

Across the Phase 3 studies through the SCS data cutoff, the number of subjects with GI perforations was small (5 [0.3%] and 9 [0.6%] subjects in the sirukumab 50 mg q4w and sirukumab 100 mg q2w groups, respectively) and the incidence rates were similar (0.23 [0.07, 0.53] and 0.41 [0.19, 0.77];). More sirukumab-treated subjects had GI perforations in ARA3003 (n=8) than in ARA3002 (n=4) or ARA3005 (n=2); no GI perforations were reported in ARA3001. Proportions were similar between the sirukumab treatment groups in each study, except in ARA3003, where 6 of the 8 events reported were in the 100 mg group.

Although the total number of GI perforations was small through the SCS cutoff date, the incidence rate (95%CI) per 100 subject-years of exposure for lower GI perforations (0.23 [0.11, 0.42]) appeared greater than that for upper GI perforations (0.07 [0.01, 0.20]).

Effect of DMARDs on GI Perforation Frequency

The proportions of subjects with GI perforations were generally similar regardless of DMARD use at baseline, although actual numbers were higher in the group on DMARDs through the SCS cutoff. All upper GI perforations and more lower GI perforations occurred in subjects taking DMARDs at baseline.

Occurrence of GI Perforations by Subgroups

Although a specific pattern of GI perforation rate increase was not apparent, more lower GI than upper GI perforations were reported in the sirukumab studies, consistent with observations that lower GI perforations have been increasingly identified as a risk for RA populations, perhaps associated with diverticula or anti-IL-6R therapy.

MACE

Given that anti IL-6 agents as a class increase lipid levels, MACE were followed closely in the sirukumab development program for RA.

MACE described in this section were defined as MI, stroke, death, hospitalization for unstable angina, and hospitalization for transient ischemic attack, and were adjudicated as such by an independent, blinded expert clinical events committee.

CHMP's comment: **The values in the below paragraphs needs to be updated, since a readjudication has been provided, see JRAR Q 14. However, since some uncertainty regarding recalculation persists, this has not yet been performed**

Integrated Placebo-Controlled Period

Through the 18-week placebo-controlled period in ARA3002 and ARA3003, MACE were reported in similar proportions of subjects in the placebo (0.2% [n=2]), sirukumab 50 mg q4w (0.4% [n=3]), and sirukumab 100 mg q2w (0.2% [n=2]) groups.

Adalimumab Controlled Period

In ARA3005, MACE were reported in similar proportions of subjects in the adalimumab 40 mg q2w (0.0% [n=0]), sirukumab 50 mg q4w (0.5% [n=1]), and sirukumab 100 mg q2w (0.5% [n=1]) groups, at a comparable time to onset

Long-Term Integrated Safety Data

A total of 33 subjects in the Phase 3 RA studies experienced MACE through the SCS cutoff date: 4in the placebo group, 20 in the sirukumab 50 mg q4w group, and 9 in the sirukumab 100 mg q2w group.

Of the 29 sirukumab-treated subjects who had 1 or more MACE, 14 had strokes, 7 had MIs, and 8 reported other MACE. Eleven out of 34 deaths in the sirukumab treated subjects in Phase 3 RA studies were cardiovascular or cerebrovascular in nature, see also section on Deaths earlier in this report.One investigator-reported MACE in the sirukumab 50 mg q4w group was adjudicated as not being MACE.

At baseline, 32 of the 33 subjects with MACE had at least 1 risk factor for MACE, including hypertension (n=25), hyperlipidemia (n=18), current or prior tobacco use (n=18), and diabetes mellitus (n=9). Eight subjects with MACE had a documented history of cardiovascular disease or coronary interventions, and 3 subjects had a history of cerebrovascular disease at baseline. Across all treatment groups, none of the 33 subjects with MACE had grade 3 or 4 increases in total cholesterol or grade 4 increases in fasting triglycerides; 2 subjects had grade 3 increases in fasting triglycerides through the SCS cutoff date.

Table 24 Incidence rate (subject based per 100 subject years of exposure) of MACE, MI, and stroke through 52 weeks of exposure

		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set	850	848	850
MACE			
Number of subjects with 1 or more MACE	4 (0.5%)	10 (1.2%)	4 (0.5%)
Number of MACE	4	10	5
Total subject-years of exposure[a]	518.9	783.8	783.5
Incidence per 100 subject-years of exposure (95%CI)	0.77 (0.21, 1.97)	1.28 (0.61, 2.35)	0.51 (0.14, 1.31)
Myocardial infarction (MI)			
Number of subjects with 1 or more MIs	1 (0.1%)	3 (0.4%)	1 (0.1%)
Number of MIs	1	3	1
Total subject-years of exposure[a]	519.3	786.1	784.4
Incidence per 100 subject-years of exposure (95%CI)	0.19 (0.00, 1.07)	0.38 (0.08, 1.12)	0.13 (0.00, 0.71)
Stroke			
Number of subjects with 1 or more strokes	1 (0.1%)	4 (0.5%)	1 (0.1%)
Number of strokes	1	4	1
Total subject-years of exposure[a]	519.4	785.4	784.3
Incidence per 100 subject-years of exposure (95%CI)	0.19 (0.00, 1.07)	0.51 (0.14, 1.30)	0.13 (0.00, 0.71)

Exposure=first dose to last dose + 16 weeks (at least 5 half-lives).
a: For subjects who have an event, the duration of exposure is only until the occurrence of the first event.

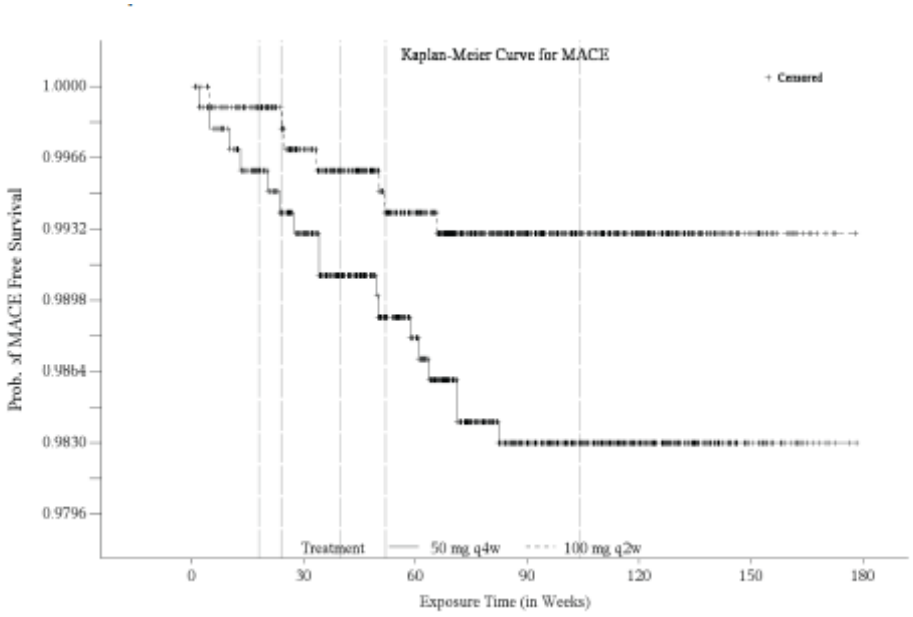
In the integrated data from ARA3002 and ARA3003 through the SCS cutoff date, the incidence of MACE per 100 subject-years of exposure was numerically higher in the combined sirukumab 50 mg q4w group (0.97) compared with the combined sirukumab 100 mg q2w group (0.41); similar trends were observed for MI and stroke. The highest observed incidence rates of MACE, MI, and stroke were in the placebo →sirukumab 50 mg q4w group.

The reason for the increased incidence of MACE with sirukumab 50 mg compared with sirukumab 100 mg is not clear, but does not appear to be due to lipid levels, which were similar in both treatment groups. Furthermore, similar numbers of fatal MACE occurred in the sirukumab 50 mg q4w (n=6) and sirukumab 100 mg q2w (n=5) groups.

Through the SCS cutoff date, incidence rates of MACE, MI, and stroke per 100 subject-years of exposure for the combined sirukumab dose groups were either similar to or numerically lower than the reported incidence rates for the general RA population receiving conventional nonbiologic DMARDs and subjects receiving tocilizumab SC.

- MACE: sirukumab combined (0.66), RA population (0.78); tocilizumab data not available
- MI: sirukumab combined (0.16), RA population (0.32), tocilizumab (0.34)
- Stroke: sirukumab combined (0.32), RA population (0.34), tocilizumab (0.45)

Figure 11 Kaplan-Meier analysis of the time to onset of MACE during the sirukumab controlled period; sirukumab controlled analysis set



Effects of DMARDs on MACE

Overall, the use of DMARDs at baseline did not consistently influence the occurrence of MACE, MI, or stroke through the SCS cutoff date. The only notable exception was a numerically higher incidence of MACE per 100 subject-years of exposure in subjects not receiving DMARDs (0.68) compared with subjects receiving DMARDs (0.34) in the sirukumab 100 mg q2w group, but the number of subjects not using DMARDs was small. Considering the small number of events, these results were similar to those seen at other time periods (ie, through 18weeks, 52 weeks, and the SCS cutoff date).

Occurrence of MACE by Subgroups

There was a trend toward numerically greater MACE incidence with increasing age. No MACE were reported in subjects <45 years of age (n=595), and the proportions of subjects who experienced MACE Prior to Week 52 were highest in subjects aged ≥75 to <85 years: 2.4% and 7.1% in the sirukumab 50 mg q4w (n=41) and 100 mg q2w groups (n=28), respectively. All other subgroup analyses, including weight, were unremarkable. Similar trends were observed at Week 24.

Applicant´s Summary and Conclusion on MACE

Despite an anti-IL-6 class effect of lipid elevations, treatment with sirukumab was associated with MACE, MI, and stroke incidence rates that were comparable with rates observed in subjects on placebo or adalimumab, and similar to or numerically lower than the incidence reported in RA patients receiving conventional nonbiologic DMARDs or tocilizumab. In most cases, subjects had pre-existing risk factors as well as active RA. Furthermore, there was no association between grade 3 or 4 lipid levels and the development of MACE in the majority of subjects in the sirukumab Phase 3 RA program. Overall, the data do not support a direct link between sirukumab-induced elevations in lipid levels and MACE.

Malignancies

Integrated Placebo-Controlled Period

Through the 18-week placebo-controlled period in ARA3002 and ARA3003, malignancies were reported in similar numbers of subjects in the placebo (n=2), sirukumab 50 mg q4w (n=1), and sirukumab 100 mg q2w (n=1) groups. These included 2 non-melanoma skin cancers (NMSCs; squamous cell carcinoma, 1 each, placebo and 50 mg), and 2 other malignancies (ovarian clear cell carcinoma [100 mg] and glioblastoma multiforme [placebo]).

Adalimumab Controlled Period

In ARA3005, malignancies were reported in similar numbers of subjects in the adalimumab (n=0), sirukumab 50 mg q4w (n=2), and sirukumab 100 mg q2w (n=1) groups. These included 1 NMSC (basal cell carcinoma [100 mg]) and 2 other malignancies (adenocarcinoma and gliomatosis cerebri [both in the 50 mg group]). All 3 malignancies occurred less than 5 months after study drug start.

Long-Term Integrated Safety Data

Multiple analyses of long-term integrated safety data were examined to assess the rates of malignancies over time and to assess dose response in rates of malignancies. Through 52 weeks of exposure, the proportions of subjects with 1 or more malignancies in ARA3002 and ARA3003 remained low: 3 (0.4%), 8 (0.9%), and 6 (0.7%) in the placebo, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups, respectively, with exposure-adjusted incidence rates of 0.58, 1.02, and 0.77, respectively.

Table 25 Incidence rate and number of subjects with 1 or more malignancies by SOC and PT through 52 weeks of exposure

	Randomized Subjects in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set	850	848	850
Subjects with 1 or more malignancies	3 (0.4%)	8 (0.9%)	6 (0.7%)
Number of malignancies	3	8	8
Total subject-years of exposure[a]	519.0	784.6	783.0
Incidence per 100 subject-years of exposure (95%CI)	0.58 (0.12, 1.69)	1.02 (0.44, 2.01)	0.77 (0.28, 1.67)
Difference of incidence rates (95%CI) with respect to placebo, per 100 subject-years of exposure		0.44 (-0.81, 1.53)	0.19 (-1.02, 1.20)
MedDRA SOC/ PT			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.4%)	8 (0.9%)	6 (0.7%)
Basal cell carcinoma	1 (0.1%)	2 (0.2%)	1 (0.1%)
Bladder cancer	0	0	1 (0.1%)
Lung adenocarcinoma	0	0	1 (0.1%)
Lung cancer metastatic	0	0	1 (0.1%)
Lymphoproliferative disorder	0	0	1 (0.1%)
Metastases to bone	0	0	1 (0.1%)
Ovarian clear cell carcinoma	0	0	1 (0.1%)
Bladder transitional cell carcinoma	0	1 (0.1%)	0
Breast cancer metastatic	0	1 (0.1%)	0
Glioblastoma multiforme	1 (0.1%)	0	0
Invasive ductal breast carcinoma	0	1 (0.1%)	0
Neuroendocrine carcinoma	0	1 (0.1%)	0
Rectal adenocarcinoma	0	1 (0.1%)	0
Squamous cell carcinoma	1 (0.1%)	1 (0.1%)	0

a: Exposure=first dose to last dose + 16 weeks (at least 5 half-lives).

In the longest-term integrated data from ARA3002 and ARA3003 (ie, through the SCS cutoff date), a dose effect on rates of malignancies was not apparent, with incidence rates for malignancies per 100 subject-years of exposure of 1.08 in the combined sirukumab 50 mg q4w group and 0.86 in the combined sirukumab 100 mg q2w group.

Across the Phase 3 studies through the SCS cutoff date, 23 (1.6%) and 19 (1.3%) subjects in the combined sirukumab 50 mg q4w and combined sirukumab 100 mg q2w groups, respectively, had a malignancy, approximately one fourth were NMSC.

Across the RA development program for sirukumab, 47 subjects had 1 or more malignancies through the SCS cutoff date: 3 on placebo, 0 on adalimumab, 21 on sirukumab 50 mg q4w, 22 on sirukumab 100 mg q2w, and 1 on sirukumab 100 mg q4w.

Effect of DMARDs on Malignancy Frequency

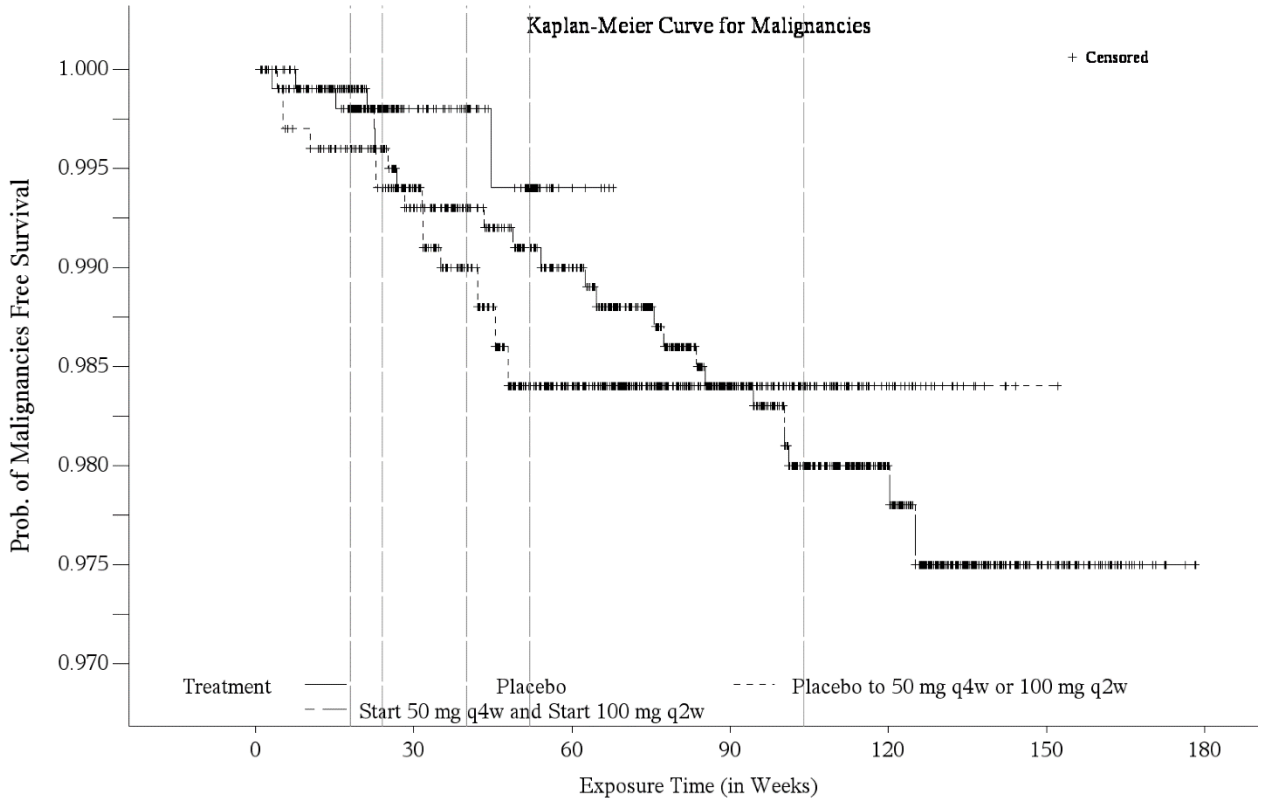
No consistent pattern was seen in the incidence of malignancies when comparing subjects in the Phase 3 studies who were and were not on DMARDs at baseline through the SCS cutoff date. Incidence rates were higher in the 50 mg group for subjects on baseline DMARDs compared with those not on baseline DMARDs (1.13 vs 0.74, respectively), but the opposite was seen in the 100 mg group, in which

subjects on baseline DMARDs had a lower incidence than those who were not on DMARDs (0.74 vs 1.36, respectively). No consistent pattern was seen at other time periods.

Rates of Malignancy Over Time

Kaplan-Meier plots among subjects exposed to placebo, as well as subjects who either started on sirukumab or switched to sirukumab (either through EE/LE or crossover) are generally linear, demonstrating that the rates of malignancy do not increase over time with continued exposure to sirukumab.

Figure 12 Kaplan-Meier Analysis of the Time to Onset of Malignancies During the Study; All subjects in CNTO136ARA3002 and CNTO136ARA3003 (Study CNTO136ISS)



The incidence rates per 100 subject-years at other time points (ie, through 18 weeks, 24 weeks, and 52 weeks of exposure, and through the SCS cutoff) were similar, indicating a constant rate of malignancy over time. Rates of malignancy over time were also similar when analyzed using Poisson regression.

Sirukumab Malignancy Data Compared with SEER Data

To evaluate the potential impact of sirukumab on malignancies, rates of malignancies were compared with rates expected in the general population according to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. SEER collects and publishes cancer incidence and survival data from population-based cancer registries that include approximately 30% of the US population (http://seer.cancer.gov/about/overview.html).

The duration of follow-up was calculated for each subject as the elapsed time from the date of the first administration of study agent to the date of the last safety assessment. For subjects with events, the

duration of follow-up was truncated at the time of the event. In addition to incidences, the expected number of subjects with events in the general US population and the standard incidence ratios (SIRs), as well as their 95% CIs, were provided. The SIR is the ratio of the observed number of subjects with 1 or more malignancies to the expected number of subjects with 1 or more malignancies based on the general US population adjusting for age, sex, and race. When the SIR is greater than 1, the observed number of subjects is higher than the expected number of cases. CIs were calculated using exact methods.

A comparison to the SEER database was made for malignancies occurring in the sirukumab program. For all malignancies, excluding NMSC, 1 malignancy occurred in the placebo group (3.84 cases expected; SIR 0.26, 95% CI [0.01, 1.45]); 7 malignancies occurred in the sirukumab 50 mg q4w group (8.44 cases expected; SIR 0.83 [0.33, 1.71]); and 11 malignancies were reported in the sirukumab 100 mg q2w group (8.34 cases expected; SIR 1.32 [0.66, 2.36]). For the combined sirukumab group, 18 malignancies were reported (16.79 cases expected; SIR 1.07 [0.64, 1.69]). Based on this, the number of malignancies reported was similar to what would be expected from the SEER database.

Through the SCS cutoff date for all malignancies (excluding non-melanoma skin cancer), 17 malignancies occurred in the combined sirukumab 50 mg q4w group (16.91 cases expected; SIR 1.01 [0.59, 1.61]) and 15 malignancies were reported in the combined sirukumab 100 mg q2w group (16.55 cases expected; SIR 0.91 [0.51, 1.50]). In the combined sirukumab group, 32 malignancies were reported (33.46 cases expected; SIR 0.96 [0.65, 1.35]). With longer exposure, the number of malignancies reported was as expected from the SEER database.

Patients with RA are known to have an increased risk of lymphoma and lung cancer compared with the general population (Simon et al, Arthritis Res Ter 2015). In the combined sirukumab groups, 1 case of non-Hodgkin lymphoma and 1 case of lymphoma were reported (1.31 lymphoma cases expected; SIR 3.05 [0.83, 7.80]). The case of non-Hodgkin lymphoma was diagnosed by biopsy and the subject was treated with high-dose prednisolone. The lymphoma case was not biopsied, and the subject was followed by CT scan after discontinuing sirukumab and MTX treatment; no specific treatment was administered for the lymphoma. In addition to these 2 lymphoma cases, 2 cases of Epstein-Barr virus (EBV)-associated lymphoproliferative disorder were reported, both of which occurred after 52 weeks. In both cases, biopsy results were suggestive of methotrexate (EBV)-related B lymphoproliferative disease. Sirukumab and MTX were discontinued in 1 subject, who was reported to improve without treatment for the malignancy. In the other case, treatment with sirukumab was also discontinued and the subject was reported to be recovering. Methotrexate treatment is known to be associated with EBV-related lymphomas that regress after methotrexate treatment is discontinued (.Kamel OW et al, N Eng J Med 1993). For lung cancer, 5 cases were reported in the combined sirukumab group (4.07 cases expected; SIR 1.23 [0.40, 2.87]). Although the SIR was >1 for lymphoma and lung cancer, because of the limited number of events, the study population size, and the wide confidence intervals, it is challenging to interpret the SIR for the individual tumor types at 52 weeks compared with the general SEER population.

