21 April 2017
EMA/292840/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kevzara

International non-proprietary name: sarilumab

Procedure No. EMEA/H/C/004254/0000

Note

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

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List of abbreviations

Quality	
AI	autoinjector
APS	aseptic process simulation
CCIT	container closure integrity testing
DP	drug product
DS	drug substance
FDS	formulated drug substance
HT	holding time
PA	process Area
PFP	prefilled pen
PFS	prefilled syringe
SNS	soft needle shield
TOR	time out of refrigeration
Non-clinical	
ADCC	Antibody-dependent cell-mediated cytotoxicity
AUC	area under the concentration vs. time curve
CDC	Complement-dependent cytotoxicity
CNS	Central Nervous System
CYP	Cytochrome P450
ECL	electrochemiluminescence
ELISA	Enzyme-Linked Immunosorbent Assay
ePPND	Enhanced Pre- and Postnatal Development
Fc	Fragment crystallizable
gp130	glycoprotein 130
IL-6Rα	Interleukin-6 receptor alpha
IV	Intravenous
KLH	Keyhole limpet hemocyanin
NCA	non-compartmental analysis
NOAEL	No observed adverse effect level
RA	rheumatoid arthritis
SC	Subcutaneous
sIL-6Rα	soluble IL-6Rα
STAT3	Signal transducer and activator of transcription 3
TK	toxicokinetics
Clinical	
ACR	American College of Rheumatology
ACR20	American College of Rheumatology 20% improvement
ACR50	American College of Rheumatology 50% improvement
ACR70	American College of Rheumatology 70% improvement
ADA	anti-drug antibody, anti-drug antibody
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANC	absolute neutrophil count

AUC0 14 days	area under the serum concentration versus time curve at steady state
CDAI	Clinical Disease Activity Index
CRP	C-reactive protein
CV	cardiovascular
DAS28-CRP	Disease Activity Score for 28 Joints using C-reactive protein
DMARD	disease modifying anti-rheumatic drug
DTL	drug tolerance level
EU	European Union
EULAR	European League Against Rheumatism
FACIT-fatigue	Functional Assessment of Chronic Illness Therapy Fatigue Scale
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire - Disability Index
IgG	immunoglobulin
IL-6	interleukin-6
LDL	low-density lipoprotein
MACE	major adverse cardiovascular event(s)
mIL-6Rα	membrane-bound interleukin-6 receptor alpha subtype
MMRM	mixed model for repeated measures
mTSS	modified Total Sharp Score
MTX	methotrexate
NCA	non-compartmental analysis
NSAID	nonsteroidal anti-inflammatory drugs
PD	pharmacodynamic
PFS	prefilled syringe
PK	pharmacokinetic
q2w	once every 2 weeks
qw	once weekly
RA	rheumatoid arthritis
SAA	serum amyloid A
SC	subcutaneous(ly)
SF-36	36-Item Short Form
sIL-6Rα	soluble interleukin-6 receptor alpha subtype
SIR	standardized incidence ratio
TNF	tumor necrosis factor

1. Background information on the procedure

1.1. Submission of the dossier

The applicant sanofi-aventis groupe submitted on 24 June 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Kevzara, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Kevzara is indicated in combination with disease-modifying anti-rheumatic drugs (DMARDs) or as monotherapy for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who responded inadequately or were intolerant to DMARDs or tumour necrosis factor (TNF) antagonists.

Kevzara has been shown to inhibit progression of joint damage and to improve physical function.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that sarilumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0067/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0067/2013 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant requested the active substance sarilumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP in 2008, 2009, 2011, 2014 and 2015. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 24 June 2016.
- The procedure started on 14 July 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 30 September 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 4 October 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 17 October 2016.
- During the meeting on 10 November 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 December 2016.
- A routine GCP inspection was adopted by the CHMP (inspection reference: GCP/2016/022) for the following pivotal clinical study: EFC10832
  - GCP inspections were conducted at 3 clinical investigator sites, one in Peru, one in Argentina and one in Mexico (routine inspections) on dates between October and December 2016. The outcome of the inspection carried out was issued on 3 February 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 January 2017.
- During the PRAC meeting on 9 February 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- The Rapporteurs circulated an updated Joint Assessment Report to all CHMP members on 17 February 2017.
- During the CHMP meeting on 23 February 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 March 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 April 2017.
- The Rapporteurs circulated an updated Joint Assessment Report to all CHMP members on 11 April 2017.
- During the meeting on 18-21 April, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Kevzara on 21 April 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Kevzara in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate (see section 5.1) .

2.1.2. Epidemiology

Rheumatoid arthritis is a chronic, systemic, inflammatory autoimmune disease, characterized by progressive and irreversible destruction of cartilage and bone and persistent synovitis in multiple diarthrodial joints, with an estimated prevalence ranging from 0.5% to 1.1% of the adult population in Europe and North America and estimated annual incidence rates varying from 20 to 50 cases per 100,000 [1] [2]. RA has a significant impact on numerous aspects of daily life and functioning[3]. Poor health-related quality-of-life is associated with reduced work productivity, absence from work, and loss of work[4]. The majority of patients with RA have fatigue, which has a significant impact on quality of life[5], and is rated by patients as a more important outcome than stiffness, joint swelling and pain[6]. Mortality rates in patients with RA are 1.5 to 1.6 fold higher than in the general population[7].