Hepatobiliary Abnormalities

Liver enzyme abnormalities have been reported in patients with RA receiving IL-6 pathway inhibitors including tocilizumab, an anti-IL6R inhibitor. In tocilizumab clinical trials, transient or intermittent mild and moderate elevations of hepatic aminotransferase levels have been commonly reported with treatment, without progression to hepatic injury. An increased frequency of these elevations was observed when potentially hepatotoxic drugs (eg, MTX) were used in combination with tocilizumab. Similar elevations have been observed in subjects in the sirukumab clinical development program.

It is critical to determine whether mild hepatotoxicity reflects a potential for severe drug-induced liver injury or reflects a capacity for only limited injury. Zimmerman observed that drug-induced hepatocellular injury (ie, aminotransferase elevation) accompanied by jaundice had a poor prognosis5 and was translated into Hy's law criteria,45 which is used as an indicator of potential drug-induced serious liver injury in clinical trials. These criteria have been incorporated into regulatory guidance and form the basis for monitoring in clinical studies. Therefore, to identify and prevent potential hepatic AEs based on this guidance, hepatobiliary abnormalities in the sirukumab RA development program resulted in study agent discontinuation if they met the following criteria:

- ALT or AST ≥5 × ULN but <8 × ULN and cannot be monitored weekly for ≥2 weeks.
- ALT or AST ≥8 × ULN
- ALT or AST ≥5 × ULN for 2 or more weeks
- ALT or AST ≥3 × ULN and total bilirubin ≥2 × ULN (>35% direct bilirubin or ALT or AST ≥3 × ULN and INR >1.5, if INR measured)
- ALT or AST ≥3 × ULN accompanied by clinical symptoms believed to be related to hepatitis or hypersensitivity such as new or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash.

Integrated Placebo-Controlled Period

Through 18 weeks of exposure in ARA3002 and ARA3003, hepatobiliary abnormalities were reported in more subjects in the sirukumab dose groups than in the placebo group: 7 (0.8%) subjects in the sirukumab 50 mg q4w group and 7 (0.8%) in the sirukumab 100 mg q2w groups, compared with 2 (0.2%) subjects in the placebo group. The incidence of hepatobiliary abnormalities per 100 subject-years through 18 weeks of exposure was numerically higher in both sirukumab groups (2.41 and 2.40 in the 50 mg and 100 mg groups, respectively) compared with placebo (0.68). The most commonly reported hepatobiliary abnormalities reported in 2 or more subjects in at least 1 dose group were Alanine aminotransferase increased and Aspartate aminotransferase increased.

Results through 24 weeks of exposure were similar to those seen through 18 weeks.

Adalimumab Controlled Period

In ARA3005, the proportions of subjects reporting hepatobiliary abnormalities were similar across the treatment groups, with 2 subjects (1.1%) in the adalimumab and sirukumab 100 mg groups, and 1 subject (0.5%) in the sirukumab 50 mg group. Incidence rates were similar in the adalimumab (1.23) and 100 mg (1.25) groups, and lower in the 50 mg (0.63) group.

Long-Term Integrated Safety Data

Through 52 weeks of exposure, the proportions of subjects with 1 or more hepatobiliary abnormalities in ARA3002 and ARA3003 was: 3 (0.4%), 7 (0.8%), and 8 (0.9%) in the placebo, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups, respectively, with exposure-adjusted incidence rates of 0.58, 0.89, and 1.02, respectively.

Table 26 Incidence rate and number of subjects with 1 or more hepatobiliary abnormalities by SOC and PT through 52 weeks of exposure

	Randomized Subjects in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set	850	848	850
Subjects with 1 or more hepatobiliary abnormalities	3 (0.4%)	7 (0.8%)	8 (0.9%)
Number of hepatobiliary abnormalities	3	12	9
Total subject-years of exposure[a]	519.1	783.8	782.5
Incidence per 100 subject-years of exposure (95%CI)	0.58 (0.12, 1.69)	0.89 (0.36, 1.84)	1.02 (0.44, 2.01)
Difference of incidence rates (95%CI) with respect to placebo, per 100 subject-years of exposure		0.32 (-0.92, 1.37)	0.44 (-0.81, 1.54)
MedDRA SOC/ PT			
Investigations	3 (0.4%)	6 (0.7%)	7 (0.8%)
Alanine aminotransferase increased	2 (0.2%)	5 (0.6%)	5 (0.6%)
Aspartate aminotransferase increased	0	2 (0.2%)	0
Hepatic enzyme increased	0	0	1 (0.1%)
Liver function test abnormal	1 (0.1%)	1 (0.1%)	1 (0.1%)
Hepatobiliary disorders	0	1 (0.1%)	1 (0.1%)
Hypertransaminasaemia	0	0	1 (0.1%)
Hepatic function abnormal	0	1 (0.1%)	0

a: Exposure=first dose to last dose + 16 weeks (at least 5 half-lives).

Most subjects with hepatobiliary AEs had them during the first 18 weeks of exposure (19 subjects in the combined sirukumab groups during the first 18 weeks of exposure), compared with 22 subjects in the combined sirukumab groups through the SCS cutoff date.

Across the Phase 3 studies through the SCS cutoff date, hepatobiliary abnormalities were reported in 8 (0.5%) and 17 (1.2%) subjects in the combined sirukumab 50 mg q4w and sirukumab 100 mg q2w groups. The treatment groups were comparable across ARA3002, ARA3003 and ARA3005; no subjects had hepatobiliary AEs in ARA3001.

The overall incidence per 100 subject-years of exposure was lower in the combined 50 mg group (0.37) than in the combined 100 mg group (0.77), with an "all subjects" hazard ratio (95% CI) of 2.119 (0.914, 4.910) for the sirukumab 100 mg q2w group compared with the sirukumab 50 mg q4w group. Based on the low numbers of events, conclusion about differences between the 2 sirukumab doses cannot be made from the present dataset.

Effect of DMARDs on Hepatobiliary Abnormality Frequency

Through the SCS cutoff date, the incidence rates and proportions of subjects with hepatobiliary abnormalities were similar with or without DMARD use at baseline, as was seen in other analyses.

Occurrence of Hepatobiliary Abnormalities by Subgroups

The proportions of subjects who had a hepatobiliary abnormality was highest in subjects aged ≥45 to <65 years: 7 (0.9%) and 11 (1.4%) subjects in the 50 mg and 100 mg groups, respectively. No hepatobiliary abnormalities were reported in subjects aged ≥ 65 years. Similar results were seen through Week 24.

Adjudicated Hepatobiliary Events

To be eligible for adjudication, a subject had to meet one of the following criteria, regardless of the treatment received (placebo or sirukumab):

- At least one ALT or AST elevation ≥3 × ULN and associated total bilirubin elevation ≥2 × ULN
- SAE within the Hepatobiliary SOC (excluding gall bladder disorders without liver involvement)
- ALT or AST toxicity grade 4 and above (>20 × ULN).

An independent committee of medical experts adjudicated blinded cases of subjects with clinically significant hepatobiliary abnormalities up to the SCS cutoff date to determine the likelihood of a relationship to treatment.

Ten cases were adjudicated: 3 subjects in the placebo group, 1 subject in the sirukumab 50 mg q4w group, and 6 subjects in the sirukumab 100 mg q2w group. Five cases were considered possibly or probably related to treatment: 2 in the placebo group (both for grade 4 ALT/AST toxicity) and 3 in the sirukumab 100 mg group (2 meeting Hys law laboratory criteria for ALT/AST ≥3×ULN and bilirubin ≥2× ULN, and 1 for grade 4 ALT/AST toxicity and HEV IgM+). No evidence for drug-induced liver injury was observed for the 50 mg dose. The 2 cases that met laboratory criteria for Hy's law were confounded by the presence of pre existing hepatic steatosis and concomitant hepatotoxic drugs, so the clinical criteria were not met and therefore the Applicant claims that no Hy's law cases were observed in the sirukumab development program.

Hypersensitivity Reactions

The most common hypersensitivity AE was dermatitis allergic. No events of anaphylaxis were reported.

Integrated Placebo-Controlled Period

Through 18 weeks of exposure in ARA3002 and ARA3003, with an average of 8 study agent administrations, serious or moderate/severe hypersensitivity reactions or serum sickness AEs were reported in 1 (0.1%), 0, and 4 (0.5%) subjects in the placebo, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups, respectively.

Stevens-Johnson syndrome was reported on Study Day 201 in a subject who EE to 100 mg q2w in ARA3002, but because this case was confounded by a number of factors (including limited swelling, redness, and tenderness in the oral cavity, no fever, and previous history of apthosis), a definitive diagnosis of Stevens-Johnson syndrome could not be confirmed.

Table 27 Number of subjects with 1 or more serious or moderate/severe systemic hypersensitivity reactions or serum sickness AEs through 18 weeks of exposure

	Randomized Treatment Groups in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set	850	848	850
Average duration of exposure (weeks)	17.94	17.99	18.01
Average number of study agent administrations	8.4	8.4	8.3
Subjects with 1 or more hypersensitivity reactions or serum sickness AEs	1 (0.1%)	0	4 (0.5%)
MedDRA SOC/PT			
Skin and subcutaneous tissue disorders	1 (0.1%)	0	2 (0.2%)
Urticaria	0		1 (0.1%)
Dermatitis	0	0	1 (0.1%)
Dermatitis allergic	1 (0.1%)	0	0
Immune system disorders	0	0	2 (0.2%)
Hypersensitivity	0	0	1 (0.1%)
Serum sickness	0	0	1 (0.1%)
General disorders and administration site conditions	0	0	1 (0.1%)
Face oedema	0	0	1 (0.1%)

Exposure=first dose to last dose + 16 weeks (at least 5 half-lives).

Through 24 weeks of exposure, 1 additional serious hypersensitivity reaction was reported in a subject in the placebo → sirukumab 100 mg q2w group. No hypersensitivity AEs were reported in the sirukumab 50 mg q4w groups through 24 weeks of exposure.

Adalimumab Controlled Period

In ARA3005, hypersensitivity reactions were reported in 2 subjects each (1.1%) in the adalimumab, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups, respectively. The most common hypersensitivity AEs were in the Skin and subcutaneous tissue disorders SOC, and all AEs occurred in single subjects.

Long-Term Integrated Safety Data

Through 52 weeks of exposure in ARA3002 and ARA3003, serious or moderate/severe systemic hypersensitivity reactions were reported in 2 (0.2%), 1 (0.1%), and 5 (0.6%) subjects in the placebo, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups, respectively. The 1 additional subject in the placebo group (since Week 18) had AEs of urticaria and angioedema, and the 1 additional subject in the sirukumab 100 mg group (since Week 18) reported dermatitis allergic, which was also the PT in the 1 subject with a hypersensitivity reaction in the sirukumab 50 mg q4w group. Dermatitis allergic and urticaria were the only PTs reported in more than 1 subject.

Before Week 52 in the Phase 3 RA studies, serious hypersensitivity reactions occurred in 3 (0.2%) and 12 (0.9%) subjects in the combined 50 mg q4w and combined sirukumab 100 mg q2w groups, respectively. More serious hypersensitivity AEs occurred in ARA3003 (8 [1.0%]) than in ARA3002 (3 [0.2%]) or ARA3005 (4 [1.1%]). No serious hypersensitivity AEs were reported in ARA3001. The most common hypersensitivity AEs were dermatitis allergic (n=4) and urticaria (n=2). All other hypersensitivity AEs occurred in single subjects.

Effect of DMARDs on Hypersensitivity Reactions

Through 18 weeks of exposure, the proportion of subjects in the combined sirukumab 100 mg group with serious hypersensitivity AEs was higher in the subjects who were not using DMARDs at baseline (2.8% [4 of 145 subjects]) compared with those who were using 1 or more DMARDs at baseline (0.4% [4 of 1,072 subjects];). Similar results were seen through 52 weeks of exposure.

Injection Site Reactions

Integrated Placebo-Controlled Period

Through 18 weeks of exposure in ARA3002 and ARA3003, with an average of 8 study agent administrations, Injection Site Reactions (ISRs) were reported in 18 (2.1%), 69 (8.1%), and 136 (16.0%) subjects in the placebo, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups, respectively (Table 28). General disorders and administration site conditions was the SOC in which AEs were most frequently reported, in 17 (2.0%), 69 (8.1%), and 135 (15.9%) subjects, respectively. The most frequently reported PTs in this SOC were Injection site erythema, Injection site pruritus, and Injection site swelling.

Most ISRs were reported as mild or moderate in severity. No subjects in the placebo or sirukumab 50 mg q4w groups discontinued due to ISRs through Week 18 in ARA3002 and ARA3003; in the sirukumab 100 mg q2w group, 5 subjects discontinued due to moderate to severe ISRs, all of them in ARA3003.

Table 28 Number of subjects with 1 or more injection-site reactions (all SOCs; PTs in ≥1% of subjects in any treatment group) through 18 weeks of exposure

	Randomized Treatment Groups in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set	850	848	850
Average duration of exposure (weeks)	17.94	17.99	18.01
Subjects with 1 or more injection-site reactions	18 (2.1%)	69 (8.1%)	136 (16.0%)
MedDRA SOC/PT			
General disorders and administration site conditions	17 (2.0%)	69 (8.1%)	135 (15.9%)
Injection site erythema	11 (1.3%)	48 (5.7%)	86 (10.1%)
Injection site pruritus	2 (0.2%)	10 (1.2%)	48 (5.6%)
Injection site swelling	0	5 (0.6%)	40 (4.7%)
Injection site pain	2 (0.2%)	1 (0.1%)	10 (1.2%)
Skin and subcutaneous tissue disorders	0	2 (0.2%)	3 (0.4%)
Nervous system disorders	1 (0.1%)	0	1 (0.1%)
Injury, poisoning and procedural complications	1 (0.1%)	0	0

Exposure=first dose to last dose + 16 weeks (at least 5 half-lives).

Adalimumab Controlled Period

In ARA3005, ISRs were reported in 8.6%, 10.8%, and 23.0% of subjects in the adalimumab, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups, respectively.

Long-Term Integrated Safety Data

In the Phase 3 studies through the SCS data cutoff, ISR AEs occurred in 12.5% and 21.4% of subjects in the combined sirukumab 50 mg q4w and combined sirukumab 100 mg q2w groups, respectively. The most common ISRs were in the General disorders and administration site conditions SOC with PTs of Injection site erythema, Injection site pruritus, and Injection site swelling. Across the studies, the

proportions of subjects with injection site AEs were lower in the 50 mg groups than in the 100 mg groups, except in ARA3001 where the proportions of ISRs were similar between the treatment groups and higher overall than those in the other studies.

ISR leading to discontinuation

Through Week 52 across the Phase 3 studies, the proportions of subjects with ISR AEs leading to discontinuation of study agent were lower in subjects treated with sirukumab 50 mg (0.3% [4/1,326]) than with sirukumab 100 mg (0.9% [12/1,328]). In ARA3005, 1 subject each (0.5%) in the adalimumab and sirukumab 100 mg groups, and no subjects in the sirukumab 50 mg group, had an ISR AE leading to discontinuation.

Effect of DMARDs on Injection-Site Reactions

Through the SCS cutoff date, the proportion of subjects with ISRs was higher among the sirukumab-treated subjects who were not receiving DMARDs at baseline (17.0% and 24.7% in the 50 mg and 100 mg groups, respectively) compared with subjects who were using DMARDs at baseline (10.9% and 20.2%, respectively, similar to observations in other analyses). Regardless of baseline DMARD use, the most frequently reported PTs were Injection site erythema, Injection site pruritus, and Injection site swelling.

Sub study to Evaluate the Usability of an autoinjector (in ARA3004

Through Week 16 in the prefilled syringe auto injector (PFS-AI) usability sub study of ARA3004, 2 of 104 subjects (1.9%) experienced mild ISR AEs; both subjects were in the sirukumab 100 mg q2w group. There were no discontinuations due to PFS-AI-related AEs.

Laboratory findings

Integrated Placebo-Controlled Period

Through 18 weeks of exposure in ARA3002 and ARA3003, across all treatment groups, the majority of the maximum decreases in leukocytes (WBCs), neutrophils, lymphocytes, and platelets were NCI-CTCAE toxicity grade 0 or 1. Grade 1 decreases in leukocytes, neutrophils, and platelets and grade 2 decreases in neutrophils were more frequent in the sirukumab groups compared with the placebo group.

Table 29 Number of subjects with post-baseline values by maximum toxicity grade for haematology lab parameters through 18 weeks of exposure

	Randomized Treatment Groups in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set, N	850	848	850
Leukocytes decreased, N	842 (99.1%)	843 (99.4%)	846 (99.5%)
Subjects with post-baseline maximum:			
Toxicity grade 0 (≥LLN)	802 (95.2%)	602 (71.4%)	592 (70.0%)
Toxicity grade 1 (<LLN-3,000/mm^3)	31 (3.7%)	156 (18.5%)	174 (20.6%)
Toxicity grade 2 (<3,000-2,000/mm^3)	7 (0.8%)	82 (9.7%)	77 (9.1%)
Toxicity grade 3 (<2,000-1,000/mm^3)	2 (0.2%)	3 (0.4%)	3 (0.4%)
Toxicity grade 4 (<1,000/mm^3)	0	0	0
Neutrophil counts decreased, N	842 (99.1%)	843 (99.4%)	846 (99.5%)
Subjects with post-baseline maximum:			
Toxicity grade 0 (≥LLN)	816 (96.9%)	576 (68.3%)	568 (67.1%)
Toxicity grade 1 (<LLN-1,500/mm^3)	19 (2.3%)	149 (17.7%)	167 (19.7%)
Toxicity grade 2 (<1,500-1,000/mm^3)	5 (0.6%)	97 (11.5%)	94 (11.1%)
Toxicity grade 3 (<1,000-500/mm^3)	1 (0.1%)	21 (2.5%)	16 (1.9%)
Toxicity grade 4 (<500/mm^3)	1 (0.1%)	0	1 (0.1%)
Lymphocyte counts decreased, N	842 (99.1%)	843 (99.4%)	846 (99.5%)
Subjects with post-baseline maximum:			
Toxicity grade 0 (≥LLN)	670 (79.6%)	695 (82.4%)	716 (84.6%)
Toxicity grade 1 (<LLN-800/mm^3)	31 (3.7%)	28 (3.3%)	36 (4.3%)
Toxicity grade 2 (<800-500/mm^3)	132 (15.7%)	105 (12.5%)	81 (9.6%)
Toxicity grade 3 (<500-200/mm^3)	8 (1.0%)	15 (1.8%)	12 (1.4%)
Toxicity grade 4 (<200/mm^3)	1 (0.1%)	0	1 (0.1%)
Platelet counts decreased, N	841 (98.9%)	843 (99.4%)	845 (99.4%)
Subjects with post-baseline maximum:			
Toxicity grade 0 (≥LLN)	836 (99.4%)	768 (91.1%)	759 (89.8%)
Toxicity grade 1 (<LLN-75,000/mm^3)	5 (0.6%)	74 (8.8%)	81 (9.6%)
Toxicity grade 2 (<75,000-50,000/mm^3)	0	1 (0.1%)	5 (0.6%)
Toxicity grade 3 (<50,000-25,000/mm^3)	0	0	0
Toxicity grade 4 (<25,000/mm^3)	0	0	0

LLN=lower limit of normal; q2w=every 2 weeks; q4w=every 4 weeks.

Long Term Integrated Safety Data

Table 30 Number of Subjects with Post-baseline values by Maximum Toxicity Grade for Hematology Lab Parameters Through Sirukumab Controlled Period by Study; Sirukumab Controlled Analysis Set Neutrophils

	CNTO136ARA3001			CNTO136ARA3002			CNTO136ARA3003			CNTO136ARA3005			All Subjects		
							Sirukumab								
	50 mg q4w	100 mg q2w	Combined	50 mg q4w	100 mg q2w	Combined	50 mg q4w	100 mg q2w	Combined	50 mg q4w	100 mg q2w	Combined	50 mg q4w	100 mg q2w	Combined
Neutrophils, Segmented decreased															
N	61 (100%)	61 (100%)	122 (100%)	793 (99.4%)	798 (99.9%)	1591 (99.6%)	414 (99.5%)	415 (99.3%)	829 (99.4%)	186 (100%)	187 (100%)	373 (100%)	1454 (99.5%)	1461 (99.7%)	2915 (99.6%)
Subjects with post-baseline maximum Toxicity grade 0	30 (49.2%)	32 (52.5%)	62 (50.8%)	451 (56.9%)	422 (52.9%)	873 (54.9%)	249 (60.1%)	226 (54.5%)	475 (57.3%)	113 (60.8%)	126 (67.4%)	239 (64.1%)	843 (58.0%)	806 (55.2%)	1649 (56.6%)
Toxicity grade 1	19 (31.1%)	13 (21.3%)	32 (26.2%)	170 (21.4%)	209 (26.2%)	379 (23.8%)	89 (21.5%)	100 (24.1%)	189 (22.8%)	35 (18.8%)	30 (16.0%)	65 (17.4%)	313 (21.5%)	352 (24.1%)	665 (22.8%)
Toxicity grade 2	9 (14.8%)	13 (21.3%)	22 (18.0%)	126 (15.9%)	131 (16.4%)	257 (16.2%)	55 (13.3%)	72 (17.3%)	127 (15.3%)	32 (17.2%)	24 (12.8%)	56 (15.0%)	222 (15.3%)	240 (16.4%)	462 (15.8%)
Toxicity grade 3	3 (4.9%)	3 (4.9%)	6 (4.9%)	40 (5.0%)	35 (4.4%)	75 (4.7%)	19 (4.6%)	17 (4.1%)	36 (4.3%)	6 (3.2%)	6 (3.2%)	12 (3.2%)	68 (4.7%)	61 (4.2%)	129 (4.4%)
Toxicity grade 4	0	0	0	6 (0.8%)	1 (0.1%)	7 (0.4%)	2 (0.5%)	0	2 (0.2%)	0	1 (0.5%)	1 (0.3%)	8 (0.6%)	2 (0.1%)	10 (0.3%)

Table 31 Number of Subjects with Post-baseline values by Maximum Toxicity Grade for Hematology Lab Parameters Through Sirukumab Controlled Period by Study; Sirukumab Controlled Analysis Set Platelets

	CNTO136ARA3001			CNTO136ARA3002			CNTO136ARA3003			CNTO136ARA3005			All Subjects		
							Sirukumab								
	50 mg q4w	100 mg q2w	Combined	50 mg q4w	100 mg q2w	Combined	50 mg q4w	100 mg q2w	Combined	50 mg q4w	100 mg q2w	Combined	50 mg q4w	100 mg q2w	Combined
Platelets decreased															
N	61 (100%)	61 (100%)	122 (100%)	793 (99.4%)	798 (99.9%)	1591 (99.6%)	414 (99.5%)	414 (99.0%)	828 (99.3%)	186 (100%)	187 (100%)	373 (100%)	1454 (99.5%)	1460 (99.7%)	2914 (99.6%)
Subjects with post-baseline maximum Toxicity grade 0	43 (70.5%)	53 (86.9%)	96 (78.7%)	653 (82.3%)	643 (80.6%)	1296 (81.5%)	342 (82.6%)	347 (83.8%)	689 (83.2%)	159 (85.5%)	163 (87.2%)	322 (86.3%)	1197 (82.3%)	1206 (82.6%)	2403 (82.5%)
Toxicity grade 1	18 (29.5%)	7 (11.5%)	25 (20.5%)	133 (16.8%)	145 (18.2%)	278 (17.5%)	66 (15.9%)	56 (13.5%)	122 (14.7%)	23 (12.4%)	24 (12.8%)	47 (12.6%)	240 (16.5%)	232 (15.9%)	472 (16.2%)
Toxicity grade 2	0	0	0	5 (0.6%)	9 (1.1%)	14 (0.9%)	6 (1.4%)	9 (2.2%)	15 (1.8%)	3 (1.6%)	0	3 (0.8%)	14 (1.0%)	18 (1.2%)	32 (1.1%)
Toxicity grade 3	0	0	0	2 (0.3%)	1 (0.1%)	3 (0.2%)	0	2 (0.5%)	2 (0.2%)	0	0	0	2 (0.1%)	3 (0.2%)	5 (0.2%)
Toxicity grade 4	0	1 (1.6%)	1 (0.8%)	0	0	0	0	0	0	1 (0.5%)	0	1 (0.3%)	1 (0.1%)	1 (0.1%)	2 (0.1%)

Through Week 52 across the Phase 3 studies, <1% of sirukumab-treated subjects were permanently discontinued because of decreased leukocytes, decreased neutrophils, or decreased platelets.

Serious infection was reported in 2 cases within 3 weeks of the occurrence of neutropenia. A 64-year-old woman in the 100 mg q2w group received 9 doses of sirukumab and developed neutropenia and a UTI, which resolved with antibiotic treatment and discontinuation of methotrexate and sirukumab. A 29-year old woman in the 100 mg q2w group received 9 doses of sirukumab and developed a neutropenia (ANC 0.46 × 109/L), was withdrawn from study agent, and 2.5 weeks later had a peritonsillar abscess that resolved with incision, drainage, and antibiotics. Grade 3/grade 4 decreases

in platelets were mostly not associated with bleeding events; the exception was Subject 20002, who had MI, cardiac arrest, GI hemorrhage, and grade 3 thrombocytopenia per local laboratory report.

Effects of DMARDs on Haematology Parameters

The AE distribution by grades was similar in subjects who used DMARDs at baseline and those who did not. In addition, across the Phase 3 studies through the SCS cutoff date, the distribution by grades for haematology parameters was similar in subjects who used DMARDs at baseline and those who did not.

Clinical Chemistry

Generally, hepatic abnormalities are mostly drug-induced in RA. Liver enzyme abnormalities have been reported in patients receiving IL-6 pathway inhibitors. An increased frequency of these elevations was observed when potentially hepatotoxic drugs (eg, MTX) were used in combination. Liver enzymes were therefore closely monitored in the sirukumab clinical development program.

Alanine Aminotransferase

Integrated Placebo-Controlled Period

An increase in ALT to ≥8 × ULN was reported in 2 (0.2%) placebo subjects, 4 (0.5%) of sirukumab 50 mg subjects, and 7 (0.8%) sirukumab 100 mg subjects.

Table 32 Number of subjects with post-baseline values for ALT by maximum toxicity grade through 18 weeks of exposure

	Randomized Treatment Groups in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set, N	850	848	850
ALT increased, N	842 (99.1%)	843 (99.4%)	846 (99.5%)
Subjects with post-baseline maximum:			
Toxicity grade 0 (≤ULN)	662 (78.6%)	348 (41.3%)	358 (42.3%)
Toxicity grade 1 (>ULN-3.0 × ULN)	170 (20.2%)	444 (52.7%)	419 (49.5%)
Toxicity grade 2 (>3.0-5.0 × ULN)	6 (0.7%)	38 (4.5%)	51 (6.0%)
Toxicity grade 3 (>5.0-20.0 × ULN)	2 (0.2%)	13 (1.5%)	18 (2.1%)
Toxicity grade 4 (>20.0 × ULN)	2 (0.2%)	0	0

ALT=alanine aminotransferase; q2w=every 2 weeks; q4w=every 4 weeks; ULN=upper limit of normal.

Long-Term Integrated Safety Data

Through 52 weeks of exposure in ARA3002 and ARA3003 an increase in ALT to ≥8 × ULN was reported in 3 (0.4%) placebo subjects, 4 (0.3%) sirukumab 50 mg combined subjects, and 11 (0.9%) sirukumab 100 mg combined subjects. Consistent findings were reported through 24 weeks of exposure and through the SCS cutoff date in ARA3002 and ARA3003, and through 52 weeks of exposure in ARA3002.

Through the SCS cutoff date across the Phase 3 studies, most maximum increases in ALT were grade 0 or 1; the percentage of ALT values with a grade of 3 or 4 was low with both sirukumab doses. There were slightly more grade 2 and grade 3 increases in ALT with sirukumab 100 mg compared with sirukumab 50 mg. An increase in ALT ≥8 × ULN was reported in 4 (0.3%) subjects in the sirukumab 50 mg group and 15 (1.0%) subjects in the sirukumab 100 mg group. Consistent findings were reported prior to Week 52 across the Phase 3 RA studies.

Effect of DMARDs on ALT

Compared with subjects who were not treated with DMARDs at baseline, subjects treated with DMARDs at baseline were more likely to have a maximum elevation in ALT of grade 1 or 2 through 52 weeks of exposure in ARA3002 and ARA3003 and through the SCS cut-off date across all Phase 3 RA studies. DMARD use had no apparent effect on elevations of ALT ≥5 × ULN in these populations. In ARA3002 and ARA3003, consistent results were reported through 18 and 24 weeks of exposure, and through the SCS cutoff.

Aspartate Aminotransferase

Integrated Placebo-Controlled Period

An increase in AST to ≥8 × ULN was reported in 2 (0.2%) placebo subjects, no sirukumab 50 mg subjects, and 1 (0.1%) sirukumab 100 mg subject.

Table 33 Number of subjects with post-baseline values for AST by maximum toxicity grade through 18 weeks of exposure

	Randomized Treatment Groups in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set, N	850	848	850
AST increased, N	842 (99.1%)	843 (99.4%)	846 (99.5%)
Subjects with post-baseline maximum:			
Toxicity grade 0 (≤ULN)	704 (83.6%)	461 (54.7%)	464 (54.8%)
Toxicity grade 1 (>ULN-3.0 × ULN)	132 (15.7%)	362 (42.9%)	354 (41.8%)
Toxicity grade 2 (>3.0-5.0 × ULN)	3 (0.4%)	18 (2.1%)	22 (2.6%)
Toxicity grade 3 (>5.0-20.0 × ULN)	3 (0.4%)	2 (0.2%)	6 (0.7%)
Toxicity grade 4 (>20.0 × ULN)	0	0	0

AST=aspartate aminotransferase; q2w=every 2 weeks; q4w=every 4 weeks; ULN=upper limit of normal.

Long-Term Integrated Safety Data

Through 52 weeks of exposure in ARA3002 and ARA3003 an increase in AST to ≥8 × ULN was reported in 2 (0.2%) placebo subjects, no sirukumab 50 mg combined subjects, and 3 (0.2%) sirukumab 100 mg combined subjects. Consistent findings were reported through 24 weeks of exposure and through the SCS cutoff in ARA3002 and ARA3003, and through 52 weeks of exposure in ARA3002.

Through the SCS cutoff date across the Phase 3 studies there were slightly more AST grade 2 and grade 3 increases with sirukumab 100 mg compared with sirukumab 50 mg. An increase in AST ≥8 × ULN was reported in no subjects in the sirukumab 50 mg group and 5 (0.3%) subjects in the sirukumab 100 mg group.

Effect of DMARDs on AST

Compared with subjects who were not receiving DMARDs at baseline, subjects who were receiving DMARDs at baseline were more likely to have a maximum elevation in AST of grade 1 through 52 weeks of exposure in ARA 3002 and ARA3003, and through the SCS cutoff date across the Phase 3 studies. DMARD use had no apparent effect on elevations of AST ≥5 × ULN in these populations. In ARA3002 and ARA3003, consistent results were reported through 18 and 24 weeks of exposure and through the SCS cutoff date.

Bilirubin

Integrated Placebo-Controlled Period

Table 34 Number of subjects with post-baseline values for total bilirubin by maximum toxicity grade through 18 weeks of exposure

	Randomized Treatment Groups in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set, N	850	848	850
Total bilirubin increased, N	842 (99.1%)	843 (99.4%)	846 (99.5%)
Subjects with post-baseline maximum			
Toxicity grade 0 (≤ULN)	832 (98.8%)	762 (90.4%)	744 (87.9%)
Toxicity grade 1 (>ULN-1.5 × ULN)	10 (1.2%)	55 (6.5%)	54 (6.4%)
Toxicity grade 2 (>1.5–3.0 × ULN)	0	25 (3.0%)	47 (5.6%)
Toxicity grade 3 (>3.0-10.0 × ULN)	0	1 (0.1%)	1 (0.1%)
Toxicity grade 4 (>10 × ULN)	0	0	0

q2w=every 2 weeks; q4w=every 4 weeks; ULN=upper limit of normal.

Long Term Integrated Safety Data

Compared with through 18 weeks of exposure, through 52 weeks of exposure in ARA3002 and ARA3003, the percentages of subjects with grade 1, 2, or 3 increases in bilirubin were slightly higher across all treatment groups. No dose relationship was observed in the grade or frequency of total bilirubin increases and there were no grade 4 increases in bilirubin through 52 weeks. Analysis of ARA3002 and ARA3003 through 24 weeks of exposure was consistent and also demonstrated no dose relationship for bilirubin increases.

Across the Phase 3 studies through the SCS cutoff date and prior to Week 52, the pattern of maximum increases in total bilirubin was consistent with observations through 18 weeks in the placebo-controlled studies. No dose relationship was observed in the grade or frequency of total bilirubin increases and there were no grade 4 increases.

Lipids

Elevations in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides, were observed in patients receiving IL-6 inhibitors, including tocilizumab. Lipid parameters were therefore followed closely in the sirukumab clinical development program.

Total Cholesterol

Through 18 weeks of exposure in ARA3002 and ARA3003, the majority of total cholesterol maximum increases were NCI-CTCAE toxicity grade 0. Grade 1 and grade 2 increases were reported more frequently with sirukumab. The percentage of total cholesterol values with a grade of 3 or 4 was low across treatment groups.

Table 35 Number of subjects with post-baseline values for total cholesterol by maximum toxicity grade through 18 weeks of exposure

	Randomized Treatment Groups in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set, N	850	848	850
Total cholesterol increased, N (%)	829 (97.5%)	827 (97.5%)	834 (98.1%)
Subjects with post-baseline maximum			
Toxicity grade 0 (≤ULN)	783 (94.5%)	667 (80.7%)	662 (79.4%)
Toxicity grade 1 (>ULN-300 mg/dL)	17 (2.1%)	51 (6.2%)	58 (7.0%)
Toxicity grade 2 (>300-400 mg/dL)	29 (3.5%)	101 (12.2%)	110 (13.2%)
Toxicity grade 3 (>400-500 mg/dL)	0	7 (0.8%)	3 (0.4%)
Toxicity grade 4 (>500 mg/dL)	0	1 (0.1%)	1 (0.1%)

q2w=every 2 weeks; q4w=every 4 weeks; ULN=upper limit of normal.

Long-Term Integrated Safety Data

Through 52 weeks of exposure in ARA3002 and ARA3003, in subjects with baseline total cholesterol ≤ 200 mg/dL, a higher percentage of subjects in the sirukumab 50 mg (71.2%) and 100 mg (75.4%) groups shifted to post-baseline values >200 mg/dL compared with the placebo group (31.5%). Among subjects with baseline total cholesterol >200 mg/dL, across treatment groups, most subjects (>90%) continued to have high total cholesterol levels. A similar pattern of total cholesterol shifts was observed in integrated analyses of sirukumab-treated subjects across the Phase 3 RA studies.

Effect of DMARDs on Total Cholesterol

Through 52 weeks of exposure in ARA3002 and ARA3003, subjects who used DMARDs at baseline and those who did not had similar shifts in total cholesterol and distributions by maximum toxicity grades.

LDL Cholesterol

Integrated Placebo-Controlled Period

Table 36 Summary of change from baseline in LDL cholesterol values (mg/dL) at Week 8 and Week 16 through 18 weeks of exposure

	Randomized Treatment Groups in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set, N	850	848	850
Week 8			
N	794	790	792
Mean (SD)	0.18 (23.034)	21.30 (28.689)	23.21 (31.379)
Median	-0.77	19.50	20.97
IQ range	(-12.4, 12.0)	(4.2, 34.7)	(4.0, 40.3)
Range	(-121.2, 153.7)	(-139.4, 187.7)	(-169.5, 211.6)
Week 16			
N	769	767	764
Mean (SD)	0.37 (23.309)	21.08 (29.725)	21.38 (32.715)
Median	-1.00	18.53	20.97
IQ range	(-12.7, 13.1)	(3.1, 36.9)	(3.0, 37.9)
Range	(-93.1, 146.7)	(-142.9, 175.7)	(-119.7, 144.8)

IQ=interquartile range; LDL=low-density lipoprotein; q2w=every 2 weeks; q4w=every 4 weeks; SD=standard deviation.

Long-Term Integrated Safety Data

Through 52 weeks of exposure in ARA3002 and ARA3003, in subjects with baseline LDL cholesterol ≤ 130 mg/dL, a higher percentage of subjects in the sirukumab 50 mg (53.9%) and 100 mg (55.8%) groups shifted to post-baseline values >130 mg/dL compared with the placebo group (21.1%). Among subjects with baseline LDL cholesterol >130 mg/d, across treatment groups, most subjects (>85%) continued to have high LDL cholesterol levels. A similar pattern of LDL cholesterol shifts was observed in integrated analyses of sirukumab-treated subjects across the Phase 3 RA studies.

HDL Cholesterol

Through 18 weeks of exposure in ARA3002 and ARA3003, HDL cholesterol increased with both doses of sirukumab relative to placebo at Week 8 and remained elevated through Week 16.

For the sirukumab dose groups across the Phase 3 RA studies, the HDL cholesterol increases observed at Week 8 were maintained through Week 52 and there was no dose relationship, consistent with observations through 18 weeks in the placebo controlled studies.

Fasting Triglycerides

Through 18 weeks of exposure in ARA3002 and ARA3003, fasting triglycerides increased with both doses of sirukumab relative to placebo at Week 8 and remained elevated at Week 16.

Table 37 Summary of change from baseline in fasting triglyceride values (mg/dL) at Week 8 and Week 16 through 18 weeks of exposure

	Randomized Treatment Groups in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set, N	850	848	850
Week 8			
N	730	714	723
Mean (SD)	-6.60 (85.947)	32.39 (79.347)	30.53 (67.828)
Median	-4.00	17.70	19.47
IQ range	(-22.1, 17.7)	(-7.1, 48.0)	(-5.0, 53.1)
Range	(-1825.8, 275.8)	(-197.4, 734.6)	(-348.7, 582.5)
Week 16			
N	692	688	698
Mean (SD)	-3.03 (97.115)	36.73 (90.653)	28.93 (85.124)
Median	-0.89	20.35	17.98
IQ range	(-22.0, 21.2)	(-3.8, 55.9)	(-6.2, 52.2)
Range	(-2083.3, 530.1)	(-137.9, 1437.8)	(-302.7, 1361.1)

IQ=interquartile range; q2w=every 2 weeks; q4w=every 4 weeks; SD=standard deviation.

Through 18 weeks of exposure in ARA3002 and ARA3003, the majority of fasting triglyceride maximum increases were NCI-CTCAE toxicity grade 0 or 1.

Table 38 Number of subjects with post-baseline values by maximum toxicity grade for fasting triglycerides through 18 weeks of exposure

	Randomized Treatment Groups in ARA3002 and ARA3003		
		Sirukumab	
	Placebo	50 mg q4w	100 mg q2w
Exposure time controlled analysis set, N	850	848	850
Fasting triglycerides increased, N (%)	829 (97.5%)	827 (97.5%)	834 (98.1%)
Subjects with post-baseline maximum:			
Toxicity grade 0 (≤150 mg/dL)	564 (68.0%)	437 (52.8%)	444 (53.2%)
Toxicity grade 1 (>150-300 mg/dL)	238 (28.7%)	314 (38.0%)	316 (37.9%)
Toxicity grade 2 (>300-500 mg/dL)	24 (2.9%)	57 (6.9%)	60 (7.2%)
Toxicity grade 3 (>500-1,000 mg/dL)	3 (0.4%)	17 (2.1%)	13 (1.6%)
Toxicity grade 4 (>1,000 mg/dL)	0	2 (0.2%)	1 (0.1%)

q2w=every 2 weeks; q4w=every 4 weeks.

Long-Term Integrated Safety Data

Through 52 weeks of exposure in ARA3002 and ARA3003, in subjects with baseline fasting triglycerides ≤250 mg/dL, a higher percentage of subjects in the sirukumab 50 mg (22.1%) and 100 mg (22.5%) groups shifted to post-baseline values >250 mg/dL compared with the placebo group (6.0%). Among subjects with baseline fasting triglycerides >250 mg/dL, across treatment groups, most subjects (>50%) continued to have high total cholesterol levels. A similar pattern of total cholesterol shifts was observed in integrated analyses of sirukumab-treated subjects across the Phase 3 RA studies.

For the sirukumab dose groups across the Phase 3 RA studies, fasting triglyceride increases observed at Week 8 were maintained through Week 52 and there was no dose relationship, consistent with observations through 18 weeks in the placebo controlled studies. Analyses of ARA3002 and ARA3003 through 24 weeks of exposure were also consistent and demonstrated no dose relationship for fasting triglyceride increases.

Effect of DMARDs on Fasting Triglycerides

Through 52 weeks of exposure in ARA3002 and ARA3003, subjects who used DMARDs at baseline and those who did not had similar shifts in fasting triglycerides and distributions by maximum toxicity grades.

Total Cholesterol to HDL Ratio

The desired total cholesterol to HDL ratio is <4.0.

Integrated Placebo-Controlled Period

Through 18 weeks of exposure in ARA3002 and ARA3003, total cholesterol:HDL ratio slightly increased with both doses of sirukumab relative to placebo at Week 8 and remained elevated at Week 16. Increases in total cholesterol:HDL ratio were not considered clinically meaningful as the observed mean total cholesterol:HDL ratio remained below 4.0 for all treatment groups.

Effect of DMARDs on Total Cholesterol to HDL Ratio

Through 18 weeks of exposure in ARA3002 and ARA3003, the total cholesterol to HDL ratio was similar in subjects who used DMARDs at baseline and those who did not.

Safety in special populations

Table 39 Number of subjects with 1 or more treatment-emergent AEs prior to Week 52 by subgroups; sirukumab controlled analysis set

	Sirukumab		
	50 mg q4w	100 mg q2w	Combined
Sex			
Male	255	252	507
Subjects with 1 or more AEs	198 (77.6%)	192 (76.2%)	390 (76.9%)
Female	1071	1076	2147
Subjects with 1 or more AEs	847 (79.1%)	869 (80.8%)	1716 (79.9%)
Race			
White	973	963	1936
Subjects with 1 or more AEs	725 (74.5%)	732 (76.0%)	1457 (75.3%)
Black or African American	41	49	90
Subjects with 1 or more AEs	32 (78.0%)	38 (77.6%)	70 (77.8%)
Asian	231	252	483
Subjects with 1 or more AEs	215 (93.1%)	233 (92.5%)	448 (92.8%)
Other	79	60	139
Subjects with 1 or more AEs	71 (89.9%)	55 (91.7%)	126 (90.6%)
Unknown	2	4	6
Subjects with 1 or more AEs	2 (100%)	3 (75.0%)	5 (83.3%)
Ethnicity			
Hispanic or Latino	228	215	443
Subjects with 1 or more AEs	169 (74.1%)	169 (78.6%)	338 (76.3%)
Not Hispanic or Latino	1078	1096	2174
Subjects with 1 or more AEs	859 (79.7%)	879 (80.2%)	1738 (79.9%)
Not Reported	18	12	30
Subjects with 1 or more AEs	15 (83.3%)	10 (83.3%)	25 (83.3%)
Unknown	2	5	7
Subjects with 1 or more AEs	2 (100%)	3 (60.0%)	5 (71.4%)
Age			
<45 years	279	316	595
Subjects with 1 or more AEs	213 (76.3%)	241 (76.3%)	454 (76.3%)
≥45 to <65 years	811	794	1605
Subjects with 1 or more AEs	636 (78.4%)	632 (79.6%)	1268 (79.0%)
≥65 to <75 years	195	190	385
Subjects with 1 or more AEs	157 (80.5%)	164 (86.3%)	321 (83.4%)
≥75 to <85 years	41	28	69
Subjects with 1 or more AEs	39 (95.1%)	24 (85.7%)	63 (91.3%)
≥85 years	0	0	0
Subjects with 1 or more AEs	0	0	0
Geographic Location			
North America	366	352	718
Subjects with 1 or more AEs	290 (79.2%)	296 (84.1%)	586 (81.6%)
Europe	574	587	1161
Subjects with 1 or more AEs	412 (71.8%)	423 (72.1%)	835 (71.9%)

Age Groups

In both the placebo and the sirukumab treatment groups through 24 or 52 weeks of exposure, and in sirukumab-treated subjects through 52 weeks of exposure, the proportions of subjects with SAEs, serious infections, MACE, and malignancies generally increased with older age.

The frequency of serious infections increased with each age strata for both placebo- and sirukumab-treated subjects, with the highest rates observed in the subjects aged ≥65 years. While the rate of serious infection through 24 weeks of exposure was higher for sirukumab compared with placebo for

each age strata, there was no clear pattern that would suggest a disproportionately greater risk of infection from sirukumab for older versus younger subjects when taking into account the differences in placebo rates in the older subjects.