2.1.3. Biologic features

The pathophysiology of clinical RA is characterized by pannus, a marked cellular infiltrate containing synovial fibroblasts, macrophages, mast cells, CD4+ T cells, CD8+T cells, natural killer cells, NKT cells, B cells, and plasma cells[8,9]. T- and B-cell activation result in increased production of cytokines and chemokines, leading to a feedback loop for additional T-cell, macrophage, and B-cell interactions. Among the many cytokines that are elaborated by the rheumatoid pannus, tumor necrosis factor (TNF) and IL-6 are known to play important roles in the joint destruction, symptoms, and disability of RA.

[1] Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Res Ther. 2009;11(3):229.
[2] Alamanos Y, Voulgari PV, Drosos AA. Incidence and Prevalence of Rheumatoid Arthritis, Based on the 1987 American College of Rheumatology Criteria: A Systematic Review. Semin Arthritis Rheum. 2006 Dec;36(3):182-8.
[3] Matcham F, Scott IC, Rayner L, Hotopf M, Kingsley GH, Norton S, et al. The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: a systematic review and metaanalysis. Semin Arthritis Rheum. 2014 Oct;44(2):123-30
[4] Cutolo M, Kitas GD, van Riel PL. Burden of disease in treated rheumatoid arthritis patients: going beyond the joint. Semin Arthritis Rheum. 2014 Feb;43(4):479-88
[5] Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of diseasemodifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012 May;64(5):625-39.
[6] Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964–75.
[7] Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. Clin Exp Rheumatol. 2008 Sep-Oct;26(5 Suppl 51):S35-61.
[8] Choy E. Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis. Rheumatology (Oxford). 2012 Jul;51(Suppl 5):v3-11.
[9] McInnes IB, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. Nat Rev Immunol. 2007;7(6):429-42

IL-6 promotes osteoporosis and joint destruction in RA by recruitment of leukocytes to involved joints, differentiation of osteoclasts, and induction of matrix metalloproteinase production by synoviocytes in pannus. IL-6 has been shown to play a role in the antibody production and been implicated in mediating the predominance of Th17 over Treg in effector CD4+ T cell subsets, which is thought to play a major role in the development of RA. Finally, IL-6 is the major regulator of the acute phase reactants and the anemia of chronic disease, both of which are hallmarks of RA[8,9,10].

2.1.4. Clinical presentation

Rheumatoid arthritis is characterized by persistent synovitis and progressive destruction of cartilage and bone in multiple joints. The hallmark of the disease is a symmetric polyarthritis characteristically involving the small joints of the hands and feet. The inflammatory process can also target other organs, characteristically bone marrow (anemia), eye (scleritis, episcleritis), lung (interstitial pneumonitis, pleuritis), cardiac (pericarditis) and skin (nodules, leukocytoclastic vasculitis). Systemic inflammation is characterized by laboratory abnormalities, such as anemia, elevated erythrocyte sedimentation rate, fibrinogen and C-reactive protein (CRP) and by clinical symptoms of fatigue, weight loss, muscle atrophy in affected joint areas. The presence of polyclonal high titre rheumatoid factors and anti-Cyclic Citrullinated Peptide (anti-CCP) antibodies provides evidence of immune dysregulation.

It has been estimated that 65% – 70% of RA patients have progressive disease that leads to joint destruction, disability and premature death.

2.1.5. Management

Progressive joint destruction is irreversible[11] and correlated with long-term disability in RA[12,13,14]; consequently, therapies that prevent progressive joint destruction and provide sustained benefit over long periods of time are of key importance in the management of RA.

Conventional disease modifying anti-rheumatic drugs (hereafter referred to as DMARDs), such as methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine, are the first line of therapy for RA[15], methotrexate (MTX) being the preferred option in either DMARD-naïve early RA (<6 months duration) or established RA[5]. Until recently, treatment with a TNF antagonist in combination with a DMARD was the recommended second line of treatment[6]. The 2013 European League Against Rheumatism (EULAR) guideline broadened recommendations such that patients responding insufficiently to MTX and/or other DMARDs, with or without glucocorticoids, should receive a biologic DMARD in combination with MTX or other DMARDs[16].

[10] Schett G, Gravallese E. Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. Nat Rev Rheumatol. 2012 Nov;8(11):656-64.
[11] Scott DL. Radiological progression in established rheumatoid arthritis. J Rheumatol Suppl. 2004 Mar;69:55-65.
[12] Mueller RB, Kaegi T, Finckh A, et al; SCQM physicians. Is radiographic progression of lateonset rheumatoid arthritis different from young-onset rheumatoid arthritis? Results from the Swiss prospective observational cohort. Rheumatology (Oxford). 2014 Apr;53(4):671-7
[13] Aletaha D, Smolen JS. Joint damage in rheumatoid arthritis progresses in remission according to the Disease Activity Score in 28 joints and is driven by residual swollen joints. Arthritis Rheum. 2011 Dec;63(12):3702-11.
[14] Bombardier C, Barbieri M, Parthan A, Zack DJ, Walker V, Macarios D,et al. The relationship between joint damage and functional disability in rheumatoid arthritis: a systematic review. Ann Rheum Dis. 2012;71:836-44.
[15] Katchamart W, Trudeau J, Phumethum V, Bombardier C. Methotrexate monotherapy versus methotrexate combination therapy with non-biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis. Cochrane Database Syst Rev. 2010 Apr 14;(4):1-111.
[16] Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2013;0:1–1