Although potential differences between the sirukumab trial population and the real-world RA population limit the ability to make direct comparisons, the increased incidence of AEs of interest with increasing age in sirukumab-treated subjects is consistent with observations in the general RA population from published literature (note, rates of these AEs of interest from observational studies discussed here are in units of 1,000 person-years, in accordance with the original units used in the publications). The Applicant points out that a study of mortality in RA patients in Ontario, Canada, found an incidence rate of 24.6 deaths per 1,000 patients in those aged 65 to 74 years and 58.4 deaths per 1,000 patients in those aged 75 to 84 years from 2008 to 2009, with mortality rates increasing with age as expected In a study of RA patients over age 65 years, the rate of serious infections was 46.4 events per 1,000 patient-years, while a study in RA patients from British Columbia found rates of cardiovascular events to be 19.6 per 1,000 person-years in patients aged 65-74 years and 54.6 per 1,000 person-years in patients older than 75 years. The rate of malignancy also is known to increase with older age in RA patients. Hence, age is an important risk factor for mortality, serious infections, cardiovascular events, and malignancy in the RA population.

Table 40 Incidence rate (subject based per 100 subject years of follow-up) and number of subjects who died or had an AE of interest by age group through the sirukumab controlled period; sirukumab controlled analysis set

	<45 years	≥45 to <65 years	≥65 to <75 years	≥75 to <85 years
Number of subjects (sirukumab 50 mg and sirukumab 100 mg groups combined)	655	1773	424	74
Deaths				
Number	0	12 (0.7%)	9 (2.1%)	8 (10.8%)
Incidence rate (95% CI)	0.00 (0.00, 0.31)	0.44 (0.23, 0.77)	1.48 (0.68, 2.81)	8.07 (3.48, 15.90)
Serious infection				
Number	27 (4.1%)	110 (6.2%)	51 (12.0%)	15 (20.3%)
Incidence rate (95% CI)	2.85 (1.88, 4.14)	4.10 (3.37, 4.94)	8.82 (6.57, 11.60)	15.57 (8.72, 25.68)
MACE				
Number	1 (0.2%)	17 (1.0%)	7 (1.7%)	4 (5.4%)
Incidence rate (95% CI)	0.10 (0.00, 0.58)	0.62 (0.36, 1.00)	1.16 (0.47, 2.39)	4.06 (1.11, 10.40)
Malignancy (excluding NMSC)				
Number	3 (0.5%)	16 (0.9%)	7 (1.7%)	6 (8.1%)
Incidence rate (95% CI)	0.31 (0.06, 0.91)	0.59 (0.34, 0.95)	1.15 (0.46, 2.38)	6.13 (2.25, 13.34)

CI=confidence interval; MACE=major adverse cardiovascular event; NMSC=non-melanoma skin cancer

Relationship Between Serum Sirukumab Concentration and Safety in RA

The relationships between steady-state trough serum sirukumab concentrations and selected safety measurements were assessed based on the PK evaluable subjects for each Phase 3 study. Within each Phase 3 study, there were no apparent relationships between individual steady-state trough serum sirukumab concentrations and the respective changes from baseline or maximum post-baseline values through Week 24 for serum chemistry parameters (albumin, total protein, ALT, AST, and total bilirubin), changes from baseline at Week 24 for lipid parameters (LDL cholesterol, HDL cholesterol, total cholesterol, and fasting triglycerides), and changes from baseline at Week 24 for hematology parameters (neutrophil count, platelet count, and WBC count).

Across the Phase 3 studies, no apparent relationships were identified between sirukumab exposure metrics (ie, cumulative AUC and steady-state Cmax, Cmin, and Cave) and the occurrence of serious

infections or triglyceride elevations, and only small ER trends were observed between sirukumab exposure and neutropenia, ALT elevation, or LDL cholesterol elevation in subjects receiving SC sirukumab treatment, consistent with the known modulation effects of anti-IL 6 agents, as reported for other anti-IL-6 biologics in subjects with RA

Vaccines Substudy

Given the role of IL-6 in mediating immune responses, a multicenter, nonrandomized, open-label vaccine response sub study was conducted to evaluate response to the tetanus, diphtheria, and acellular pertussis (Tdap) and pneumococcal vaccines in subjects who received at least 6 months of treatment in ARA3002. A total of 153 subjects at selected sites who were still receiving study agent at Week 28 received a single administration of the Tdap and pneumococcal vaccines in this optional substudy and were followed for safety and vaccine responses for 4 weeks. These results are summarized below:

- Pneumococcal vaccine. The proportion of subjects with a response (at least 12 of 23 serotypes had >2-fold increase in antibody level from before vaccination to after vaccination) to pneumococcal vaccine was higher in the placebo group (89.3%) compared with the sirukumab 50 mg (83.3%) and 100 mg (74.2%) groups. For the majority of serotypes, the response rate was numerically higher for the sirukumab 50 mg group compared with the 100 mg group. The clinical significance of these differences cannot be determined by this type of immunological response study.

- Tdap vaccine. The response to Tdap (a >4-fold increase in antibody level from before vaccination to after vaccination with Tdap) was comparable in the placebo (42.9%), sirukumab 50 mg (39.6%), and sirukumab 100 mg (41.7%) groups.

Baseline DMARD Use

DMARDs were the most common medication, which were used by almost 90% of subjects in each treatment group. Approximately 60% of subjects in each group were taking MTX ≥12.5 mg/week at baseline.

Increases in ALT and AST were the other events for which a difference was noted between subjects who were and were not receiving DMARDs at baseline. Subjects receiving DMARDs at baseline were more likely to have a maximum elevation of grade 1 or 2 (ALT) or grade 1 (AST) through 52 weeks of exposure in ARA3002 and ARA3003 and through the SCS cutoff date across the Phase 3 RA studies. DMARD use had no apparent effect on elevations of ALT or AST ≥5 × ULN in these populations. In ARA3002 and ARA3003, consistent results were reported through 18 and 24 weeks of exposure, and through the SCS cutoff date. Through the SCS cutoff date, the proportions of subjects with hepatobiliary abnormalities were similar regardless of DMARD use at baseline, as was seen with other analyses. Methotrexate is known to be associated with liver enzyme elevations (methotrexate prescribing information) and therefore, the increased grade 1 and 2 elevations seen in subjects on baseline DMARDs may reflect MTX use.

Comparison of Safety Data from ARA3002 and ARA3003 (DMARD Inadequate Response vs Anti-TNF Inadequate Response)

The rates of SAEs, serious infections, malignancy, and GI perforations were higher in ARA3003 than in ARA3002, although the numbers of the latter two events were too small to draw definitive conclusions (Table 41). The rate of deaths was higher in ARA3002 than 3003 but, the numbers were small. Based on this, it is possible that subjects in ARA3003 who were intolerant or refractory to anti-TNFα therapy may have had more advanced disease and comorbidities than those in ARA3002, and therefore were more prone to develop SAEs or some AEs of special interest.

Table 41 Incidence rates (95% CIs) for deaths, SAEs, and AEs of special interest per 100 subject-years of exposure through the SCS cutoff date for ARA3002 and ARA3003 (combined 50 mg and 100 mg groups)

	ARA3002	ARA3003
Number of subjects	1597	834
Death	0.81 (0.51, 1.22)	0.49 (0.18, 1.08)
SAE	11.27 (10.00, 12.66)	18.31 (15.85, 21.03)
MACE	0.66 (0.39, 1.05)	0.75 (0.34, 1.42)
Malignancy	0.81 (0.51, 1.23)	1.32 (0.76, 2.15)
Serious infection	4.06 (3.33, 4.90)	6.42 (5.06, 8.03)
GI perforation	0.15 (0.04, 0.38)	0.66 (0.28, 1.30)
Hepatobiliary abnormality	0.55 (0.31, 0.91)	0.58 (0.23, 1.19)

Use in Pregnancy and Lactation

No studies of sirukumab were conducted in pregnant or lactating women. The sirukumab protocols mandated the use of highly effective contraception during the studies, and for 4 months after receiving the last dose of study agent. Discontinuation of study agent was required in the event that a subject became pregnant.

Immunological events

Relationship Between Antibodies to Sirukumab and Safety in RA

The number of subjects who were positive for antibodies to sirukumab was small (ARA3002 through Week 52: 16/654 [2.4%]; ARA3003 through Week 52: 2.8% [22/780]; ARA3005 through Week 24: 11/343 [3.2%]).

The relationship between antibodies to sirukumab and injection site reactions in the combined Phase 3 RA studies (ARA3001, ARA3002, ARA3003, and ARA3005 through Week 24; ARA3001, ARA3002 and ARA3003 through Week 52) is summarized below:

- Among subjects who were **positive** for antibodies to sirukumab through Week 24, 7 (22.6%) of 31 subjects had ISRs, including 1 subject (ARA3003) who had severe ISRs that led to discontinuation of sirukumab treatment; however, no subjects had serious ISRs. Among subjects who were **negative** for antibodies to sirukumab through Week 24, 250 (15.2%) of 1,643 subjects had ISRs through Week 24, including 3 subjects who had severe ISRs and 6 subjects who had ISRs that led to discontinuation of sirukumab treatment; however, no subjects had serious ISRs.
- Among subjects who were **positive** for antibodies to sirukumab through Week 52, 8 (18.2%) of 44 subjects had ISRs, including the previously mentioned ARA3003 subject who had a severe ISR that led to discontinuation of sirukumab treatment; however, none of the subjects had serious ISRs. Among subjects who were **negative** for antibodies to sirukumab through Week 52, 283 (18.7%) of 1,512 subjects had ISRs, including 2 subjects who had severe ISRs and 9 subjects who had ISRs that led to discontinuation of sirukumab treatment; however, none of the subjects had serious ISRs.

The relationship between the presence of antibodies to sirukumab and hypersensitivity in the Phase 3 RA studies is summarized below:

- In ARA3002, hypersensitivity was reported in 2 subjects in the placebo group, 2 subjects in the combined sirukumab 50 mg q4w group, and 2 subjects in the combined sirukumab 100 mg

q2w group before Week 52. Five of the 6 subjects who developed hypersensitivity were tested for antibodies to sirukumab; none was positive for antibodies to sirukumab.

- In ARA3003, hypersensitivity was reported in 4 subjects in the placebo → 100 mg q2w group and 5 subjects in the sirukumab 100 mg q2w group before Week 52; none was positive for antibodies to sirukumab.
- In ARA3005, hypersensitivity was reported in 1 subject in the combined sirukumab 50 mg q4w group and 3 subjects in the combined sirukumab 100 mg q2w group; 1 subject (sirukumab 100 mg) was positive for antibodies to sirukumab.

Discontinuation due to AES

Through the 18-week placebo controlled period in ARA3002 and ARA3003, the numbers of subjects who discontinued study agent were: 47 (5.5%) subjects in the placebo and sirukumab 50 mg q4w groups and 55 (6.5%) subjects in the sirukumab 100 mg q2w group. Adverse event was the most common reason for discontinuation in the sirukumab 50 mg and 100 mg groups (in 26 and 33 subjects, respectively); in the placebo group, the most common reason was lack of efficacy (in 18 subjects).

Through the SCS cutoff date, 33.3%, 31.5%, and 28.4% of subjects in ARA3002 and ARA3003 discontinued study agent early in the placebo group, sirukumab 50 mg, and sirukumab 100 mg groups, respectively. The most common reasons for early discontinuation of study agent in the placebo, sirukumab 50 mg, and sirukumab 100 mg groups were AE (11.9%, 13.1%, and 14.1%, respectively), lack of efficacy (6.8%, 5.8%, and 4.4%, respectively), and withdrawal of consent (6.0%, 5.2%, and 4.9%, respectively). More subjects in the placebo group met EE criteria (33.1%, all of whom were rerandomized) compared with the sirukumab 50 mg q4w (15.0%) and sirukumab 100 mg q2w (11.9%) groups. The proportions of subjects who met LE criteria (in ARA3002 only) were similar among the groups: 2.8%, 2.1%, and 2.5% in the placebo, sirukumab 50 mg, and sirukumab 100 mg groups, respectively.

Across all studies of sirukumab in RA (ie, the all-subjects analysis population), more subjects discontinued study agent administration early in the placebo group (32.3%) compared with the combined sirukumab group (20.3%) and the adalimumab group (15.6%). Adverse event was the most common reason for early discontinuation of study agent in the placebo, combined sirukumab, and adalimumab groups (11.6%, 9.4%, and 5.9%, respectively).

Integrated Placebo-Controlled Period

Through 18 weeks of exposure, the proportions of subjects discontinuing study agent administration due to 1 or more AEs in ARA3002 and ARA3003 were generally similar between the sirukumab treatment groups: 22 (2.6%) in the placebo group, 34 (4.0%) in the sirukumab 50 mg q4w group, and 45 (5.3%) in the sirukumab 100 mg q2w group. The SOC with the most frequently reported AEs leading to discontinuation was Investigations (in 4, 13, and 10 subjects, respectively); across the 3 treatment groups, most events in this SOC were events related to increases in hepatic enzymes.

Adalimumab Controlled Period

In ARA3005, 7.0% (n=13), 12.4% (n=23), and 10.2% (n=19) of subjects in the adalimumab, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups had AEs that led to permanent discontinuation of study agent during the sirukumab controlled period. No pattern of events was seen; the most common PT, Alanine aminotransferase increased, was reported in 2 subjects in each of the 3 treatment groups.

Long-Term Integrated Safety Data

Across the Phase 3 studies through the SCS cutoff date, 11.9% of subjects in the sirukumab 50 mg q4w group and 13.4% of subjects in the sirukumab 100 mg q2w group had AEs that led to discontinuation of study agent. Infections and Infestations was the SOC in which these AEs were most frequently reported, in similar proportions between the 50 mg and 100 mg groups (3.4% and 3.8%, respectively), followed by Investigations (2.0% and 2.3%, respectively). The most frequently reported PTs were in the Investigations SOC: Alanine aminotransferase (ALT) increased (in 14 [1.0%] and 15 [1.0%] subjects) and Aspartate aminotransferase (AST) increased (in 9 [0.6%] and 11 [0.8%] subjects) in the combined 50 mg and combined 100 mg groups, respectively.

Effect of DMARDs on Discontinuations due to AEs

Through the SCS cutoff date, the proportions of subjects with AEs that led to discontinuation were similar in the sirukumab dose groups regardless of baseline DMARD use.

3.4.8. Discussion on clinical safety

The Applicant provided safety data from the 7 studies included in the sirukumab RA development program. The following populations were analysed:

- Exposure time controlled analysis set (ARA3002 and ARA3003) through 18, 24, and 52 weeks of exposure
- Adalimumab controlled analysis set: ARA3005
- Sirukumab controlled analysis set: all subjects who received at least 1 (partial or complete) dose of sirukumab during the Phase 3 clinical studies ARA3002 and ARA3003 (including data during ARA3004 for each study), plus ARA3001 and ARA3005, up to Week 52, and through the SCS cutoff date
- All subjects in ARA3002 and ARA3003 through the SCS cutoff date: (including data during ARA3004 for each study)
- All subjects analysis set: ARA3002 and ARA3003 (including data during ARA3004 for each study), ARA3001, and ARA3005, plus ARA1001 and C1377T04 through the SCS cutoff date

Within the development program 3,120 subjects have received sirukumab up to 3.4 years. More than 2000 of these have received sirukumab for more than a year, whereof approximately half received the dose proposed for marketing, and half a four-fold higher dose. The size of the safety data base is considered sufficient. Across the Phase 3 studies, demographic characteristics at baseline of the primary study were similar to those in the placebo-controlled population and between the sirukumab 50 mg and 100 mg groups.

In the placebo controlled Phase 3 studies (ARA3002 and ARA3003), more than 80% were taking MTX at baseline. 60% of the included subjects were taking ≥12.5 mg/week. Across all Phase 3 studies, approximately 70 % were taking MTX at baseline. Approximately 51% were taking ≥12.5 mg/week.

Approximately 83% of sirukumab treated subjects in ARA 3002 (placebo-controlled studies in MTX refractory patients) and 82% in ARA3003 (TNF-inhibitor refractory patients) experienced AEs through 52 weeks of exposure, as compared to 64% in the integrated placebo group. The fact that subjects with a response less 20% in swollen and tender joints received active drug from week 18 (ARA2002

and 3003) or 40 (ARA3002), "early escape or late escape", hampers the assessment, since the cohorts are thereafter no longer randomized the placebo group being healthier.

The most obvious difference in AE between the higher and lower sirukumab dosing groups through week 52 was the rate of injection site reactions, 12.1% vs 19.3%. It is also noted that there were numerically slightly more GI perforations (4 vs 2) and systemic hypersensitivity reaction (6 vs 1) in the higher dosed group. However, numbers are small, and no firm conclusions may be drawn.

Not surprisingly there were more serious infections among the sirukumab-treated than the placebo-treated subjects, but no major difference between dosing groups. There were also more hepatobiliary abnormalities in the sirukumab-treated groups, which is also in line with the known safety profile of IL-6-inhibitors. GI perforations have also been described for the IL-6R-inhibitor tofalizumab. There were more deaths among sirukumab-treated subjects. This, and SAEs of special interest are further discussed below.

Since average duration of exposure differed between sirukumab treated and placebo treated groups, exposure adjusted incidence rates are needed in order interpret and evaluate the results. The Applicant has provided this upon request.

Deaths

Of the 35 deaths reported in the sirukumab RA development program, 1 occurred in a placebo treated patient. Of the 34 deaths in sirukumab treated subjects, 30 occurred within 16 weeks of last dose of study agent.

The mortality incidence rate adjusted for follow-up time was 0.75 deaths per 100 subject-years (95% CI 0.52, 1.04) for all deaths reported in sirukumab-treated subjects in the RA studies, regardless of the death occurring within 16 weeks of the last dose, excluding deaths that occurred more than 16 weeks after the last sirukumab dose. This calculation provided incidence rates of deaths per 100 subject-years of exposure of 0.66 for the 2 groups combined. However, the remaining 4 cases should be included when calculating incidence rate, since not being exposed to the drug at the time of death does not necessarily mean that the event leading to death did not start during drug exposure.

The majority of deaths (22/35) occurred in study ARA 3002, i.e. in the MTX inadequate responder-population. Fourteen of 29 deaths in subjects who participated in ARA3002 and ARA3003 were in placebo group subjects who had transitioned to sirukumab via EE, LE, or CO (cross-over, re-randomized placebo subjects). The Applicant argues that the subjects who received sirukumab after reaching the cross-over, showed inflammatory parameters up to introduction of active substance that were slightly lower, but persisted over a more extended time than the EE/LE subjects, and the two groups therefor carried a comparable inflammatory burden, which is a risk factor for increased mortality. In addition the Applicant claims that subjects who transitioned from placebo to sirukumab introduces a bias when combined with subjects randomized to sirukumab as frontline treatment, due to the higher inflammatory activity in these subjects. The Applicant argues that this created at decrease in the risk of mortality in the placebo group, and an increased risk of mortality risk in the sirukumab groups, due to other factors than sirukumab treatment.

An ITT analysis is not informative regarding the imbalance in mortality since the majority of patients in the placebo group eventually also are exposed to sirukumab at some time during the study period. Only 14% of the study population remain unexposed to sirukumab. The attenuation of incidence rate differences from adjustment for baseline age and HAQ using Poisson regression is informative regarding the impact of some baseline risk factors for mortality but does not provide further clarity.

If patients are censored after the escape/cross-over time points this may be seen as an attempt to deal with the problem that it is patients with increased risk for mortality that have the highest likelihood to meet criteria for transition from placebo to active treatment with sirukumab. The results from this analysis still suggest a 3-5 times increased mortality risk associated with sirukumab exposure. Due to the low number of event the precision of these estimates is very poor and this may be the main concern with these analyses. Censoring is also likely informative and a key assumption for this analysis is consequently violated. The consequences of informative censoring in this case remain speculative. These analyses must anyway be interpreted with caution and are unable to provide further substantial clarity regarding the observed imbalance in mortality.

In "scenario analyses" the Applicant compares patients assigned sirukumab from study start to those patients that switched from placebo to sirukumab during the study. These analyses rest on several assumptions that can be questioned. The conclusions by the Applicant are not fully agreed. The analyses provide some support for the impact of disease activity on mortality risk. However, calculations based on the assumption that difference between start and switch groups can be attributed to disease activity can be questioned. It remains to be considered how much of the imbalance in mortality that can be explained by disease activity. Both sirukumab and disease activity can act in parallel as causal factors.

One key problem with the observed imbalance in mortality, apart from the fact that it rests on few observations, is that exposure to sirukumab in individual patients has changed over the course of the study period, guided by patient characteristics that are also related to mortality risk. A possible analytical strategy for this type of problem is to use marginal structural models (MSM) as originally proposed by Robins et al 2000 (for a review on the application to drug safety analyses see Gibbons 2016). Two dynamic models are applied in sequence. The first part serves to derive inverse probability weights from the treatment selection process, and the second to account for the dynamic effect of treatment on mortality.

In the results presented the estimated mortality rate for those initially randomized to sirukumab is lower than those randomized to placebo and switching to sirukumab, when patient characteristics related to the change in exposure status and disease severity over time are adjusted for in the MSM analysis (see Table 4 below from Response to D180 LoOI). This provides some support for the absence of a dose-response relation between sirukumab exposure and mortality. This consequently does not provide support for a causal relation between sirukumab and mortality but does not directly support that the mortality imbalance is caused by severity of disease among switchers. For this the direct contrast between pure placebo exposure and pure sirukumab exposure could provide further insight.

Table 4: Mortality Rate Marginal Structural Model (SCS)

Treatment Regime	Deaths†	N†	Exposure†	Rate* (95% CI)	Rate Ratio (95% CI)	P-value
d(50;50,50)	8	848	1488.6	0.54 (0.27, 1.08)	0.55 (0.20, 1.52)	0.246
d(Placebo;50,50)	8	483	763.7	0.99 (0.46,2.10)	1	
d(100;100,100)	6	850	1501.4	0.47 (0.21, 1.06)	0.49 (0.17, 1.45)	0.199
d(Placebo;100,100)	8	484	763.4	0.95 (0.47, 1.92)	1	

* Marginal Structural Mortality rate per 100 subject-years using modelled IPTWs
† Unweighted

In the final MSM analysis requested, the study design is ignored and data analysed based on actual exposure, and an IPTW weighted MSM approach is utilized. In the MSM, the probability of escape is associated with disease burden. Based on clinical consideration and data exploration, Disease Activity Score (DAS)28 (C-reactive protein [CRP]) measured at the time of escape, with a high disease cutpoint of 5.1 (DAS28 ≤5.1 versus DAS28 >5.1) was considered by the Applicant as an appropriate predictor for escape. This variable has also been identified as being related to mortality. Table 1 below shows the association between DAS28 and escape.

Table 1: Concordance between DAS28 and escape (EE/LE)

	DAS28 ≤5.1	**DAS28 >5.1**
ARA3002	N=2432	N=583
Escape	113 (4.7%)	275 (47.2%)
No Escape	2319 (95.4%)	308 (52.8%)
ARA3003	N=569	N=309
Escape	44 (7.7%)	140 (45.3%)
No Escape	525 (92.3%)	169 (54.7%)
Note: Subjects in ARA3002 who did not escape at Week 18 are counted twice in the table: one at Week 18 and the other at Week 40.		
Abbreviation: DAS=Disease Activity Score		

The analysis approach is then based on a Poisson regression model with MSM derived weights. As age is a critical predictor for mortality, it is included (≤65 and >65 years old) as the single covariate for a parsimonious model. The results are presented below in Table 2. In study ARA3002, the rate ratio is 1.91 (rate difference=0.86) but the precision of this estimate is poor due to the low event rate. Due to the limited number of events in study ARA3003, the model cannot be fit separately for that study, however, these data are included in the pooled analysis for studies ARA3002 and ARA3003. The results for the pooled analysis are consistent with those from study ARA3002. The model was also fit using Health Assessment Questionnaire (HAQ) and dichotomous age as covariates with results similar to the final model as HAQ was not statistically significant.

Table 2: Mortality Rate Marginal Structural Model

Treatment Group	Deaths	N	Exposure	Rate* (95% CI)	Rate Difference (95% CI)	Rate ratio** (95% CI)
ARA3002						
Placebo	1	345	312.0	0.94 (0.07, 12.71)	0.86 (-2.18, 3.89)	1.91 (0.12, 29.72)
Other	11	1325	1263.5	1.80 (0.67, 4.86)		
ARA3003						
Placebo	0	200	91.0	N/A	N/A	N/A
Other	1	678	304.8	N/A		
ARA3002 + ARA3003						
Placebo	1	545	403.0	0.72 (0.07, 7.58)	0.78 (-1.35, 2.91)	2.08 (0.17, 24.94)
Other	12	2003	1568.3	1.50 (0.64, 3.55)		

* Least square mean mortality rate per 100 subject-years using modelled IPTW weights.
** Placebo row used as reference.
Abbreviation: CI = confidence interval; N/A=not applicable

It is concluded that the analyses using MSM suggests some attenuation of the risk estimates when attempting to adjust for measured patient characteristics that are related to mortality risk as well as to the dynamic probability for exposure to sirukumab in individual patients. These analyses are, however, severely hampered by the low number of events. The analyses consequently do not strengthen the concern regarding mortality risk but do not convincingly show that the imbalance can be explained by the severity of disease among patients switching from placebo to sirukumab treatment.

To further contextualise the mortality rates in the sirukumab development program the Applicants states that the incidence rate and pattern of deaths do not differ significantly from the RA population in general, or other RA trials. Such inter-study comparisons may help to contextualise the problem but must be interpreted with great caution for several reasons. Random differences in baseline risk between study populations are expected and within-study comparisons are therefore key. It is, however, acknowledged that imbalances in mortality, based on few observations and in both directions have been observed in previous RA study populations. The comparison must, however, be interpreted with caution, since the underlying selection mechanisms and study design features may not be comparable.

The Applicant acknowledges the limitations of the historical comparisons with other RA studies and has therefore also conducted studies in three different contemporary RA cohorts (from Sweden, Hungary, and the US), selecting comparison cohorts from these by applying the study inclusion/exclusion criteria and then calculating two-year mortality rates. The estimated mortality rates in these cohorts are found comparable to what is observed for sirukumab. These efforts are acknowledged and provide some further reassurance but the same fundamental limitations mentioned above of such analyses still apply.

The main causes of deaths in the sirukumab development program were cardiovascular events, infections and malignancies. Eleven of the 32 deaths were MACE. The Applicant has investigated

whether other risk factors were unevenly distributed, and found that cardiovascular disease-related risk factors were in general equally distributed between subjects randomized to placebo as compared to subjects randomized to sirukumab. Numerical differences were seen for current smoking, hypertension and hyperlipidaemia which all were seen with a higher proportion in the placebo group.

It may be argued that no specific cause of death has been identified as causing the imbalance in mortality. It is, however, identified risks such as severe infections, MAC and malignancy behind the majority of deaths. This may be seen as a logical and not entirely unexpected consequence of these identified risks.

Regarding the mechanism it is noted that sirukumab binds specifically to IL-6 while other monoclonal antibodies that inhibit the IL-6 pathway, such as tocilizumab and sarilumab, bind instead to the soluble and membrane-bound forms of the IL-6 receptor. The clinical significance of targeting the cytokine versus the receptor is unknown. Sirukumab is therefore potentially be more selective for the IL-6 pathway but the implications for a potential difference in safety profile are unclear.

Other SAEs

There were numerically slightly more SAEs in the 100mgq2w sirukumab group, in the investigations and hepatobiliary disorders SOCs: through 52 weeks an incidence per 100 PTY were 11.07, 15.05 and 12.69 respectively. However, numbers are small and evaluations need to be made with great caution. When looking at all sirukumab treated subjects, the incidence rate per 100 subject years was identical (13.2) between the 2 dosing regimens. No major differences per SOC were observed.

Table 42: AEI Incidence per 100 Subject-Years

	Studies ARA3002 and ARA3003						Studies ARA3001, ARA3002, ARA3003, ARA3004, and ARA3005	
	18 week			Through 52 weeks[a]			Through SCS Cutoff	
	Placebo N=850	50 mg N=848	100 mg N=850	Placebo N=850	50 mg N=848	100 mg N=850	50 mg comb N=1461	100 mg comb N=1465
Exposure (subject-yrs)[b]	291.3-292.3	289.9- 292.3	291.0-293.3	516.2-519.5	775.3-786.6	774.0-784.4	2145-2193.3	2161- 2210.6
Death								
Number of subjects	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	4 (0.5%)	6 (0.7%)	15 (1.0%)	14 (1.0%)
Incidence	0.34	0.34	0.34	0.19	0.51	0.76	0.68	0.63
95% CI	(0.01, 1.91)	(0.01, 1.91)	(0.01, 1.90	(0.00, 1.07)	(0.14, 1.30)	(0.28, 1.66)	(0.38, 1.13)	(0.35, 1.07)
Serious infection								
Number of subjects	7 (0.8%)	16 (1.9%)	14 (1.6%)	14 (1.6%)	41 (4.8%)	36 (4.2%)	102 (7.0%)	101 (6.9%)
Incidence	2.40	5.52	4.81	2.71	5.29	4.65	4.76	4.67
95% CI	(0.97, 4.95)	(3.15, 8.96)	(2.63, 8.07)	(1.48, 4.55)	(3.79, 7.17)	(3.26, 6.44)	(3.88, 5.77)	(3.81, 5.68)
GI perforations								
Number of subjects	0	1 (0.1%)	3 (0.4%)	1 (0.1%)	2 (0.2%)	4 (0.5%)	5 (0.3%)	9 (0.6%)
Incidence	0	0.34	1.02	0.19	0.25	0.51	0.23	0.41
95% CI	(0, 1.02)	(0.01, 1.91)	(0.21, 2.99)	(0.00, 1.07)	(0.03, 0.92)	(0.14, 1.31)	(0.07, 0.53)	(0.19, 0.77)
MACE[c]								
Number of subjects	2 (0.2%)	3 (0.4%)	2 (0.2%)	4 (0.5%)	10 (1.2%)	4 (0.5%)	20 (1.4%)	9 (0.6%)
Incidence	0.68	1.03	0.68	0.77	1.28	0.51	0.92	0.41
95% CI	(0.08, 2.47)	(0.21, 3.00)	(0.08, 2.46)	(0.21, 1.97)	(0.61, 2.35)	(0.14, 1.31)	(0.56, 1.42)	(0.19, 0.77)
Malignancy								
Number of subjects	2 (0.2%)	1 (0.1%)	1 (0.1%)	3 (0.4%)	8 (0.9%)	6 (0.7%)	23 (1.6%)	19 (1.3%)
Incidence	0.68	0.34	0.34	0.58	1.02	0.77	1.05	0.86
95% CI	(0.08, 2.47)	(0.01, 1.91)	(0.01, 1.91)	(0.12, 1.69)	(0.44, 2.01)	(0.28, 1.67)	(0.67, 1.58)	(0.52, 1.35)

	18 week			Through 52 weeks[a]			Through SCS Cutoff	
	Placebo N=850	50 mg N=848	100 mg N=850	Placebo N=850	50 mg N=848	100 mg N=850	50 mg comb N=1461	100 mg comb N=1465
Hepatobiliary abnormalities[d]								
Number of subjects	2 (0.2%)	7 (0.8%)	7 (0.8%)	3 (0.4%)	7 (0.8%)	8 (0.9%)	8 (0.5%)	17 (1.2%)
Incidence	0.68	2.41	2.40	0.58	0.89	1.02	0.37	0.77
95% CI	(0.08, 2.47)	(0.97, 4.96)	(0.97, 4.95)	(0.12, 1.69)	(0.36, 1.84)	(0.44, 2.01)	(0.16, 0.72)	(0.45, 1.23)

Excludes events occurring >16 weeks after last dose of study agent.
[a] All groups Through 52 weeks are those subjects originally randomized to that treatment, and exclude events occurring after placebo escape or crossover to sirukumab
[b] Range of subject-years exposure due to censoring of data at time of event
[c] MACE are cases adjudicated as being MACE
[d] Hepatobiliary abnormalities are defined as discontinuation criteria as described in Section 5.2.11

Infections

A higher incidence of Serious, but not non-serious infections, were seen for sirukumab as compared to placebo. Unexpectedly, there was a trend of higher infection AEs in the lower dosing regimen group. The Applicant is asked to discuss plausible explanations to this finding. **LooI**

No serious opportunistic infections were reported through the SCS cut off date. Four cases of Herpes Zoster were reported among sirukumab treated subjects whereof 1 in the 50 mg q4w group. It is noted that 3 cases were reported in the adalimumab group. The exposure time adjusted incidence rates for this event through 52 weeks of exposure in the 3002 and 3003 studies were 1.55 for the placebo treated group, 2.70 for the 50 mg treated group and 1.67 for the 100 mg treated group. These data do not show an obvious increased risk for Herpes Zoster reactivation, however, given the experience from previously approved IL-6-inhibitors, and the biological plausible mechanism, viral reactivation, covering both hepatitis and HZV should be added among potential risks in the Safety Specification.

GI perforations

CHMP's comment: **The figures in this section need to be updated in accordance with the values in the readjudication that has been performed and was provided as a response to Q14 in this round. However, some uncertainties regarding the recalculations persist and the Applicant has been asked for clarifications.**

There were more cases of GI perforation in the sirukumab treated groups, than in the placebo group, numerically more with the higher dose (incidence rates 0.23 and 0.41 per 100 PY for 50mg q4w and 100mg q2w respectively). A trend towards more cases of lower gastric perforation than what is usually seen in the RA population was shown. The incidence rate (95%CI) per 100 subject-years of exposure for lower GI perforations by SCS cutoff date 0.23 (0.11, 0.42) appeared greater than that for upper GI perforations 0.07 (0.01, 0.20).

The number of subjects with 1 or more GI perforations before Week 52 by demographic subgroups among all sirukumab treated subjects was provided. According to the provided table, 10 sirukumab treated subjects experienced this AE, 4 in the 50mg q4w group, and 6 in the 100mg 2w group before week 52. Four subjects were younger than 65 years (n=2200), and 6 subjects were ≥ 65 years to <75 years (n=385). No subjects ≥ 75 years (n=69) experienced this AE. Although numbers are small and evaluation should be made with caution, there is a trend towards increasing risk with older age, which is not unexpected. Gastrointestinal perforation is proposed to be included in the SmPC safety information by the Applicant, which is endorsed.

MACE

CHMP's comment: **The figures in this section need to be updated in accordance with the values in the readjudication that has been performed and was provided as a response to Q14 in this round. However, some uncertainties regarding the recalculations persist and the Applicant has been asked for clarifications.**

No clear increased risk for MACE could be observed in the studies. The exposure time adjusted incidence in all sirukumab treated subjects through cutoff date in phase 3 studies was lower in the higher treatment group, 0.92 (0.56, 1.42) and 0.42 (0.19, 0.77) per 100 PTY for the 50 mg and 100mg groups, respectively, and comparable to placebo through 18 weeks 0.68 (0.08, 2.47)0.34 (0.01, 1.91). The lower dosing group thus reported a lower incidence than the placebo group. The MACE incidence was highest in the oldest subjects, ≥75 to <85 years (no subjects above 85 years were

recruited), which is not surprising. It is noted that in this age group, MACE incidence rate was higher in the 100mg q2w treatment group.

The Applicant points out that the incidence of MACE was comparable in the sirukumab treated and placebo treated subjects, in spite of lipid elevation associated with the drug. However, the effect of such elevation is not likely to be measurable within a years' time, this needs to be followed over a longer period. It is noted that current data do not suggest an increasing risk over time. The Applicant has proposed to classify MACE as a potential risk in the RMP, which is endorsed.

The Applicant was invited to further discuss the unexpected finding of a higher incidence rate of MACE in the lower sirukumab group as compared to the higher dosed group. No clear explanation is available, which is accepted.

Malignancies

Through 52 weeks of exposure, the proportions of subjects with 1 or more malignancies in ARA3002 and ARA3003 was 3, 8 and 6 in the placebo, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups, respectively, with exposure-adjusted incidence rates of 0.58, 1.02, and 0.77, respectively.

The Applicant used standardized incidence ratios, SIRs, to describe the incidence of malignancies (excluding non-melanoma skin cancer) in the development program relative to the general population. Through cutoff date seventeen malignancies occurred in the combined sirukumab 50 mg q4w group (16.91 cases expected; SIR 1.01 [0.59, 1.61]) and 15 malignancies were reported in the combined sirukumab 100 mg q2w group (16.55 cases expected; SIR 0.91 [0.51, 1.50]). In the combined sirukumab group, 32 malignancies were reported (33.46 cases expected; SIR 0.96 [0.65, 1.35]). This information is appreciated.

The current data does not appear to be suggestive of a higher malignancy frequency for sirukumab. Malignancies are proposed to be classified as a potential risk, which is endorsed, since a continued monitoring of this subject is needed post-approval.

Hepatobiliary abnormalities

More cases of hepatobiliary abnormalities were reported in sirukumab treated subjects compared to placebo, without obvious association to dose. Incidence rate was similar between adalimumab and sirukumab in study ARA 3005, 1.23, 0.63 and 1.25 per 100 PTY in adalimumab and low dose and high dose sirukumab respectively.

Most cases of hepatobiliary AEs occurred during the first 18 weeks of exposure (19 sirukumab treated subjects during the first 18 weeks compared with 22 subjects through the SCS cutoff date).

The narratives for and assessments of adjudication cases were provided and reviewed. Three of the 7 sirukumab treated subjects that were eligible for adjudication, were judged to be probably/possibly related to drug. Among the remaining 5, 2 were found to have gall bladder concrements, and causality was therefore considered unlikely. One died later in renal pelvic cancer, and the liver abnormalities may have been caused by this disease. Two had antibodies to hepatitis E, 1 of these was adjudicated as a plausible hepatitis from clinical course and biochemical course. The other subject showed very high ALT/AST in combination with high bilirubin and normal alkaline phosphatase, and was judged to be possibly related. Due to pre-existing hepatic steatosis and concomitant hepatotoxic drugs (MTX and sulphasalazine) the case was not considered to fulfil Hy´s law. This case may be classified as drug induced liver injury (DILI). Of the remaining 2 cases that were adjudicated as possible/probably drug related, one had hepatobiliary steatosis, which is a more severe condition that simply elevated AST/ALT. The other subject was on a stable dose MTX but had recently initiated isoniazide when

elevated liver enzymes were found. Isoniazide is known to induce elevated liver function tests, and this case was thus confounded, although an additive effect of sirukumab may be possible.

IL-6 pathway neutralization with anti-interleukin-6 receptor antibody enhanced hepatic steatosis in mice with methionine-choline deficient (MCD) diet-induced non-alcoholic steatohepatitis (NASH) via decreasing suppressor of cytokine signaling (SOCS)3 expression; suppressing STAT3 activation; increasing fatty acid uptake and hepatic triglyceride biosynthesis; leading to decreased Cyp2E1 expression, reactive oxygen species (ROS) production and hepatic apoptosis.

Based on preclinical findings and the hepatobiliary abnormalities captured in the studies, serious liver toxicity is listed among potential risks in the Safety Specification and will be further monitored.

Hypersensitivity

The incidence of hypersensitivity reactions in sirukumab was comparable to that in adalimumab. It is noted that one case of lip swelling occurred in the 100mg q2w group.

Systemic hypersensitivity reactions occurred primarily during the first 18 weeks of treatment. The incidence of moderate/severe or and serious reactions occurred with higher incidence in the 100mg q2w group as compared to the 50 mg q4w treated group. No events of anaphylaxis were reported. There was no apparent association between the presence of antibodies to sirukumab and hypersensitivity reactions.

Injection-site reactions

Injection-site reactions occurred commonly in the sirukumab Phase 3 studies. Through the SCS data cutoff, ISR AEs occurred in 12.5% and 21.4% of subjects in the combined sirukumab 50 mg q4w and combined sirukumab 100 mg q2w groups respectively. The most frequently reported reactions were injection site erythema, pruritus, and swelling.

The incidence of ISRs in study ARA 3005was also greater in the sirukumab 100 mg q2w group compared with other treatment groups. The incidence between adalimumab and sirukumab 50 mg q2w was comparable, (8.6% vs 10.8%), but the higher sirukumab dosing regimen group reported almost twice as many ISRs (23.0%) in this study.

The number of ISR AEs leading to discontinuation of study agent was also lower in subjects treated with sirukumab 50 mg (0.3% [4/1,326]) than with sirukumab 100 mg (0.9% [12/1,328].

The proportion of subjects with ISRs was higher among the sirukumab-treated subjects who were not receiving DMARDs at baseline (17.0% and 24.7% in the 50 mg and 100 mg groups, respectively) compared with subjects who were using DMARDs at baseline (10.9% and 20.2%, respectively).

Haematology

Neutropenia and thrombocytopenia occurred more often in sirukumab treated subjects. No clear dose association was seen in 18 weeks data. Through cutoff date, in all phase 3 trials, 8 subjects in the 50 mg q4w group and 2 subjects in the 100 mg q2w group experienced grade 4 toxicity (<500/mm3) in neutropenia, for grade 3 toxicity (<1,000-500/mm3) the numbers were 68 and 61 respectively.

Regarding Platelet decrease, 1 in each dosing regimen experienced grade 4 toxicity (<25,000/mm3) , and 2 in the lower and 3 in the higher dosing regimen experienced grade 3 toxicity (<50,000-25,000/mm3).

Serious infection was reported in 2 cases within 3 weeks of the occurrence of neutropenia, both in the higher dosing group. Leukopenia and neutropenia are listed as common ADR for tocilizumab. For

sirukumab, the Applicant proposes to label neutropenia, leukopenia and thrombocytopenia as common ADRs. This is endorsed. The Applicant also proposes a wording on severe cases in section 4.8, this is agreed to but modifications are needed, see SmPC.

Liver function tests

Both ALT and AST increases occurred more often in sirukumab treated subjects, see also discussion on hepatobiliary events above. No apparent dose association was noted. DMARDs appear to have an effect on liver enzymes increase, but this has been seen mostly in the lower elevation ranges. Bilirubin increases also occurred more frequently in the treated group. Most bilirubin increases were toxicity grade 0 (≤ULN). It is noted that the incidence of toxicity grad 2 (>1.5–3.0 × ULN) was almost doubled in the 100mg q2w group compared to the 50mg q4w group.

The Applicant has included routinely monitoring of bilirubin levels and/or when earlier clinically indicated in the SmPC.

AST, ALT and bilirubin increase are proposed to be listed in table 4.8 in the SmPC. This is endorsed.

Lipids

Total cholesterol, LDL and triglycerides were more often elevated in sirukumab treated subjects, without apparent dose association. The increased levels tended to remain. No effect of DMARDs was noted. HDL increased as well, so the total cholesterol to HDL ratio increased only slightly, but the Applicant claims that this is not clinically meaningful, since after 52 weeks the mean ratio in all treatment groups in the pooled 3002 and 3003 studies remained below 4.0 (3.61, 3.71 and 3.71 in the placebo group, Sirukumab 50mg q4W and 100mg q2w respectively), which is the desired ratio.

Approximately half of subjects who shifted from normal LDL levels to above ULN returned to normal values 16 weeks after discontinuation. The Applicant is asked to provide mean and median lipid values in subjects who did not return to normal after 16 week **LoOI**.

The Applicant proposes to include Hypercholesterolemia and Triglycerides increased in table 4.8 in the SmPC.

Special populations

No major differences in frequency of AE between subgroups in gender, race, ethnicity or geographic location were seen. It is noted that subjects in the lowest quartile of weight experienced more AEs (85% vs appr 77%).

The Applicant provided upon request a table including safety data for elderly per age group (< 65 years, 65-74 years, 75-84 years, > 85 years). Elderly were in general at risk of adverse events as compared to younger subjects, regarding CNS disorders, vascular disorders, cardiac & cerebro-vascular disorders, and falls and fractures, for both placebo and active treatment. The nature of the AEs was also more severe for elderly, including mortality. For sirukumab specifically, but not for placebo, the risk for infections increased with age. This has been adequately addressed in the SmPC.

Vaccination

A multicenter, nonrandomized, open-label vaccine response sub study was conducted to evaluate response to the tetanus, diphtheria, and acellular pertussis (Tdap) and pneumococcal vaccines in subjects who received at least 6 months of treatment in ARA3002.The proportion of subjects with a response (at least 12 of 23 serotypes had >2-fold increase in antibody level from before vaccination to after vaccination) to pneumococcal vaccine was higher in the placebo group (89.3%) compared with the sirukumab 50 mg (83.3%) and 100 mg (74.2%) groups. The response to Tdap vaccine was

comparable between the groups (42.9%, 39.6% and 41.7% in the placebo, low dose and high dose sirukumab respectively). The proposed wording on vaccinations in section 4.4 in the SmPC needs further justification.