Tumor necrosis factor inhibitors (etanercept, infliximab, and adalimumab) were the first biologic DMARDs to be approved as therapy for patients with RA. However, not all patients achieve the desired therapeutic response with a TNF inhibitor. During the first year after starting treatment with a TNF antagonist, 26% to 36% of patients discontinue treatment and after 5 years, 38% to 55% of patients discontinue treatment[17]. For the patients who have an inadequate response or are unable to tolerate a first TNF antagonist, there is some evidence that suggests these patients may ultimately derive clinical benefit when they switch to a mechanistically different class of biologic therapy (eg, antagonists or inhibitors of IL-1, IL-6, CD20, or T-cell activation), used either in combination with DMARDs[18,19] or as monotherapy[20,21].

About the product

Sarilumab is a recombinant human immunoglobulin (IgG)1 monoclonal antibody that binds specifically to both soluble and membrane-bound interleukin-6 (IL-6) receptors (sIL-6Rα and mIL-6Rα) and inhibits IL-6-mediated signaling. IL6 receptor is a known target with respect to the indication rheumatoid arthritis.

By binding to IL-6Rα, sarilumab prevents the formation of the high-affinity complex of IL-6 with IL-6Rα and thus blocks IL-6 signaling. Because sarilumab blocks both mIL-6Rα and sIL-6Rα, it has the potential to inhibit both intra-articular and systemic IL-6 signaling.

The claimed indication was:

Kevzara is indicated in combination with disease-modifying anti-rheumatic drugs (DMARDs) or as monotherapy for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who responded inadequately or were intolerant to DMARDs or tumour necrosis factor (TNF) antagonists.

Kevzara has been shown to inhibit progression of joint damage and to improve physical function.

The approved indication is:

Kevzara in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate (see section 5.1).

The recommended dose of Kevzara is 200 mg once every 2 weeks administered as a subcutaneous injection.

Reduction of dose from 200 mg once every 2 weeks to 150 mg once every 2 weeks is recommended for management of neutropenia, thrombocytopenia, and liver enzyme elevations.

[17] Neovius M, Arkema EV, Olsson H, Eriksson JK, Kristensen LE, Simard JF, et al; ARTIS Study Group. Drug survival on TNF inhibitors in patients with rheumatoid arthritis comparison of adalimumab, etanercept and infliximab. Ann Rheum Dis. 2015 Feb;74(2):354- 60.
[18] Favalli EG, Biggioggero M, Marchesoni A, Meroni PL. Survival on treatment with secondline biologic therapy: a cohort study comparing cycling and swap strategies. Rheumatology (Oxford). 2014 Sep;53(9):1664-8
[19] Smolen JS, Aletaha D. Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. Nat Rev Rheumatol. 2015 May;11(5):276-89.
[20] Dougados M, Kissel K, Sheeran T, Tak PP, Conaghan PG, Mola EM, et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). Ann Rheum Dis. 2013 Jan;72(1):43
[21] Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, Klearman M, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet. 2013;381 (9877):1541-50

Type of Application and aspects on development

Legal basis: Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

During the Clinical development program seven scientific advices were received from CHMP between 2008 and 2015. Advice was also obtained from national competent authorities MHRA, and AEMPS.

The design of the studies was almost compliant with CHMP guideline. However, changes in the guidance are reflected in the new version not in force yet.

The Applicant was almost fully compliant with the CHMP SAs, with the exception of conducting two separate (one phase II and one phase III) studies instead of the operationally seamless EFC11072 study.

2.2. Quality aspects

2.2.1. Introduction

The finished medicinal product (hereafter referred to as the drug product) is presented as a solution for subcutaneous injection available in two dosage strengths, 131.6 and 175 mg/mL providing doses of 150 and 200 mg of sarilumab as active substance, respectively.

Other ingredients are: histidine, arginine, sucrose, polysorbate 20 and water for injection (WFI). The product is available in two different single-use presentations, a pre-filled syringe and an autoinjector/pre-filled pen.

Pre-filled syringe: The pre-filled syringe (type 1 glass) is equipped with a stainless steel staked needle and an elastomer plunger stopper. The syringe has a styrene-butadiene elastomer needle cap and is equipped with a white polystyrene plunger rod and a light-orange polypropylene finger flange.

Pre-filled pen: The syringe components are pre-assembled into a single-use pre-filled pen with a yellow needle cover and dark-orange cap.

2.2.2. Active Substance

General Information

Sarilumab is a fully humanized monoclonal antibody (IgG1 isotype) directed against IL6Ra and produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells. Sarilumab is a covalent heterotetramer consisting of two disulfide-linked human heavy chains, each covalently linked through a disulfide bond to a human kappa light chain. There is a single N-linked glycosylation site (Asn^{296}) on each heavy chain, located within the CH2 domain of the Fc constant region in the molecule. The relative molecular mass is 143.9 kDa (in the absence of N-linked glycosylation).

The complementarity-determining regions (CDRs) within the sarilumab heavy chain and light chain variable domains combine to form the binding site for its target, IL-6Rα (interleukin-6 receptor α subunit). Sarilumab binds specifically to both soluble and membrane-bound IL-6 receptors.