Baseline DMARD use

Concomitant DMARD impacted the frequency of increased transaminases for sirukumab. However, exposure adjusted incidence rate was lower in patients on concomitant DMARDs. The same pattern was not seen for serious infectious events.

The rates of SAEs, serious infections, malignancy, and GI perforations were higher in ARA3003 than in ARA3002. It may be assumed that subjects in study ARA3003, who were refractory to TNF-inhibitors, suffered from a more advanced and long-standing disease. The Applicant suggested that this group might be more prone to AEs, which may be true. On the other hand, there were significantly more deaths in the ARA3002 study.

Pregnancy

The Applicant provided a table (not shown here) presenting 16 prospective cases of pregnancy involving sirukumab, whereof 6 still ongoing or not reported outcome. Seven live births without congenital anomaly or other AE have been reported. Two ended in early spontaneous abortion, whereof on was fathered by a sirukumab treated patient. The third was a blighted ovum. In addition, 1 retrospective case ended in missed abortion at 6 weeks of gestation. No cases of late miscarriage or foetal death associated with sirukumab treatment have been reported.

Discontinuations due to AEs

Infections and liver enzyme elevations were the most common cause for discontinuation due to AE.

3.4.9. Conclusions on clinical safety

The safety profile of sirukumab appears to be largely in line with that of the currently approved IL-6 inhibitors. However, as a consequence of the design of the main studies the comparison of incidence of major safety outcomes to placebo beyond 18 weeks exposure is likely confounded. This means that the long-term safety of sirukumab cannot be considered as well characterized. Due to this limitation, as illustrated by the observed potential imbalance in mortality rate between exposed and not exposed patients, it is crucial that a reassuring long-term safety profile is confirmed after a potential approval of a marketing authorization. This requires robust estimation of the risk for all relevant safety outcomes in comparison to a relevant active comparator. The Applicant should discuss different alternatives for a post marketing study program, eg. a randomized controlled study and/or observational study/ies. Any study proposal should be accompanied by a study synopsis for a relevant study design of sufficient detail to allow a feasibility assessment.

3.5. Risk management plan

Safety Specification

The applicant identified the following safety concerns in the RMP:

Table 43: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Serious infection Gastrointestinal perforation

Summary of safety concerns	
	Serious systemic hypersensitivity reactions Severe thrombocytopaenia Severe neutropenia
Important potential risks	Major adverse cardiovascular events (MACE) Malignancy Serious hepatotoxicity Viral reactivation
Missing information	Use in paediatric patients Use during pregnancy Use in nursing mothers Long-term safety

The Applicant has provided an updated RMP version 1.2 which addresses the outstanding issues identified in the D150 assessment report(s). The updated RMP (version 1.2) with the above listed safety specification.

In brief, the list of safety concerns (see Table Summary of the safety concerns above) has been updated with newly added important Identified Risks Severe thrombocytopenia and Severe neutropenia. Furthermore, Important potential risk Viral reactivation has been added and previous Missing information term Use in hepatitis B infected patients has been removed.

The MAA has also revised the RMP according to the updates in the PI. Amendments have also been made in the clinical data concerning Gastrointestinal perforations (Important identified risk), and MACE (Important potential risk). There are also minor editorial revisions throughout the RMP document.

<New safety specification that should be taken into account by the PRAC>

Pharmacovigilance Plan

Table 44 Ongoing and planned studies in the PhV development plan

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
CNTO136ARA3004 A Multicenter, Placebo-group Study of Long-term Safety and Efficacy of CNTO 136 (sirukumab) for Rheumatoid Arthritis in Subjects Completing Treatment in Studies CNTO136ARA3002	To evaluate the long-term safety of sirukumab in subjects with RA who are refractory to disease modifying anti-rheumatic drugs (DMARDs) or anti-TNF α agents.	• Serious infection • Gastrointestinal perforation • Serious systemic hypersensitivity reactions • Severe thrombocytopaenia • Severe neutropenia • Major adverse cardiovascular	Ongoing	Interim study report 30 October 2019 Final study report 30 October 2021

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
and CNTO136ARA3003 (randomised, controlled trial, category 3)		events (MACE) • Malignancy • Serious hepatotoxicity • Long-term safety		
RABBIT Long-term Observation of Treatment with Biologics in Rheumatoid Arthritis (Germany) (observational postauthorization safety study [PASS] cohort study, category 3)	To evaluate the long-term safety of sirukumab and comparator treatment in subjects with RA. Patients treated with sirukumab will be followed for a period of 5 years.	• Serious infection • Gastrointestinal perforation • Serious systemic hypersensitivity reactions • Severe thrombocytopaenia • Severe neutropenia • Major adverse cardiovascular events (MACE) • Malignancy • Serious hepatotoxicity • Viral reactivation • Use during pregnancy • Long-term safety	Planned	Interim reports: annually from November 2019 Final study report: June 2029
ARTIS Anti-rheumatic Treatment in Sweden (observational postauthorization safety study [PASS] cohort study, category 3)	To evaluate the long-term safety of sirukumab in subjects with RA.	• Serious infection • Gastrointestinal perforation • Serious systemic hypersensitivity reactions • Severe thrombocytopaenia • Severe neutropenia • Major adverse cardiovascular events (MACE) • Malignancy • Serious hepatotoxicity • Viral reactivation • Use during pregnancy	Planned	Interim reports: annually from November 2019 Final study report: June 2029

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
		• Long-term safety		
Evaluation of Long-Term Safety of Sirukumab Using Real-World Data (observational postauthorization safety study [PASS] - cohort study, category 3)	To assess the long-term safety of sirukumab related to events of interest including serious infection, malignancy, and MACE in patients exposed to sirukumab versus other biologics. All-cause mortality will also be evaluated.	• Serious infection • Major adverse cardiovascular events (MACE) • Malignancy • Long-term safety	Planned	Final study report: March 2025
Sirukumab Pregnancy Exposure Study (planned US/Canada; active surveillance registry, category 3)	To monitor planned and unplanned pregnancies exposed to sirukumab and to evaluate the possible teratogenic effect of this medication with regard to the primary pregnancy outcome of major birth defects and the secondary pregnancy outcomes of preterm delivery, small for gestational age infants and spontaneous abortion or stillbirth.	• Use during pregnancy	Planned	Final study report: December 2025

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The Pharmacovigilance plan

MAA has updated the Pharmacovigilance plan for sirukumab according to the revised safety specification.

The pharmacovigilance plan has been updated concerning the newly included risks Severe Thrombocytopaenia and Severe neutropenia. The additional pharmacovigilance activities for these include Clinical Trials, Registries and Epidemiology Studies: CNTO136ARA3004; RABBIT (Germany); and ARTIS (Sweden).

Correspondingly, Additional pharmacovigilance activities for newly included Important potential risk Viral reactivation include the following Clinical Trials, Registries and Epidemiology Studies: RABBIT (Germany), and ARTIS (Sweden).

Study synopsis for the planned (category 3) study "Sirukumab Pregnancy Exposure Study" has been amended. The MAH has updated the synopsis with a more detailed description and estimation of power of the study to detect adverse pregnancy outcomes. The amendment to the study plan (Synopsis) is endorsed. However, as notified in the specific assessment of the Applicants responses to the LoI (Question 21), the Applicant should commit to:

Propose another approach to the issue of lacking data on safety of sirukumab exposure during pregnancy in case sirukumab is not available for patients in US/Canada within reasonable time in such degree that the proposed Sirukumab Pregnancy Exposure study could be successfully conducted.

a) MAA should be ready to amend the corresponding PhV plan in case a promising new source for the pregnancy exposure data becomes available.

Concerning the planned category 3 study "Real world data" has been modified. The milestone of Interim report has been deleted. This study is expected to use the existing RA registries and health care claims databases in the US and EU. The study is planned to investigate (Outcomes of Interest) MACE, serious infection, and malignancy. Secondary outcome is all-cause mortality. MAA's proposal is to delete the Interim report –milestone in the RMP. The MAA has not yet defined the exact data sources and methodology to be used in the study. Therefore, the MAA has earlier been proposed to consider having a feasibility step included in the study plan. The Applicant could still consider a feasibility step and report such outcome in the PSUR(s) despite no interim reports are planned.

Rapporteur's Conclusion

The Pharmacovigilance plan could be approvable if the Applicant commits to:

a) Propose another approach to the issue of lacking data on safety of sirukumab exposure during pregnancy in case sirukumab is not available for patients in US/Canada within reasonable time in such degree that the proposed Sirukumab Pregnancy Exposure study could be successfully conducted.

b) MAA should be ready to amend the corresponding PhV plan in case a promising new source for the pregnancy exposure data becomes available.

c) As a consequence of the design of the main studies the comparison of incidence of major safety outcomes to placebo beyond 18 weeks exposure is likely confounded. This means that the long-term safety of sirukumab cannot be considered as well characterized. Due to this limitation, as illustrated by the observed potential imbalance in mortality rate between exposed and not exposed patients, it is crucial that a reassuring long-term safety profile is confirmed after a potential approval of a marketing authorization. This requires robust estimation of the risk for all relevant safety outcomes in comparison to a relevant active comparator. The Applicant should discuss different alternatives for a post marketing study program, eg. a randomized controlled study and/or observational study/ies. Any study proposal should be accompanied by a study synopsis for a relevant study design of sufficient detail to allow a feasibility assessment.

Risk minimisation measures for Plivensia

Table 45 Summary table of additional Risk Minimisation Measures (only safety concerns having additional risk minimisation measures have been listed below)

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Serious infection	SmPC: Guidance is provided in Posology and Method of Administration (4.2), Contrainidcations (4.3), Special Warnings and Precautions for Use (4.4), and Undesirable Effects (4.8). PLIVENSIA is subject to restricted medical prescription by physicians experienced in the diagnosis and treatment of RA.	The MAH will provide a Patient Alert Card to inform patients about important safety information regarding the risk of serious infection.
Gastrointestinal perforation	SmPC: Guidance is provided in Special Warnings and Precautions for Use (4.4) and Undesirable Effects (4.8). PLIVENSIA is subject to restricted medical prescription by physicians experienced in the diagnosis and treatment of RA.	The MAH will provide a Patient Alert Card to inform patients about important safety information regarding the risk of gastrointestinal perforation.
Use during pregnancy	SmPC: Guidance is provided in Fertility, Pregnancy, and Lactation (4.6). PLIVENSIA is subject to restricted medical prescription by physicians experienced in the diagnosis and treatment of RA.	The MAH will also provide a Patient Alert Card to inform patients about important safety information regarding the use of PLIVENSIA during preganancy.

Risk minimisation measures

Additional risk minimisation measures are proposed to be in place for Serious infections, Gastro-intestinal perforation, and concerning the safety in case of use during pregnancy. The additional risk minimisation measures for sirukumab have now been mostly revised as requested. The initially proposed HCP education material has been removed and the Patient alert card (PAC) has been amended. The PAC addresses serious infections, gastrointestinal perforation and the risks related to exposure during pregnancy.

A need for further amendment of the RMM (PAC) has been noticed, however. The Applicant is requested to amend the objectives and key elements to be communicated with this RMM, with information on "when to seek medical advice" for the patient, in order to facilitate recognition of serious infections or gastrointestinal perforations in an early stage and subsequent start of the treatment as soon as possible. Specifically, the RMP Section V.I shall be amended (Patient alert card -

Objective and justification of why needed for Serious infection and Gastro-ntestinal perforation). Proposed amendment underlined:

The goal of the Patient Alert Card is to provide patients with important safety information about the risk of serious infection/gastrointestinal perforation, *when to seek medical advice, as well as information* which should be shared with any HCP involved in the patient's care.

Also RMP Section V.3 need minor edition in order to capture the two aspects of the RMM; namely inform the patients on the symptoms when to seek medical advice, as well as information to be presented to HCP the patients meets. The same applies the RMP Section VI.1.4, and Section VI.2.5 (sentence: A *Patient Alert Card to provide patients with important safety information about the risks of serious infection and gastrointestinal perforation, including what to do if symptoms occur*. to be re-inserted).

The PAC should be amended accordingly; the text to be (re-)inserted in the PAC:

WHEN TO SEEK MEDICAL PROFESSIONAL ADVICE:

Infections

When you are treated with Plivensia, you might get infections more easily. Infections may progress more rapidly and may be more severe than they usually would. In addition, some important warning symptoms of an infection such as fever may be lessened or not present due to your treatment with Plivensia. Tell your doctor if you have signs of an infection. Signs include fever, headache, cough, congestion, chills, change in urine frequency or burning feeling while urinating, redness or swelling of the skin or a joint, night sweats, persistent back pain combined with fever.

Tears (perforation) of the stomach or intestines.

Patients with diverticulitis (inflammation in parts of the intestine), stomach ulcers or intestinal ulcers treated with Plivensia may develop complications, which can become serious if not treated. Seek immediate medical attention if you develop stomach pain, unexplained changes in bowel habits, and/or a fever.

Concerning effectiveness of the RMM, the Applicant proposes routine pharmacovigilance activities to be used to assess the effectiveness of routine risk minimisation measures. "An absence of any trends suggestive of a safety issue" is considered indicator of successive risk minimization.

Rapporteur's conclusion: Proposed Risk minimisation measures could be acceptable with the amendment described above.

Public summary of the RMP

The public summary of the RMP does require minor revision:

A minor edition in order to capture the two aspects of the additional RMM; namely inform the patients on the symptoms when to seek medical advice, as well as information to be presented to HCP the patients meets. This applies the RMP Section VI.1.4, and Section VI.2.5 (sentence: A Patient Alert Card to provide patients with important safety information about the risks of serious infection and gastrointestinal perforation, including what to do if symptoms occur. to be re-inserted).

3.6. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

4. Orphan medicinal products

N/A

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

The indication for RA proposed by the applicant is as follows:

Plivensia in combination with methotrexate (MTX), is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs) (see section 5.1). In these patients, Plivensia can be given as monotherapy when treatment with MTX is inappropriate for safety or tolerability reasons.

Rheumatoid arthritis is a chronic, systemic, autoimmune inflammatory disease in adults that leads to swelling and tenderness of the joints in the hands, feet, wrists, elbows, knees, and ankles. If the inflammation is left untreated, it results in significant joint damage culminating in disability and joint deformity.

Control or reversal of the systemic inflammation in RA is the most important therapeutic goal. Diverse validated composite endpoints are available for assessment of efficacy reflecting different signs and symptoms of disease. These endpoints include ACR response, DAS28 (including DAS28 remission) and CDAI. A limitation with ACR scores is that these scores represent a relative change from baseline and not necessary reflect treatment targets of remission or low disease activity. Physical function, often measured by HAQ-DI as well as biomarkers (CRP) should also be reported. Moreover, also patients who are considered to be in clinical remission can have subclinical synovitis and progress to structural damage of cartilage and bone. Since prevention of structural damage is a key objective for new DMARDs, bone involvement should therefore be assessed and reported separately.

5.2. Available therapies and unmet medical need

Traditional therapeutic approaches include nonsteroidal anti-inflammatory drugs NSAIDs, cDMARDs, and corticosteroids. Current European guidelines (*EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update)* recommend that the cDMARD MTX is part of the first line treatment strategy unless there are contraindications, in which case sulfasalazine or leflunomide should be considered as part of the (first) treatment strategy. If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another csDMARD strategy should be considered but when poor prognostic factors are present, addition of a bDMARD should be considered. In patients responding insufficiently to MTX and/or other csDMARD strategies, bDMARDs should be commenced

with MTX. If a first bDMARD has failed, patients should be treated with another bDMARD. Currently, approved biologic therapeutics for RA includes the following modes of action: TNFα inhibition, IL-6 receptor inhibition, T-cell co-stimulation blockade, and B-cell depletion.

None of the approved drugs can achieve treatment target, i.e. remission or at least low disease activity, in all patients. In addition, many patients discontinue their DMARD or are never candidates for DMARDs because of safety reasons. Biologic and non-biologic DMARDs have a safety profile that includes the risk of serious infections and other consequences of immunosuppression such as a potential for malignancy. However, depending on the medical history and comorbidities, one biologic may be suited better to certain patients than others.

Overall, despite multiple treatment options being available for the treatment of adult patients with moderately or severely active RA, there still remains a considerable unmet need in this chronic disease that requires lifelong therapy. New therapies are required in addition to currently approved biologic therapies that provide efficacy in combination with an acceptable safety profile.

5.3. Main clinical studies

C1377T04 was a blinded, phase 2 RCT that included subjects with RA refractory to MTX. The study had 2 parts; Part A was the initial proof-of-concept portion and Part B the dose-finding portion. In Part A sirukumab 100 mg q2w (n=17) was compared against placebo (n=19). In Part B four different sirukumab dose groups; sirukumab 100 mg q2w (n=30), sirukumab 100 mg q4w (n=30), sirukumab 50 mg q4w (n=30) and sirukumab 25 mg q4w (n=31) were compared against placebo (n=30).

ARA3002 was a blinded, phase 3 RCT that included subjects with active RA with at least one poor prognostic factor who were refractory to conventional first line treatment. Sirukumab 100 mg q2w (n=557) and Sirukumab 50 mg q4w (n=557) were compared against placebo (n=556). The majority of subjects were treated with concomitant conventional DMARDs, mostly MTX. The study included 18 weeks that were pure placebo-controlled. From week 18 onwards, there were two opportunities for placebo non-responders i.e. subjects that had <20% improvement from baseline in both swollen and tender joint counts, to escape to sirukumab, at Week 18 (Early Escape, EE) and Week 40 (Late Escape, LE). In total, the placebo controlled period lasted 52 weeks.

ARA3003 was a blinded, phase 3 RCT that included subjects with moderately to severely active RA who were refractory or intolerant to anti-TNF agents. Sirukumab 100 mg q2w (n=292) and Sirukumab 50 mg q4w (n=292) were compared against placebo (n=294). The majority of subjects were treated with concomitant conventional DMARDs, mostly MTX. The study included 18 weeks that were pure placebo-controlled. At week 18, placebo subjects that had <20% improvement from baseline in both swollen and tender joint counts escaped to sirukumab. At week 24, all subjects were crossed-over to sirukumab.

ARA3005 was a blinded, phase 3 RCT that included biologically naïve patients with active RA for whom their physicians have judged that MTX therapy would not be of benefit. Randomization was stratified by the reason for which subjects failed MTX; either for efficacy alone or for any safety/tolerability reason. Sirukumab 100 mg q2w (n=187) and Sirukumab 50 mg q4w (n=186) as monotherapy were compared against the TNF-blocker adalimumab as monotherapy (n=186) for 52 weeks. At Week 16, subjects in all treatment groups who had <20% improvement from baseline in both swollen and tender joint counts qualified for early escape; subjects receiving adalimumab 40 mg q2w would change to every week dosing, subjects on sirukumab 50 mg q4w would change to 100 mg q2w dosing, while subjects on sirukumab 100 mg q2w would remain on their randomized dose at EE.

The dose escalation is coherent with the SmPC for adalimumab and the currently proposed SmPC for sirukumab.

5.4. Favourable effects

In **C1377T04,** in Part A, a relevant effect in terms of DAS28 (CRP), ACR 50 response and CRP suppression was demonstrated for Sirukumab 100 mg q2w compared to placebo. Thus, it is agreed that proof-of-concept for sc sirukumab in subjects with active RA despite MTX therapy was shown.

In **ARA3002**, the proportion of ACR 20 responders at week 16 was one of the co-primary endpoints. The proportion of ACR 20 response rate was 54.8% in the Sirukumab 50 mg group and 53.5% in the Sirukumab 100 mg group compared to 26.4% in the placebo group ($p<0.001$ for both comparisons). Also in the small subgroups not using any DMARD at baseline, the odds for a subject to achieve an ACR 20 response at Week 16 was higher in both sirukumab groups relative to the placebo group.

The other co-primary endpoint was mean change (SD) from Baseline in vdH-S Score at Week 52. The mean change (SD) from Baseline in vdH-S Score was 0.50 (2.961) in the Sirukumab 50 mg group, 0.46 (3.258) in the Sirukumab 100 mg group and 3.69 (9.245) in the placebo group ($p<0.001$ both comparisons). For patients not taking DMARD at baseline, the median difference (95% CI) for change from baseline in vdH-S Score at Week 52 vs placebo in the Sirukumab 50 mg q4w and 100 mg q2w groups, were 0.50 (0.0-2.8) and 1.18 (0.0-3.0), respectively.

For all 4 major secondary endpoints; change in HAQ-DI score, ACR 50 response, DAS 28 (CRP) remission at week 24 and major clinical response at week 52, a statistical difference vs placebo was demonstrated for both sirukumab doses.

Mean (SD) change from baseline in CRP at week 16 was -0.49 (3.18) in the placebo group compared to -2.28 (2.44) in Sirukumab 50 mg group and -2.32(2.65) in the Sirukumab 100 mg group ($p <0.001$ for both comparisons). At week 16, also the mean percent improvements from baseline for the other individual ACR components (mean number of swollen joints, number of tender joints, patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, HAQ-DI score) were numerically higher in both sirukumab groups compared to placebo with no large differences between the two dose groups of sirukumab.

No large differences with regards to efficacy were noted between the two sirukumab doses studied in ARA3002 for the primary or the major secondary endpoints.

In **ARA3003,** at Week 16, the primary endpoint ACR 20 response was achieved by a greater proportion of subjects in both the sirukumab 50 mg q4w (40.1%) and sirukumab 100 mg q2w (45.2%) groups compared with the placebo group (24.1%, both $p<0.001$).

The outcome of the analysis of the secondary endpoints was generally in line with the outcome for the primary endpoint i.e. sirukumab was superior to placebo, but no large differences between the two different sirukumab dose regimens were observed. Mean improvement in HAQ-DI score from baseline at Week 24 was 0.31 in the sirukumab 50 mg q4w group and 0.33 in the sirukumab 100 mg q2w group vs 0.12 in the placebo group (both $p<0.001$). ACR 50 response at Week 24 was 20.9% in the sirukumab 50 mg q4w and 21.6% in the sirukumab 100 mg q2w groups compared to 8.8% in the placebo group (both $p<0.001$). Proportion of subjects achieving DAS28 (CRP) remission at Week 24 was 19.2% in the sirukumab 50 mg q4w and 21.6% in sirukumab 100 mg q2w groups compared to 8.2% in the placebo group (both $p<0.001$).