Manufacture, process controls and characterisation

Description of the manufacturing process and process controls

Sarilumab drug substance (DS) is manufactured by Regeneron Pharmaceuticals, Inc. (NY, USA). The manufacture of sarilumab drug substance is achieved in three main parts, the upstream process, which produces the antibody, the downstream process, which purifies the antibody and the formulation of the drug substance. Sarilumab is produced by batch suspension culture of recombinant CHO cells.

Sarilumab protein is expressed and is secreted into the culture medium. The recombinant protein is harvested by centrifugation followed by filtration steps and is purified using a series of chromatographic and filtration steps.

Sarilumab formulated drug substance (FDS) is produced at final concentrations of 131.6 mg/mL or 175 mg/mL. The DS batches are thawed, pooled and mixed. Following the mixing with dilution buffer and excipient buffer, sterile filtration, mixing dispensing and storage of the FDS is performed.

Control of materials

All raw materials used in upstream and downstream operations are animal-component free except for the CHO cells. All chemical raw materials and the concerned quality are listed. All non-compendial grade raw materials and non-chemical raw material with their specifications are provided. The results of a risk assessment covering leachables and extractables from plastic and elastomeric components used in the sarilumab manufacturing process were provided as well.

The generation of the sarilumab cell bank system, the characterization and testing is sufficiently described and conforms to ICH Q5A/B. Sarilumab was generated by immunization of Regeneron's VelocImmune mice whereafter specific antibodies to human IL6R were identified and cloned. The CHO K1 host cell line was developed by transfection and stable integration of sarilumab expression plasmids into the host cell genome. The cell line was single cell derived using the Beckman-Coulter MoFlo flow cytometer, characterized for stability and homogeneity, and banked in medium lacking animal-derived products. Information concerning cloning, construction of plasmid, primer expression system were provided.

A Master Cell Bank (MCB) was generated and consequently expanded to a Working Cell Bank (WCB). The sarilumab production cell line stability and homogeneity was evaluated also at the limit of in vitro cell age (LIVCA) and the stability of the genetic construct was proven.

New sarilumab WCBs will be manufactured from the MCB according to approved manufacturing records. The procedure to create new WCBs, as well as the storage and use, will be the same as that for the initial WCB.

Control of critical steps and intermediates

For the control of critical steps a cumulative assessment of risk and importance was performed. Critical quality attributes (CQA), critical process parameters (CPP), general quality attributes (GQA) or general process parameters (GPP) were defined. In addition to action limits or acceptance criteria, control limits have been applied to all parameters and attributes (critical or general) that are trended by statistical process control. Hold times were validated and are reflected in the limits.

Process validation

The validation activities confirm that the sarilumab manufacturing process reproducibly produces drug substance and formulated drug substance meeting predetermined specifications and quality attributes. Process consistency and robustness, including impurity clearance capabilities, have been demonstrated. Overall the process has been demonstrated to be suitable for the manufacture of DS and FDS.

Manufacturing process development

Manufacturing development was sufficiently outlined. Preclinical process development focused on increased productivity, process robustness, and product safety, efficacy, and potency. All materials used for phase 3 clinical trials have been manufactured with the process intended for commercial production.

Two process improvements following transfer to Clinical GMP Production were performed.

Characterisation

The overall characterization approach is considered acceptable. Extensive analytical characterization was performed which included determination of primary, secondary and tertiary structure, charge variants, aggregation, purity and potency.

Results indicate that sarilumab exhibits properties representative of a fully human monoclonal antibody containing heavy and light chains bound by disulfide linkages.

The process-related impurities were identified. The purification during the process was assessed. Toxicology and clinical profile risk assessment were provided and acceptable daily exposure (ADE) evaluated.

Specification

Specifications were set in accordance with ICH Q6B. The testing includes identity by peptide map and immunoassay, purity under reducing and non-reducing conditions by Capillary Electrophoresis Sodium Dodecyl Sulfate (CE-SDS), low and high molecular impurities by size Exclusion-High Performance Liquid Chromatography (SE-HPLC), charge variants by capillary isoelectric focusing (cIEF) analysis, oligosaccharide profiling by glycan analysis, residual host proteins and DNA, bioburden, endotoxin, general characteristics colour, clarity, pH, total protein content by spectrophotometry, osmolality and potency by bioassay. The selection of tests covers the CQAs that have been defined to be relevant for sarilumab. The proposed release specification is based on data obtained from relevant lots of DS and FDS representing commercial lots, clinical experience and stability. Impurities have been studied in nonclinical and clinical studies as relevant. Potency is determined using a cell-based assay.

Analytical methods

Brief descriptions of all the analytical methods were provided. The provided details and information are considered sufficient. Analytical validation has been conducted in accordance with guideline ICH Q2(R1). The validation reports were provided. The analytical methods are considered validated with respect to accuracy, precision, specificity, linearity and robustness. The presented method validation results are acceptable.

The sarilumab potency assay measures the ability of sarilumab to bind human IL-6Rα and inhibit IL-6 mediated signaling in a biological system.

Batch analysis

The batch analyses of the sarilumab DS process PPQ lots met the proposed commercial specifications. Batch analysis results from 175 mg/ml and 131.6 mg/ml formulated drug substance (FDS) were provided as well. All batch data confirm compliance to the specification at time of release and thus demonstrate the consistency of the manufacturing process.

Reference materials

The establishment and history of the in-house reference standard has been outlined.

The same reference material is used both for drug substance and drug product in analytical testing and is sufficiently described.

Stability

The long-term storage condition of drug substance and formulated drug substance are supported with real time data.

Based upon stability data presented a shelf-life of 36 month frozen storage is permitted for sarilumab DS and a shelf-life of 36 months frozen storage is permitted for sarilumab FDS.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Sarilumab solution for injection is a clear, colourless to pale yellow, sterile solution with pH 6.0. Kevzara is supplied in two single-use pharmaceutical forms, pre-filled syringes (PFS) and pre-filled pens (PFP), containing 150 mg or 200 mg sarilumab in 1.14 ml solution (131.6 mg/ml and 175 mg/ml respectively). PFS and PFP use the same bulk. Composition and concentrations of the excipients are identical for PFS and PFP and the two strengths: histidine/L-histidine monohydrochloride monohydrate, L-arginine hydrochloride, sucrose, polysorbate 20 and water for injection.

The excipients are of compendial grade and controlled by the manufacturers using analytical procedures to full compendia monograph requirements.

The primary packaging material for both PFS and PFP is the bulk PFS. Bulk PFS consists of a borosilicate type I glass syringe barrel (with inner lubrication with silicone oil) equipped with a stainless steel staked needle, protected by a soft elastomeric needle shield (SNS), and an elastomeric plunger stopper (polystyrene). The SNS is made of a styrene-butadiene elastomeric formulation and does not contain dry natural rubber, natural latex rubber or any of its derivatives. The choice of the container closure system is considered acceptable for the type of product and adequate to provide protection from microbial contamination.

The PFS presentation is composed of the bulk PFS with SNS, a plunger rod (white polystyrene) and finger flange. The PFP does not need to have a CE marking in agreement with Council Directive 93/42/EEC Art. 1(3) since it is intended for single-use only and the device and the medicinal product form a single integral product which is intended exclusively for use in the given combination.

Extractable and leachable study results do not raise concerns with regard to the container closure system.

Manufacture of the product and process controls

Manufacturing of PFS is performed at Sanofi Winthrop Industrie, Le Trait, France and manufacturing of PFP is performed at Sanofi Aventis Deutschland GmbH, Frankfurt am Main, Germany. The manufacturing process for production of Bulk PFS consists of thawing and pooling of FDS, followed by filtration and filling.

Critical process parameters were defined and adequate in-process-controls were set. The Bulk PFS is defined as intermediate and adequate specifications and acceptance criteria are set. The manufacture of the final presentations PFS and PFP consist of assembling, labelling and secondary packaging. In-process control results of commercial scale batches demonstrated that the manufacturing process is capable of consistently generate sarilumab 131.6 mg/mL and 175 mg/mL in Bulk PFS in line with the defined specifications.

Manufacturing process validation on sarilumab solution for injection has been performed on three batches of Bulk PFS for each dosage strength 131.6 and 175 mg/mL. Overall the data demonstrated that for all validation batches the predefined parameters and holding times were met. The process was shown capable of producing bulk drug product in prefilled syringes in a robust manner. Media fill testing has been adequately described.

The impact of transport on product quality, integrity and performance was assessed.

A Post approval change management protocol was provided to introduce changes to the assembly and labelling process for the PFP. The Validation and Comparability Plan provided were considered acceptable.

Product specification

Specifications were set in accordance with ICH Q6B. The method of manufacture and route of administration were considered when setting release and shelf life specifications. Release tests performed on PFP comprise *Appearance*, *Identity by Dot blot* or *ELISA,* and *Total protein content* and the PFP-specific parameters *Activation force, Dose accuracy, Injection depth* and *Injection time*. It is accepted that the tests *Appearance of solution, colour of solution, pH, Potency, Purity by CE-SDS (reduced and non-reduced), Purity by SE-HPLC, Charge variant analysis, Bacterial endotoxin content, Sterility, Particulate matter, Expellable volume, Break loose and glide force* are performed on Bulk PFS and these results are reported at PFS level and – except for the last two tests – at PFP level.

The DP release specifications and numerical acceptance criteria are reasonably set and supported by batch analysis results. The batch analysis data are acceptable. Analytical procedures and their validations are acceptable. It can be concluded that DP specifications have been adequately justified and are fully compliant with Ph.Eur. 2031 *Monoclonal antibodies for human use* and Ph.Eur. 0520 *Parenteral preparations*.

Stability of the product

The proposed shelf-life is 24 months for the Bulk PFS, 24 months for the PFS calculated from the date of fill of the bulk PFS and 24 months for the PFP calculated from the date of fill of the bulk PFS. The long-term storage condition for the DP is 2-8°C. This is supported by real-time data and is acceptable.

The distribution and patient time out of refrigeration (TOR), of which the end user may use up to 14 days, is acceptable.

Results from a photostability study, carried out in accordance with ICH Q1B Stability Testing: Photostability Testing of New Drug Substances and Products indicate that exposure to light should be limited. The SmPC consequently includes a statement that the pre-filled syringe/pre-filled pen should be stored in the original carton in order to protect from light.

Adventitious agents

TSE compliance

Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) has been sufficiently demonstrated. The drug substance is produced in a culture medium. No material of bovine origin is added during fermentation of Sarilumab. The MCB is free from TSE-risk substances.