Demonstration of efficacy in terms of CDAI is of great importance as it is a CRP-independent endpoint. In this regard it is further noted that there was a clear numerical difference in mean (SD) change from

baseline in CRP (mg/dl) at week 16 for in favour of active treatment vs placebo: -0.08 (2.277) in the placebo group compared to -1.89 (2.302) in the sirukumab 50 mg group and -2.08 (2.423) in the sirukumab 100 mg group. However, also the mean percent improvement from baseline for the other individual (non-CRP) ACR components (mean number of swollen joints, number of tender joints, patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, HAQ-DI score) were generally numerically higher in both sirukumab groups even though the difference between placebo and active treatment were not as pronounced for these outcomes as for CRP. Generally, a greater improvement in the individual ACR components was seen for the sirukumab 100 mg q2w compared to the sirukumab 50 mg q4w dose. The difference between the dose groups was most apparent for the swollen joint count for which the mean percent difference from baseline was 43% for the sirukumab 100 mg q2w group and 30% for the sirukumab 50 mg q4w group vs 28% for the placebo group.

Overall it is noted that there was no clear difference in terms of efficacy between the sirukumab 50 mg q4w and 100 mg q2w dosing regimens in study ARA3003. For some study endpoints, as well as many of the individual ACR components, there seem to be a better clinical response for the sirukumab 100 mg q2w group than the 50 mg q4w group but this finding was not consistent throughout the endpoints.

In **ARA3005,** the monotherapy study, the co-primary efficacy endpoint 1, mean change (SD) in DAS28 (ESR) at week 24 was -2.19 (1.437) in the adalimumab arm and -2.58 (1.524) and -2.96 (1.580) in the sirukumab 50 mg q4w and sirukumab 100 mg q2w respectively (LS mean difference [95% CI] = -0.39 [-0.69; -0.08] and -0.76 [-1.07; -0.46] respectively). The results were numerically similar in the stratum of subjects who failed MTX at baseline for safety reasons (i.e. the population that the current monotherapy claim includes), but no formal hypothesis testing was conducted.

For the co-primary endpoint 2, ACR 50 Response at Week 24, sirukumab was not demonstrated to be superior to the comparator adalimumab. The proportion of responders in the adalimumab arm was 31.7% vs 26.9% in the sirukumab 50 mg q4w (% difference vs the comparator with 95% CI=-4.8 [-14.1; 4.4]) and 35.3% in the sirukumab 100 mg q2w (% difference vs the comparator with [95% CI] =3.6 [-6.0; 13.1]). The results in the stratum that failed MTX due to safety reasons were consistent with the result in the overall population.

Of the two major secondary endpoints, DAS 28 (ESR) remission at week 24 is the most clinically relevant. In the whole study population, proportion of subject that achieved DAS 28 (ESR) remission at week 24 was 7.5% in the comparator arm, 12.9% in the sirukumab 50 mg q4w arm and 20.3% in the sirukumab 100 mg q2w arm (% difference vs the comparator with [95% CI] = 5.4 [-0.7; 11.4] and 12.8 [5.9; 19.7] respectively). In the stratum that failed MTX for safety reasons, the proportion of subject that achieved DAS 28 (ESR) remission at week 24 was 7.5% in the comparator arm, 20.0% in the sirukumab 50 mg q4w arm and 23.8% in the sirukumab 100 mg q2w arm (no p-value or 95% CI provided). For the second major efficacy endpoint, ACR 20 response at week 24, sirukumab did not appear superior to the comparator adalimumab.

Proportion of subjects who achieved the clinically relevant outcomes DAS28 (ESR) Low Disease Activity and DAS28 Remission was numerically higher in the sirukumab groups compared to the comparator both at week 16 (i.e. before subjects were given the early escape possibilities) and at week 24. At week 16, the proportion of subjects with Low Disease Activity was 16.1% in the comparator group vs 24.7% (% Difference [95% CI] = 8.6 [0.5; 16.7]) in the sirukumab 50 mg q4w group and 34.2% (% Difference [95% CI] = 18.1 [9.5; 26.7]) in the sirukumab 100 mg q2w group. Proportion of subjects in DAS28 (ESR) Remission week 16 was 7.0% in the comparator group vs 15.1% in the sirukumab 50 mg q4w(% Difference [95% CI] =8.1 [1.8; 14.4]) and 20.3% in the sirukumab 100 mg q2w (% Difference

[95% CI] =13.3 [6.5; 20.2]). There was a numerical difference between the comparator and sirukumab in the proportion of subjects with Low Disease Activity and remission for both doses of sirukumab. However, the difference relative the comparator was numerically higher for the 100 mg q2w-dose.

Mean CRP reductions at Week 24 were -0.85 mg/dL for adalimumab 40 mg q2w, -1.78 mg/dL for sirukumab 50 mg q4w (nominal p-value 0.001) and -1.72 mg/dL for sirukumab 100 mg q2w (nominal p-value 0.003). Mean reduction in ESR (mm/hr) at week 24 was -13.7 for adalimumab 40 mg q2w, -34.1 for sirukumab 50 mg q4w and -34.7 for sirukumab 100 mg q2w (nominal p<0.001 for both analyses). When examining the mean percent change from baseline in the individual, non-CRP, ACR components at week 24, the numerically lowest percent change was consistently found in the sirukumab 50 mg q4w. However, differences between the groups with regards to percent change from baseline for the individual non-CRP ACR components were not large.

Superiority for sirukumab vs the comparator was not noted for the CDAI change from baseline.

In conclusion, taking all into account all efficacy outcomes of importance in the ARA3005 study, including the primary endpoints; change in DAS28 (ESR) and ACR 50 response, remission and CDAI (which is relevant in terms of its CRP-independence), changes in CRP as well as in non-CRP ACR components, the efficacy of sirukumab as monotherapy appears roughly similar to adalimumab monotherapy. As monotherapy, sirukumab 100 mg q2w generally appears slightly more effective than monotherapy with sirukumab 50 mg q4w. In pooled analyses, the response to the 100 mg q2w dose was more robust regarding HAQ-DI (physical function).

5.5. Uncertainties and limitations about favourable effects

In the dose-finding Part B of **C1377T04**, taking into account the outcome all efficacy analysis of this trial, it is noted that the best response was generally found in the highest dose group (100 mg q2w) while the most modest response was generally found in the lowest dose group (25 mg q4w). This could be interpreted as at least a slight tendency for a dose response and it could also be questioned whether the plateau in such dose response has been reached i.e. whether an even higher dose would confer incremental benefit to patients. This finding, together with pharmacokinetic data (see separate AR) and some of the efficacy data from the phase 3 studies, especially from the monotherapy study ARA3005 (in which there were generally numerical differences that favoured sirukumab 100 mg q2w over sirukumab 50 mg q4w), leads to a question on whether the posology that is currently proposed by the applicant needs revision in order to allow dose escalation. ***In response to the second LoQ, the proposed posology has now been revised.***

Comprehensive data from sirukumab monotherapy was derived from ARA 3005. For a complete discussion on the wording of the indication, including the wording regarding monotherapy, see section 5.7.3.

For **ARA3002**, the assessments of the endpoints that were evaluated after week 18 were overall complicated by the study design with the two escape-possibilities in the placebo arm. However, the result of relevant sensitivity analysis supports the result of the primary analyses. Moreover, many of the variables of interest were measured also before escape-time points. Most clinical efficacy variables, including the remission variables and the CRP-independent CDAI-variable, were evaluated before week 16 and there were generally differences in outcome in favour of the active treatment arms compared to placebo.

For **ARA3003**, just as for ARA3002, the assessment of the endpoints evaluated beyond week 18 is complicated by the study design with early escape only in the placebo arm. For the primary endpoint

this is not a concern since it was evaluated before week 18 but for the secondary endpoints it is. However, the primary analyses for the secondary endpoints all exclude data post early escape for patients in all treatment groups imputing failure for binary variables and using LOCF for continuous variables and this is endorsed. Moreover, ACR response, mean changes from baseline in DAS28 (CRP), the remission measures, HAQ, SDAI, CDAI and CRP were all assessed also at week 16 and the outcome generally favoured sirukumab over placebo.

The outcome of the primary analysis of ARA3003 for sirukumab appeared roughly comparable to, but somewhat less favourable than, the results in the RADIATE study that concerned the currently approved IL-6 blocker tocilizumab. This might partly be due to the relatively high placebo-response in sirukumab trials as compared to historic tocilizumab trials, providing less contrast in the treatment effect. However, given the limitations of historic controls, no conclusions regarding the relative efficacy between sirukumab and tocilizumab can be done.

In **ARA3005,** just as in ARA3002 and ARA3003, there are some difficulties in the interpretation of data due to some aspects of the study design. However, a conservative sensitivity analysis supports the conclusion that sirukumab was indeed superior to adalimumab in terms of DAS28 (ESR) change from baseline to week 24. This conclusion is further supported by the fact that for this variable, a difference between sirukumab and the comparator in favour of the former was noted already at week 16 i.e. before the EE possibility. It should also be noted that that actually <10% of the randomized patients in each treatment arm qualified for the early escape limiting the impact that this aspect of the study design had on the main outcome of the study. A conservative sensitivity analysis was performed for the co-primary endpoints of study ARA3005 at Week 24 allowing for dose escalation in adalimumab EE subjects (using observed data), and not allowing for dose escalation in sirukumab 50 mg q4w EE subjects (using imputed data) ***coherent with the initially proposed posology***. The co-primary endpoints in study ARA3005 were change from baseline in DAS28 (ESR) and ACR 50 response at Week 24; with EE at Week 16. ACR 50 response rates were unchanged from the original analysis. Mean improvement in DAS28 (ESR) from baseline remained numerically higher for the sirukumab 50 mg group compared with the adalimumab group. However, compared with the primary efficacy analysis, the difference between the sirukumab 50 mg group and the adalimumab group was numerically smaller and no longer statistically significant. ***The outcome of the various analyses that have now been conducted, allow for an acceptable estimation of the study results despite the limitations regarding interpretation of data that derives from the specific study design. The corresponding SmPC text is approvable provided that a small addendum is made to increase clarity.***

Uncertainties and limitations about favourable effects in subpopulation across the three pivotal studies

Elderly

Even though sirukumab appears to have an effect in all studied age categories, the effect seems somehow less pronounced in the elder categories. A thorough analysis of this finding was requested from the applicant. In response to the LoQ, the applicant performed a statistical analysis to model the treatment by age interaction, using age as a continuous variable and concluded that there was no consistent impact of age on the treatment effect across studies (ARA3002, ARA3003, and ARA3005), endpoints (ACR 20, ACR 50 or change in DAS28), visits (Week 16, Week 24, or Week 52 [ARA3002 only]) or dose of sirukumab. In the light of the outcome of the additional analysis conducted by the applicant, it appears possible that the previously noted trend of lower treatment effect in the elderly could be chance finding and the issue will not be further pursued.

Heavy weight and diabetic patients

As the pharmacokinetic data indicate that there are differences in exposure between the diabetic and the non-diabetic population (see separate AR), the primary efficacy outcomes in the three pivotal trials ARA3002, ARA3003 and ARA3005 according to whether subjects had diabetes at baseline was requested. In the response to the LoQ, the applicant stated that for both doses of sirukumab, there was a trend across all 3 studies for a numerically lower clinical response in subjects with diabetes compared with subjects without diabetes, however, 95% CIs overlapped and similar observations were made for placebo and adalimumab comparator arms. Moreover, the applicant states that despite the higher PK exposure with the sirukumab 100mg q2w dose compared with the 50 mg q4w dose, a clinically meaningful difference in response between sirukumab doses in diabetic subjects was not apparent. And thus, dose escalation to sirukumab 100 mg q2w would not provide a meaningful incremental benefit despite the approximate 6-fold increase in sirukumab serum trough levels. The requested data has been provided. As the numbers of diabetics in the different treatment groups in the three studies were small it is difficult to draw any firm conclusions on the benefit of dose escalation in this patient group. The data presented are suggestive of a slightly better effect in the sirukumab 100 mg q2w dose group compared to the 50 mg q4w group but the applicant is not in favor of dose escalation. The data provided are considered too limited to justify any SmPC changes specifically pertaining to this patient group and thus, for the time being, the issue will not be further pursued.

When the results for the primary outcome in the three pivotal studies were examined according to weight quartiles, a clear pattern was difficult to discern even though there seem to be a tendency for lower response for some endpoints in the higher weight quartiles. As the pharmacokinetic data indicate that there are distinct differences in exposure between subjects with weight<100 kg vs subjects with weight>100 kg, the results for the primary efficacy variables in the three pivotal trials ARA3002, ARA3003 and ARA3005, in subjects with weight<100 kg vs subjects with weight>100 kg were requested. Moreover, data in subjects with diabetes and >100 kg as well as non-diabetic subjects with weight<100 kg and subjects that are either diabetic or have a body weight>100 kg, were requested. In response to the LoQ, the applicant stated that despite the higher pharmacokinetic (PK) exposure with the sirukumab 100 mg q2w dose compared with the 50 mg q4w dose, a clinically meaningful difference in response between sirukumab doses in subjects with diabetes or ≥100 kg was not apparent and thus dose escalation to sirukumab 100 mg q2w would not provide a meaningful incremental benefit. As the numbers of subjects that weighed ≥100 kg in the different treatment groups in the three studies were small, it is difficult to draw any firm conclusions on the benefit of dose escalation in this patient group although the data presented are suggestive of a slightly better effect in the sirukumab 100 mg q2w dose group compared to the 50 mg q4w group. However, the data provided are considered too limited to justify any SmPC changes specifically pertaining to this patient group.

5.6. Unfavourable effects

The size of the safety data base (3,120 subjects who received at least one dose of sirukumab) is considered sufficient.

Deaths

In the overall safety analysis deaths occurred more frequently in the sirukumab-treated population: 34 out of 35 cases through the cutoff date were reported among sirukumab-treated subjects. Incidence rate was 0.75 per 100 PTY in the combined sirukumab group, as compared to 0.19 per 100 PTY in the placebo-treated population. Among the 29 deaths in study 3002 and 3003, 14 occurred in the EE/LE/CO populations (incidence per 100 PTY approximately 1.48). There was no imbalance in mortality during the 18-week strictly randomised comparison.

Infections

The most frequent serious adverse events observed in the RA development program were serious infections that occurred with an incidence rate through cutoff date of 4.76 per 100 PTY for sirukumab 50 mg q4w, and 4.67 per 100 PTY for sirukumab 100 mg q2w vs 2.71 per 100 PTY in the placebo group through 52 weeks. Through the first 18 weeks in the ARA3002 and 3003 studies, representing a true randomization period (see under uncertainties), the incidence rate in the placebo group was 0.8%, vs 1.9% in the 50mg group, and 1.6% in the 100mg group. No major impact of concomitant DMARDs was seen.

The most common serious infection was pneumonia, which was reported in 0.4% of the placebo treated subjects in the integrated placebo controlled studies, and 1.4% in the 50mg q4w treated group. Other serious infections were cellulitis 0.1% in placebo group and 0.7% in the 50mg q4w treated subjects, and sepsis 0.2% vs 0.5%.

Among non-serious infections, respiratory tract infection, nasopharyngitis and urinary tract infection were the most frequently reported, however not considerably more often in treated than untreated subjects. Through 52 weeks of exposure in ARA3002 and ARA3003, the exposure-adjusted incidence rates in subjects with 1 or more infections were 67.9, 68.7, and 62.9 per 100 subject-years, in the placebo, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups, respectively. Thus a higher incidence was seen in the lower dosing regimen.

Gastrointestinal tract

CHMP's comment: **The values in the below paragraph needs to be updated, since a readjudication has been provided, see JRAR Q 14. However, since some uncertainty regarding recalculation persists, this has not yet been performed**

In the placebo controlled analysis set, the incidence rate for gastrointestinal perforation was (95% CI) per 100 PTY was 0.19 (0.00, 1.07) for placebo vs 0.25 (0.03, 0.92) for the 50 mg q4w group. Among the 100mg q2w treated subjects the incidence rate was 0.51 (0.14, 1.31). It is noted that through the cutoff date incidence rate (95%CI) per 100 subject-years of exposure for lower GI perforations (0.23 [0.11, 0.42]; seems greater than that for upper GI perforations (0.07 [0.01, 0.20]. Patients with active diverticulitis were excluded from the placebo controlled RA studies.

More cases of hepatobiliary abnormalities were reported in sirukumab treated subjects compared to placebo. Incidence rate was similar between adalimumab and sirukumab in study ARA 3005, 1.23, 0.63 and 1.25 per 100 PTY in adalimumab and low dose and high dose sirukumab respectively.

MACE

CHMP's comment: **The values in the below paragraph needs to be updated, since a readjudication has been provided, see JRAR Q 14. However, since some uncertainty regarding recalculation persists, this has not yet been performed**

Despite an increment of lipids following sirukumab treatment, no clear increased risk for MACE could be observed in the studies. The exposure time adjusted incidence in all sirukumab treated subjects through cutoff date was lower in the higher treatment group, 0.92 (0.56, 1.42) and 0.42 (0.19, 0.77) per 100 PTY for the 50 mg and 100mg groups, respectively, and comparable to placebo through 18 weeks 0.68 (0.08, 2.47). The lower dosing group thus reported a lower incidence than the placebo group.

Malignancies

The current data does not appear to be suggestive of a higher malignancy frequency for sirukumab, for malignancies including NMSC. Malignancies are proposed to be classified as a potential risk, which is endorsed, since a continued monitoring of this subject is needed post approval, in a larger population than could be reasonably obtained in trials.

Laboratory

Laboratory abnormalities were commonly observed in sirukumab-treated subjects, including decreases in neutrophils, leukocytes, and platelets, and increases in liver enzymes, bilirubin, cholesterol and triglycerides. Most subjects with hepatobiliary AEs experienced them during the first 18 weeks of exposure (19 subjects in the combined sirukumab groups during the first 18 weeks of exposure), compared with 22 subjects in the combined sirukumab groups through the SCS cutoff date. Through the SCS cutoff date, the overall incidence per 100 subject-years of exposure was lower in the combined 50 mg group (0.37) than in the combined 100 mg group (0.77), with an "all subjects" hazard ratio (95% CI) of 2.119 (0.914, 4.910) for the sirukumab 100 mg q2w group compared with the sirukumab 50 mg q4w group.

Through 18 weeks of exposure in ARA3002 and ARA3003, with an average of 8 study agent administrations, serious or moderate/severe hypersensitivity reactions or serum sickness AEs were reported in 1 (0.1%), 0, and 4 (0.5%) subjects in the placebo, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups, respectively. Stevens-Johnson syndrome was reported on Study Day 201 in a subject who EE to 100 mg q2w in ARA3002, however, this case was not confirmed.

Through 52 weeks of exposure, the proportions of subjects discontinuing study agent administration due to AEs in the placebo controlled studies (ARA3002 and ARA3003) were 31 (3.6%) in the placebo group, 76 (9.0%) in the sirukumab 50 mg q4w group, and 80 (9.4%) in the sirukumab 100 mg q2w group. The SOC with the most frequently reported AEs leading to discontinuation was Investigations (in 4, 13, and 10 subjects, respectively); across the 3 treatment groups, most events in this SOC were events related to increases in hepatic enzymes.

5.7. Uncertainties and limitations about unfavourable effects

Death rates

The assessment of the imbalance in mortality rate observed in the overall safety analysis is hampered by the fact that placebo subjects with a response less than 20% in swollen and tender joints also received active drug from week 18 (ARA2002 and 3003) or 40 (ARA3002) "early escape or late escape". Comparisons after week 18 may therefore be confounded by patients remaining in the placebo group being healthier, and switchers overall having more severe disease than those initially

randomised to sirukumab. Further, this together with the "crossover" design (all placebo treated subjects in study ARA3002 were re-randomized at week 52 and all placebo treated subjects in study ARA3003 were rerandomized at week 24) caused a multitude of population groups: sirukumab treated and not treated, higher and lower dose (50mg q4w vs 100mg q2w), placebo→50mg q4w and placebo→100mg q2w. Further, the crossover design entails varying drug exposure periods. Exposure time adjusted incidence rates for the integrated placebo group and the integrated sirukumab treated groups through cutoff date (both doses) have been considered in the evaluation.

The exposure-adjusted comparison above is complicated by being based on very few events, and potentially being confounded by treatment switch from placebo to sirukumab being informative also of the patients' risk for mortality. Comparisons of mortality rates with previous RA studies and contemporary RA cohort does not add further concern but such inter-study comparisons must be interpreted with great caution.

Overall, as a consequence of the design of the main studies, the comparison of incidence of major safety outcomes to placebo beyond 18 weeks exposure is likely confounded. This means that the long-term safety of sirukumab cannot be considered as well characterized.