Virus safety

The cells used for production of sarilumab have been extensively screened for viruses. These tests did not reveal presence of any viral contaminant in the MCB with the exception of intracellular A-type retroviral particles which are well known to be present in in rodent cells. This is acceptable since there is sufficient capacity within the manufacturing procedure of sarilumab for reduction of this type of viral particles.

The purification process includes several steps for virus inactivation/removal. The effectiveness of these steps (low pH, chromatography and filtration steps) has been sufficiently demonstrated. The virus safety of sarilumab is sufficiently demonstrated**.**

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

A Post approval change management protocol was provided to introduce changes to the assembly and labelling process for the PFP. The Validation and Comparability Plan provided were considered acceptable.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3. Non-clinical aspects

2.3.1. Introduction

The toxicology studies were conducted in accordance with GLP, except for the exploratory studies. Some exceptions to GLP were noted, however these exceptions are not considered to affect the interpretation of study data or the scientific validity of the study.

The nonclinical testing strategy for sarilumab followed a development pathway typical of a biopharmaceutical product and is consistent with applicable existing regulatory guidance, specifically ICH S6 (R1) *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (2011)*.

During the development of sarilumab, several scientific advices have been obtained by CHMP and European regulatory agencies. The non-clinical programme for sarilumab presented in this MAA is in line with the given advice.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Primary pharmacology in vitro

Sarilumab (REGN88) is a human mAb specific for human IL-6Rα. Sarilumab binds with high affinity to human IL-6Rα and inhibits the binding of IL-6 to its receptor. In in vitro functional assays, sarilumab blocked IL-6-induced effects in cells expressing membrane IL-6Rα and gp130; i.e. sarilumab inhibited IL-6-induced STAT3 signalling in hepatocarcinoma HepG2 cells and prevented IL-6-dependent proliferation of human DS-1 B cells. Sarilumab also inhibited trans-signalling mediated by the complex of IL-6/sIL-6Rα in cells which express only gp130. Importantly, sarilumab demonstrated no agonist activity in the absence of IL-6.

Given that sarilumab is a human IgG1 molecule, it may mediate Fc-effector function upon binding to cell surface-expressed IL-6Rα. In BiaCore analyses, sarilumab bound to FcγRI, FcγRIIa (R131, H131), FCγRIIb, FcγRIIIa (V176, F176) and FcγRIIIB with affinities similar to those reported for human IgG1. Binding to sIL-6Rα or clustering of sarilumab with anti-$(Fab')_2$ antibodies modestly increased the affinities to Fcγ receptors. However, sarilumab did not induce ADCC or CDC against target cells expressing membrane IL-6Rα.

Cross-reactivity of sarilumab with IL-6Rα from non-clinical species was tested in vitro. As shown by BiaCore analysis, sarilumab bound to cynomolgus IL-6Rα with slightly lower affinity (approx. 2.3x) than to human IL-6Rα. An additional flow cytometry study with PBMC confirmed reactivity of a chimeric version of sarilumab with macaque IL-6Rα and demonstrated the lack of reactivity with other non-clinical species.

Primary pharmacology in vivo

The in vivo activity of sarilumab was evaluated in humanized mice, expressing both human IL-6 and human IL-6Rα. By injection of turpentine an IL-6-dependent inflammatory response is induced. When given prior to turpentine, sarilumab blocked the inflammatory response at doses ≥ 1.5 mg/kg, as indicated by a decrease in the acute phase protein SAA and an increase in IL-6. The latter finding is consistent with the inhibition of receptor-mediated clearance of IL-6.

Additional in vivo studies in wild-type mice were conducted with REGN844, a surrogate mAb specific for murine IL-6Rα. This mAb blocked the interaction of IL-6 with muIL-6Rα and inhibited the IL6-dependent proliferation of a murine B cell line. In the model of turpentine-induced inflammation, REGN844 achieved the expected pharmacologic effect. Preventive treatment was associated with a reduction in SAA and an increase in circulating IL-6. Pertinent to the proposed indication of rheumatoid arthritis, the effect of blocking IL-6Rα was evaluated in a murine model of collagen-induced arthritis. In a prophylactic setting, REGN844 prevented development of joint inflammation and bone erosion. The study provides proof-of-concept for the inhibition of IL-6Rα rheumatoid arthritis.

Secondary pharmacodynamic studies

Literature data indicate that IL-6 plays a role in initiation and propagation of tumour growth. This is attributed partly to a direct growth-promoting effect of IL-6 on tumour cells and partly to the creation of an IL-6-driven inflammatory milieu leading to the release of growth factors that stimulate tumour growth. Thus, the effect of blocking IL-6Rα on tumour cell growth was evaluated in mice transplanted with human tumour xenografts. Treatment with sarilumab after establishment of tumours led to a reduction in tumour volume. This correlated

with an inhibition of IL-6Rα-mediated signalling and an increase of a marker for apoptosis, as demonstrated by ex vivo analysis of tumour xenografts. While the reduction of tumour volume in this study was moderate, the data indicate that blockade of IL-6 is associated with inhibition of tumour cells rather than promotion of carcinogenesis.

Safety pharmacology programme

In line with ICH S6(R1) safety pharmacology endpoints were evaluated as part of the repeat-dose toxicity studies in cynomolgus monkeys. This was considered acceptable by CHMP.