5.8. Effects Table

Table 46 Effects Table for Sirukumab for the treatment of RA

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
I. Disease activity						
ACR 20 Response in RA refractory to conventional first line treatment	Proportion of responders at week 16 (co-primary endpoint)		54.8% Sirukumab 50 mg q4w 53.5% Sirukumab 100 mg q2w	26.4% placebo	p<0.001 for both comparisons	ARA3002
ACR20 Response in RA refractory or intolerant to anti-TNF	Proportion of responders at week 16 (primary endpoint)		40.1% sirukumab 50 mg q4w 45.2 % Sirukumab 100 mg q2w	24.1% placebo	p<0.001 for both comparisons	ARA3003
ACR 50 Response in RA for which MTX is not of benefit, monotherapy	Proportion of responders at Week 24 (co-primary endpoint)		26.9% Sirukumab 50 mg q4w 35.3% sirukumab 100 mg q2w	31.7% Comparator Adalimumab	% difference Sirukumab 50 mg q4w vs Adalimumab (95% CI)=-4.8 (-14.1; 4.4) % difference Sirukumab 100 mg q2w vs Adalimumab (95% CI)=3.6 (-6.0; 13.1)	ARA3005

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
DAS28 (ESR) change in RA for which MTX is not of benefit, monotherapy	Mean change from baseline in DAS 28 (ESR) at week 24 (co-primary endpoint)		-2.58 Sirukumab 50 mg q4w -2.96 Sirukumab 100 mg 2qw	-2.19 Comparator Adalimumab	p<0.001 for 100 mg q2w comparison, p=0.013 for 50 mg q4w comparison	ARA3005
DAS28 (CRP) remission in RA refractory to conventional first line treatment	Proportion of subjects with DAS28 (CRP) remission week 16		21.2% Sirukumab 50 mg q4w 21.9% Sirukumab 100 mg q2w	5.8% placebo	Nominal p < 0.001 for both comparisons	ARA3002
DAS 28 (CRP) remission in RA refractory or intolerant to anti-TNF	Proportion of subjects with DAS28 (CRP) remission week 16		17.5 % Sirukumab 50 mg q4w 15.8% Sirukumab 100 mg q2w	5.8% placebo group	Nominal p < 0.001 for both comparisons	ARA3003
DAS28 (ESR) remission in RA for which MTX is not of benefit, monotherapy	Proportion of subjects with DAS28 (ESR) remission week 16		15.1% Sirukumab 50 mg q4w 20.3% Sirukumab 100 mg q2w	7.0% Comparator Adalimumab	Nominal p=0.013 and <.001 respectively	ARA3005
CDAI change in RA refractory to conventional first line treatment	Mean change from baseline in CDAI at week 16		-18.04 Sirukumab 50 mg q4w -17.75 Sirukumab 100 mg q2w	-10.86 placebo	LS Mean Difference (95% CI) for Sirukumab 50 mg q4w vs placebo -7.18 (-8.808, -5.542) LS Mean Difference (95% CI) for Sirukumab 100 mg q2w vs placebo -6.89 (-8.519, -5.254)	ARA3002
CDAI change in RA refractory or intolerant to anti-TNF	Mean change from baseline in CDAI at week 16		-14.5 Sirukumab 50 mg q4w -16.6 Sirukumab 100 mg 2qw	-10.2 placebo	LS Mean Difference (95% CI) for Sirukumab 50 mg q4w vs placebo -4.252 (-6.793, -1.711) LS Mean Difference (95% CI) for Sirukumab 100 mg q2w vs placebo -6.347 (-8.886, -3.809)	ARA3003

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
CDAI change in RA for which MTX is not of benefit, monotherapy	Mean change from baseline in CDAI at week 16		-21.80 Sirukumab 50 mg q4w -25.51 Sirukumab 100 mg q2w	-23.90 Comparator Adalimumab	LS Mean Difference (95% CI) Sirukumab 50 mg q4w vs the comparator 2.13 (-0.91; 5.17) LS Mean Difference (95% CI) Sirukumab 100 mg q2w vs the comparator -1.58 (-4.62; 1.46)	ARA3005
II. Function						
HAQ-DI change in RA refractory to conventional first line treatment	Mean change from baseline in HAQ-DI at week 16		-0.409 Sirukumab 50 mg q4w -0.433 Sirukumab 100 mg group	-0.201 placebo group	LS Mean Difference (95% CI) for Sirukumab 50 mg q4w vs placebo -0.226 (-0.287, -0.165) LS Mean Difference (95% CI) for Sirukumab 100 mg q2w vs placebo -0.245 (-0.305, -0.184)	ARA3002
HAQ-DI change in RA refractory or intolerant to anti-TNF	Mean change from baseline in HAQ-DI at week 16		-0.245 Sirukumab 50 mg q4w -0.318 Sirukumab 100 mg q2w	-0.116 placebo	LS Mean Difference (95% CI) for Sirukumab 50 mg q4w vs placebo -0.112 (-0.190, -0.034) LS Mean Difference (95% CI) for Sirukumab 100 mg q2w vs placebo -0.193 (-0.271, -0.115)	ARA3003
HAQ-DI change in RA for which MTX is not of benefit, monotherapy	Mean change from baseline in HAQ-DI at week 16		-0.4397 Sirukumab 50 mg q4w -0.4550 Sirukumab 100 mg q2w	-0.4767 Comparator Adalimumab	LS Mean Difference (95% CI) Sirukumab 50 mg q4w vs the comparator 0.06 (-0.06; 0.18) LS Mean Difference (95% CI) Sirukumab 100 mg 2qw vs the comparator -0.00 (-0.12; 0.11)	ARA3005
III. Radiographic progression						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Prevention of radiographic progression in RA refractory to conventional first line treatment	Mean change from baseline in vdH-S Score at week 52 (co-primary endpoint)		0.50 for Sirukumab 50 mg q4w 0.46 for the Sirukumab 100 mg q2w	3.69 for placebo group	p<0.001 both comparisons	ARA3002
Unfavourable Effects						
Deaths	34 cases through cutoff date for SCS, whereof 1 in placebo group	Per 100 PY	50mg q4w: 0.68 100mg q2w:0.63	0.19	Due to early escape and cross-over, groups are not fully randomized after week 18. Deaths more than 16 weeks after drug discontinuation not included.	All phase 3
	1 in each group	Per 100 PY	50mg q4w: 0.34 100mg q2w: 0.34	0.34	Short period	Placebo controlled 18 weeks
Serious Infections	Increased, with no dose association	Per 100 PY	50mg q4w: 4.76 100mg q2w: 4.67	2.71		All phase 3
GI-perforations	Increased, dose association	Per 100 PY	50mg q4w: 0.23 100mg q2w:0.41	0.19	Low numbers. A tendency towards more low GI perforations.	All phase 3
MACE	Major Cardiovascular events	Per 100 PY	50mg q4w:0.92 100mg q2w:0.71	0.77	More events in lower dosed cohort.	All phase 3
Malignancies	All except NMSC	Per 100 PY	50mg q4w: 0.78 100mg q2w: 0.68	0.19	Slightly higher incidence among treated subjects, but not more cases than expected from the SEER database (SIR 0.96(0.65,1.35)	All phase 3
Hepatobiliary abnormalities	ALT or AST ≥ 8xULN, ALT or AST ≥5xULN >2weeks, ALT or AST ≥ 3xULN and bili ≥2xULN or clinical symptoms	Per 100 PY	50mg q4w:0.37 100mg q2w: 0.77	0.58	Low numbers. Trend towards dose association	All phase 3
Neutropenia	Toxicity grade 1 <LLN-1,500/mm^3	%	50mg q4w:17.7 100mg q2w:19.7	2.3	Increased No obvious dose association	18 weeks placebo controlled

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
	Toxicity grade 3 <1,000-500/ mm^3	%	50mg q4w: 4.7 100mg q2w:4.2	0.4	Increased	Placebo ARA3002 and 3003, vs all phase 3 treated subjects
Thrombocytopenia	Toxicity grade 1 <LLN-75,000/ mm^3	%	50mg q4w:8.8 100mg q2w:9.6	0.6	Increased	18 weeks placebo controlled
	Toxicity grade 3 <50,000-25,000/ mm^3	%	50mg q4w: 0.1 100mg q2w:0.2	0	Small numbers (2 and 3 respectively)	Placebo ARA3002 and 3003, vs all phase 3 treated subjects
Triclycerides	Toxicity grade 3 <500-1,000 md/dL	%	50mg q4w: 2.1 100mg q2w:1.6	0.4	Increased risk for higher toxicity grades in active treatment	18 weeks placebo controlled

5.9. Benefit-risk assessment and discussion

5.9.1. Importance of favourable and unfavourable effects

Regarding the favourable effects of Sirukumab, it has been demonstrated that Sirukumab has a relevant effect on clinical measures of disease activity, including the two clinically important outcomes low disease activity and remission. As expected, for a DMARD targeting IL-6, a clear effect is seen on acute phase reactants and acute phase reactant dependent outcomes. However numerical differences vs placebo are seen also for acute phase reactant-independent outcomes such as the composite CDAI-score and non-CRP components of the ACR score, including HAQ which is a measure of function. Finally, there seems to be an effect on radiographic progression which is an important outcome related to long-term prognosis. Effect has been demonstrated both in populations that are refractory to/ intolerant to conventional DMARD and anti-TNF respectively. Efficacy has been shown also as monotherapy.

Concerning the magnitude of effect, the effect on disease activity of Sirukumab in the placebo controlled studies ARA3002 and ARA3003 measured by ACR 20 Response at week 16 (included as a primary endpoint in both studies) appeared roughly comparable to data presented for the already approved IL-6 inhibitor tocilizumab. In ARA3005, the TNF-blocker adalimumab was used as an active comparator and overall the efficacy of sirukumab appeared largely comparable to this comparator. The ACR 50 response rate for adalimumab monotherapy observed in ARA3005 was roughly consistent with what has been found in previous studies. The response rates for sirukumab in ARA3005 were slightly lower than what might be expected for IL-6 inhibitor monotherapy in the studied population based on historic data with tocilizumab which was superior to adalimumab. But as head-to-head comparisons

with tocilizumab are lacking, and study populations may differ, no final conclusion could be drawn regarding relative efficacy towards other IL-6 antagonists.

Sirukumab could be an alternative to the already approved DMARDs used to treat RA-patients for whom treatment target is not achieved with conventional biologic or non-biologic DMARDs. It is of benefit that a rich arsenal of therapeutic alternatives is available for this population as none of the approved drugs can achieve treatment target in all patients. In addition, many patients discontinue their DMARD or are never candidates for DMARDs because of safety reasons and depending on the medical history and comorbidities, one biologic may be better suited to certain patients than others.

Regarding long term safety adverse events during the truly placebo controlled parts of the pivotal studies seem to be similar as what has been seen for other products in this drug class. However, as a consequence of the design of the main studies, the comparison of incidence of major safety outcomes to placebo beyond 18 weeks exposure is likely confounded. This means that the long-term safety of sirukumab cannot be considered as well characterized. Due to this limitation, as illustrated by the observed potential imbalance in mortality rate between exposed and not exposed patients, it is crucial that a reassuring long-term safety profile is confirmed after a potential approval of a marketing authorization.

There also seem to be an increased rate of lower gastrointestinal perforation associated with sirukumab. Although the total number of GI perforations was small through the SCS cutoff date, the incidence rate (95%CI) per 100 subject-years of exposure for lower GI perforations (0.23 [0.11, 0.42]) appeared greater than that for upper GI perforations (0.07 [0.01, 0.20]). Active diverticulitis was an exclusion criterion for the ARA3002 and ARA3003 but not history of diverticulitis. Numbers are small, however, through cutoff date 5 gastric perforations among 50 mg q4w treated subjects, and 9 among 100 mg q2w treated subjects were reported (1 in the placebo group). More subjects had GI perforations in ARA3003 (n=8) than in ARA3002 (n=4) or ARA3005 (n=2). This could be due to a more treatment resistant disease among the TNF- inadequate responders, with e.g. a more extensive historical NSAID use resulting in higher vulnerability in this population. GI perforations are known for this class of IL-6 antagonists, and adequate warnings have been included in the SmPC.

Assessor's comment: **The numbers in the above paragraph may be modified since a readjudication has been performed. The current information needs clarification before numbers are changed (LoOI).**

The risk of infections seems to be raised in treatment with IL-6 blockade, just like with other biologics. The number of subjects with serious infection was similar in the adalimumab and sirukumab 100 mg q2w groups, but higher in the sirukumab 100 mgq2w group, in the ARA3005 study. The infection risk is well known, and possible to handle in clinical practice. Only one case of invasive opportunistic infection, and 2 cases of TB have been reported. None of the TB cases were disseminated, and may have been primary illness. The Applicants recommendation to screen patients for TB before treatment with sirukumab is endorsed.

No clear increased risk for MACE could be observed in the studies. The exposure-time adjusted incidence in all sirukumab treated subjects through cutoff date was lower in the higher treatment group and comparable to placebo. The lower dosing group reported a lower incidence than the placebo group. This does not point towards an immediate effect on cardiovascular events for sirukumab. This risk does however need to be followed, and MACE is proposed as an important potential risk in the RMP safety specification, which is endorsed since the number of lethal cases was higher for sirukumab.

Although the number and type of malignancies reported in the development program for sirukumab causes no immediate concern, malignancies will be classified as an important potential risk, as larger,

non-selected, populations are needed to evaluate relatively rare events. This will thus be followed in coming PSURs which is endorsed.

The Applicant proposes to label neutropenia, leukopenia and thrombocytopenia as common ADRs. This is endorsed. Monitoring of leukocytes and platelets is also recommended in the SmPC, and is endorsed as an appropriate way of handling these risks in clinical practice. Both total cholesterol and HDL as well as triglycerides seem to increase during sirukumab treatment. The Applicant claims that the increased cholesterol to HDL ratio observed in sirukumab treated subjects is not clinically meaningful, since the mean ratio in all treatment groups remained below. Recommendations on monitoring of lipids are included in the SmPC, which is endorsed. The wording on observed elevations should however be revised in order to increase clarity.

5.9.2. Balance of benefits and risks

There is a clinically relevant benefit of Sirukumab for the treatment of RA both concerning disease activity as well as function and radiographic progression. However, as a consequence of the design of the main studies, the comparison of incidence of major safety outcomes to placebo beyond 18 weeks exposure is likely confounded. This means that the long-term safety of sirukumab cannot be considered as well characterized. Due to this limitation, as illustrated by the observed potential imbalance in mortality rate between exposed and not exposed patients, it is crucial that a reassuring long-term safety profile is confirmed after a potential approval of a marketing authorization. This requires robust estimation of the risk for all relevant safety outcomes in comparison to a relevant active comparator. The benefit-risk balance is currently negative.

5.9.3. Additional considerations on the benefit-risk balance

Discussions regarding the wording of the indication

The initially proposed wording of the indication was: "Plivensia in combination with methotrexate (MTX), is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more conventional nonbiologic or biologic disease-modifying anti-rheumatic drugs (DMARDs) (see section 5.1). In these patients, Plivensia can be given as monotherapy when treatment with MTX is inappropriate for safety or tolerability reasons."

The initially proposed indication was considered acceptable-after a minor rewording of the second line conditions- for the following reasons:

1) *Efficacy has essentially been demonstrated in all the RA populations included in the wording of the indication proposed by the applicant i.e. a second line indication in patients with moderate-severe RA, add-on to MTX or in monotherapy in case of when treatment with MTX is inappropriate due to intolerance/irresponsiveness towards MTX.*

   An amendment was requested regarding the definition of the second line populations in section 4.1, which did include "adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more conventional nonbiologic or biologic disease modifying anti rheumatic drugs (DMARDs)". Align recent CHMP decisions (e.g. Xeljanz, Olumiant and Kezvara), a more general wording of the second indication was proposed, i.e. adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs. With the extended treatment modalities that were registered in the last years, and as availability of alternative treatments and local treatment

guidances may differ among European treatment centers, the more general wording of the definition of the second line was preferred. The more general wording was also considered supported by data, as sirukumab was not only effective in patients failing on MTX or TNF, but also in a small subgroup of patients with prior treatment of tocilizumab, a IL-6 antagonist.

6. CHMP list of outstanding issues to be addressed in an oral explanation and/or in writing

6.1. Quality aspects

Major objections

None.

Other concerns

None.

6.2. Non clinical aspects

Major objections

None

Other concerns

None

6.3. Clinical aspects

Major objections

Safety/RMP

1) As a consequence of the design of the main studies the comparison of incidence of major safety outcomes to placebo beyond 18 weeks exposure is likely confounded. This means that the long-term safety of sirukumab cannot be considered as well characterized. Due to this limitation, as illustrated by the observed potential imbalance in mortality rate between exposed and not exposed patients, it is crucial that a reassuring long-term safety profile is confirmed after a potential approval of a marketing authorization. This requires robust estimation of the risk for all relevant safety outcomes in comparison to a relevant active comparator. The Applicant should discuss different alternatives for a post marketing study program, eg. a randomized controlled study and/or observational study/ies. Any study proposal should be accompanied by a study synopsis for a relevant study design of sufficient detail to allow a feasibility assessment.

   The discussion should include (but not necessarily be limited to) aspects such as:

   - The adequate patient population

- Relevant study outcomes

- Suitable comparator(s) (eg other IL6 antibodies or anti-tnf alfa)

- Feasability of recruiting sufficient number of patients. This should include a discussion on the feasibility to enroll patients to an interventional study with safety as a primary aim in the context of the observed apparent imbalance in mortality.

- Time lines

Other concerns

Pharmacokinetics

None

Pharmacodynamics

None.

Efficacy

None.

Safety

2) (from safety Q 13)

The Applicant is requested to modify the wording on lipids in section 4.8 in accordance with the below:

During the controlled trials, increases of lipid parameters such as total cholesterol, triglycerides, LDL cholesterol have been commonly reported. With routine laboratory monitoring it was seen that approximately x% of patients receiving Plivensia in clinical trials experienced elevations in total cholesterol ≥ 6.2 mmol/ l, with y% experiencing a increase in LDL to ≥ 4.1 mmol/ l.

Increases observed at week 16 remained stable thereafter.

3) The recalculations of incidence rates after the readjudication (Q 14) are not fully understood. From Table 15 it appears that 5 sirukumab-treated MACE cases were added among the patients reviewed at the SCS data lock point, and this is reflected in Table 13, where the previously reported number in the 50mg group has been revised from 20 to 25. For data lock point DSU 120, which occurred later, 2 MACE cases were added according to Table 15. In Table 13 the previously reported numbers 26 is updated to 28. However, it is unclear to the assessor why not the 5 added MACE cases from SCS DLP were transferred to DSU 120 so that instead of adding 2 to 26, 2 cases was added to 31. The correspondent discrepancy is applicable for the 100mg group, and for GIP.

It is also noted that in Table 15 some subjects seem to be added at both data lock points, which adds to the unclarity.

The Applicant is requested to clarify, and revise figures including the incidence rates, both in this response and in other relevant documents, or provide a justification why this is not needed.

4) The planned sample size of the pregnancy exposure study is rather small and capable of detecting increase in the frequency of adverse pregnancy outcomes only when they are far beyond the acceptable risk. Consequently, the study cannot be used to exclude a significant risk alone. Due to expected intentional or unintentional off label use during pregnancy, more data characterizing the safety in case of inadvertent exposure during pregnancy is necessary. On the other hand the justification by the MAA that no alternative data sources are available is endorsed.

The currently proposed Sirukumab Pregnancy Exposure Study is planned to include women who reside in the U.S. or Canada, exposed to sirukumab during pregnancy. This presumes a MA and significant patient exposure in those countries.

At the moment the rapporteur could accept the proposed Pharmacovigilance plan for gathering data on pregnancy exposure (and the updated RMP in this respect), in case the Applicant commits to:

a) Propose another approach to the issue in case sirukumab is not available for patients in US/Canada within reasonable time in such degree that the proposed study could be successfully conducted.

b) MAA will be willing to amend the plan in case a promising novel source for the pregnancy exposure data becomes available.

The Applicant is requested to amend the objectives and key elements to be communicated with the additional RMM; namely PAC, with information on "when to seek medical advice" for the patient, in order to facilitate recognition of serious infections or gastrointestinal perforations in an early stage and subsequent start of the treatment as soon as possible. Specifically, the RMP Section V.I shall be amended (Patient alert card - Objective and justification of why needed for Serious infection and Gastro-ntestinal perforation).

Proposed amendment underlined:
The goal of the Patient Alert Card is to provide patients with important safety information about the risk of serious infection/gastrointestinal perforation, when to seek medical advice, as well as information which should be shared with any HCP involved in the patient's care.

Also RMP Section V.3 need minor edition in order to capture the two aspects of the RMM; namely inform the patients on the symptoms when to seek medical advice, as well as information to be presented to HCP the patients meets.

The same applies the RMP Summary Section VI.1.4, and Section VI.2.5 (sentence: A Patient Alert Card to provide patients with important safety information about the risks of serious infection and gastrointestinal perforation, including what to do if symptoms occur. to be re-inserted).

The PAC should be amended accordingly; the text to be (re-)inserted in the PAC:

WHEN TO SEEK MEDICAL PROFESSIONAL ADVICE:

Infections
When you are treated with Plivensia, you might get infections more easily. Infections may progress more rapidly and may be more severe than they usually would. In addition, some important warning symptoms of an infection such as fever may be lessened or not present due to your treatment with Plivensia. Tell your doctor if you have signs of an infection. Signs include fever, headache, cough, congestion, chills, change in urine frequency or burning feeling while urinating, redness or swelling of the skin or a joint, night sweats, persistent back pain combined with fever.
Tears (perforation) of the stomach or intestines.
Patients with diverticulitis (inflammation in parts of the intestine), stomach ulcers or intestinal ulcers treated with Plivensia may develop complications, which can become serious if not treated. Seek immediate medical attention if you develop stomach pain, unexplained changes in bowel habits, and/or a fever.

The public summary of the RMP does require minor revision:
A minor edition in order to capture the two aspects of the additional RMM (PAC); namely inform the patients on the symptoms when to seek medical advice, as well as information to be presented to HCP the patients meets. This applies the RMP Section VI.1.4, and Section VI.2.5 (sentence: A Patient Alert Card to provide patients with important safety information about the risks of serious infection and gastrointestinal perforation, including what to do if symptoms occur. to be re-inserted).

SmPC

5) In the response to the previous List of questions, the applicant had added the 100mg strength to the PI. Since it is not possible to add a strength while the evaluation is ongoing procedure, the applicant was requested remove it from the PI and send an updated PI as soon as possible. However, the updated PI was received very late during this assessment round. Consequently, the applicant is now asked to revise the SmPC according to the current proposals from the Rapporteurs, please see separate document, also removing the 100 mg strength from the PI.

6.4. Pharmacovigilance system

None

7. Recommended conditions for marketing authorisation and product information in case of a positive benefit risk assessment

7.1. Other conditions

Additional risk minimisation measures

The PRAC Rapporteur considers that the following additional risk minimisation measures are necessary for the safe and effective use of the product:

A patient alert card to address the risk(s) of

- serious infection
- GI perforation
- Use during pregnancy with special reference to vaccinations of the infant

7.2. Summary of product characteristics (SmPC)

Please see separate document with the product information and the Rapporteur's comments.

7.3. Labelling

Please see separate document with the product information

7.4. Package leaflet (PL)

Please see separate document with the product information

User consultation

User test for Plivensia pre-filled pen and bridging for pre-filled syringe as well as user test for "Instructions for use" for pre-filled pen and pre-filled syringe have been are acceptable. Please see Day 180 List of Outstanding Issues for the assessment of the full tests and bridging.

As stated in the day 180 LoOI:

"The rapporteur is also worried, bearing the lay-out complaints from the test group in mind, how it will be if the IFU is printed togheter with leaflet (in the same document). The leaflet will probably be even bigger, since the IFU will also be printed several times due to multilanguage. The tested multiligual leaflet (3 languages) is 398mmx700mm.

The rapporteur supports the applicant idea to have the leaflet and the IFU as two separately printed documents. The PL and IFU should however remain as one word document in the application."