No sarilumab-related effects were observed on cardiovascular, respiratory or CNS functions.

Pharmacodynamic drug interactions

The approved indication for Kevzara is in combination with methotrexate (MTX) for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate. DMARDS act differently from sarilumab, IL-6Rα, thus PD interactions are not expected.

2.3.3. Pharmacokinetics

The pharmacokinetics of sarilumab was evaluated in single-dose PK studies in rats and cynomolgus monkeys after IV and SC administration. The latter reflects the proposed clinical route of administration. Additional PK studies were conducted in both species to evaluate PK comparability of sarilumab manufactured according to different processes or from different cell lines. Toxicokinetics after repeated administration were evaluated as part of the toxicity studies in cynomolgus monkeys. TK of the surrogate mAb REGN844 was evaluated in mice.

A qualified ELISA was used for detection of free sarilumab in rat serum. Validated ELISAs were used for detection of total sarilumab in cynomolgus serum and for detection of REGN844 in mouse serum. For detection of anti-sarilumab antibodies in cynomolgus, initially a validated ELISA was used. Later in the development programme a more sensitive bridging ECL assay was developed and validated.

PK characteristics of sarilumab after single IV and SC administration were typical for a monoclonal antibody. In rats, the concentration-time profile of free sarilumab was characterized by an initial distribution or absorption phase following IV or SC administration, respectively, followed by a single elimination phase. The mean half-life of free sarilumab ranged from 5.58 to 8.29 days and was similar following IV or SC administration. The bioavailability in rats following SC dosing was high (≥ 77%). In rats, free sarilumab displayed linear and dose-proportional kinetics, consistent with the lack of sarilumab binding to rat IL-6Rα.

In cynomolgus monkeys, the concentration-time profile of total sarilumab in monkey serum is described by an initial distribution (after IV dosing) or absorption phase (after SC dosing) followed by a biphasic elimination consisting of a long β elimination phase and a more rapid terminal target elimination phase. The mean t1/2 of total sarilumab in monkeys was 113 to 233 hours (4.71 to 9.71 days) at serum concentrations above IL-6Rα target saturation binding (7 to 39 µg/mL). At concentrations where target-mediated elimination was a primary clearance process, a more rapid mean t1/2 of 35.6 to 69.9 hours (1.48 to 2.91 days) was observed. The bioavailability in monkeys following SC dosing was high (>77%). Total sarilumab in serum of monkeys displayed

nonlinear PK at doses < 5 mg/kg, where saturable target-mediated disposition is a primary clearance mechanism at lower concentrations; this nonlinear PK is expected in a species with a high-affinity target (monkey IL-6Rα) for binding sarilumab. After repeated, once weekly administration at doses of up to 50 mg/kg there was limited accumulation (up to 2.8x after 6 months).

Additional PK studies in rats and cynomolgus monkeys were conducted to compare the PK characteristics of sarilumab manufactured from different cell lines, processes and formulated in different formulations. In the different studies, treatment with sarilumab manufactured according to the commercial process (C2P1F3) resulted in a lower exposure than treatment with sarilumab from the initial process (C1P1F1). However, no differences were observed in the toxicity profile of the different sarilumab versions.

In accordance with ICH S6 (R1), studies on distribution, metabolism and excretion were not conducted.

Systemic exposure during pregnancy, as well as transport of sarilumab across the placental barrier, was evaluated in pregnant cynomolgus monkeys, including maternal function (see section on Reproductive Toxicity below).

2.3.4. Toxicology

Single dose toxicity

No single dose toxicity studies have been conducted as findings of acute toxicity are rare for monoclonal antibodies. This is consistent with current ICH and CHMP guidelines.

Repeat dose toxicity

The toxicity of sarilumab was evaluated in an extensive non-clinical in vivo programme. Repeated dose studies of up to 26 weeks duration were conducted in cynomolgus monkeys which were shown to be a relevant species based on binding of sarilumab to cynomolgus IL-6Rα. Reproductive and developmental toxicity of sarilumab was evaluated in an ePPND study in cynomolgus monkeys. In addition, the effect of IL-6Ra blockade on fertility and juvenile toxicity was evaluated in mice using a murine surrogate mAb directed against mouse IL-6Rα.

Table 1: Overview of cynomolgus repeat-dose studies:

Study ID	Number/ group	Route / Dose (mg/kg)	Duration	NOAEL (mg/kg/wk)	Major findings
IL6R-TX-06029	1-2/sex	IV: 10 SC: 10	4 weeks IV: QW SC: BIW		• minimal decrease in neutrophil count and fibrinogen
REGN88-TX-06040	3/sex (main) 2/sex (recovery)	IV, 0, 5, 10, 40	5 weeks QW	40	• decrease in neutrophil count, partially reversible • decrease in fibrinogen, reversible • decrease in CRP, partially reversible
REGN88-TX-06037	4/sex (main) 2/sex (recovery)	IV, 0, 1, 10, 50	13 weeks QW	50	• 2 unscheduled deaths 1 M @ 50 mg/kg on day 31, due to gavage error, not sarilumab-related 1 F @ 10 mg/kg, day 123; gastrointestinal amoebiasis; unclear relationship to sarilumab • decrease in neutrophil count, partially reversible • decrease in fibrinogen, reversible • decrease in CRP, partially reversible
REGN88-TX-06038	4/sex (main) 2/sex (recovery)	SC, 0, 1, 5, 15, 50	13 weeks BIW	100	• slight decreases in neutrophil counts, fibrinogen and CRP, reversible • minimal to moderate mixed inflammatory infiltrates at SC injection sites, evidence of reversibility • 1 F @ 5 mg/kg/dose: severe diffuse subacute inflammation in heart; 1 M @ 1 mg/kg/dose: minimal focal subacute inflammation accompanied by mild perivascular mononuclear cell infiltrates in brain both findings not considered related to sarilumab
REGN88-TX-08031	4/sex (main) 2/sex (recovery)	IV, 0, 1, 5, 15, 50	26 weeks QW	50	• 2 unscheduled deaths 1 M @ 0.5 mg/kg on day 159, due to accidental choking death, not sarilumab-related 1 M @ 15 mg/kg, day 133; moderate typhlocolitis; unclear relationship to sarilumab • slight decreases in neutrophil counts and fibrinogen, reversible • increases in serum IL-6, reversible • reduced 1° and 2° IgG response after immunization to KLH

QW: once per week, BIW: twice per week, wk: week

In the repeated-dose studies in cynomolgus monkeys, treatment with sarilumab alone was generally well tolerated. Consistent findings throughout the studies were related to the pharmacology of the mAb, i.e. decrease in neutrophil counts, decrease in serum fibrinogen concentration, decrease in CRP concentration and increase in IL-6 concentration. In general, these findings were variable, not dose-related and not always statistically different from control group values or pre-dose values. At the end of the treatment-free period, these findings were reversible or partially reversible.

A total of 4 deaths occurred throughout the study programme. Two of these were accidental and not related to sarilumab (gavage error, choking). Cause of death in 1 animal in the 13-wk IV study was gastrointestinal amoebiasis. Cause of 1 death in the 26 wk study was determined as typholocolitis, a spontaneous gastro-intestinal inflammation as occasionally observed in cynomolgus.

In studies were sarilumab was given SC, there were microscopic findings (i.e. inflammatory infiltrates) at the SC injection sites. In addition, severe diffuse subacute inflammation in the heart was detected in 1 female and minimal focal subacute inflammation was observed in the brain of 1 male.

In the 13 week SC comparability study, a cortical adenoma in the adrenal gland was detected in 1 M in the 100 mg/kg/wk C1F1P1 group.

The NOAEL was the highest dose administered and was associated with an AUC0-168h of 381,040 µg*h/ml at 50 mg/kg/week IV in the chronic toxicity study.

Genotoxicity

Genotoxicity studies have not been conducted, in accordance with ICH S6 (R1). This is considered acceptable by CHMP.

Carcinogenicity

No carcinogenicity studies were conducted which is in line with ICH S6 (R1). However, an assessment of the carcinogenic potential of sarilumab was made based on literature data on the role of the IL-6 pathway in tumour development and on non-clinical data for sarilumab.

The majority of literature data indicate that IL-6 is an autocrine growth factor in the pathogenesis of cancers. Consistently, studies which inhibit IL-6 have been shown to inhibit different tumour types in vitro and in vivo. Also studies with sarilumab in human xenograft models show a reduction of tumour growth in vivo possibly through induction of apoptosis.

Results from the repeated-dose toxicity studies in cynomolgus do not contain findings which indicate a carcinogenic risk, including the presence of a cortical adenoma in the adrenal gland of a single high-dose male in the 13-week SC comparability study, given that this type of cancers occurs spontaneously in macaques.

Reproduction Toxicity

The effect of IL-6Rα inhibition on fertility and early embryonic development was evaluated in mice treated with the surrogate anti-mouse IL-6Rα mAb REGN844 at doses up to 200 mg/kg/week. There were no test article-related microscopic findings in male and female reproductive organs, except for an increased incidence of implantation-site degeneration in the high-dose group. However, REGN844 treatment had no effect on male and female reproductive and fertility parameters.

No sarilumab-related microscopic findings were observed in the male and females reproductive organs of cynomolgus monkeys included in the repeated-dose toxicity studies; however, it should be noted that only a minority of these animals was sexually mature. No compound-related effects were observed on the placentae.

Samples for TK analysis were collected at the necropsy, for males (10/group) at 2-3hrs post-dose; for F (all animals) on GD14 (i.e. 7 days after the last dose). Mean REGN844 serum concentrations are tabulated below

(Table 6). Due to the differences in times in blood collection (which are related to the logistics of the fertility study), comparison of male and female REGN844 serum concentrations is not meaningful.

Table 2: fertility study - mean REGN844 serum concentrations

Gender	Collection Time	20 mg/kg/week [a] (µg/mL)	50 mg/kg/week [a] (µg/mL)	200 mg/kg/week [a] (µg/mL)
Male	2-3 hours after last dose	184 ± 48.4	600 ± 115	2190 ± 291
Female	GD14 (7-10 days after last dose)	BLQ	9.16 ± 7.29	60.6 ± 28.2 [b]

The evaluations of embryo-fetal toxicity and pre-/post-natal developmental toxicity were conducted in a combined study design of the enhanced pre- /postnatal developmental toxicology study in monkeys.

In the cynomolgus enhanced pre-/post-natal development study, there were no sarilumab-related effects on pregnancy out-come. The length of gestation was slightly shorter in the high-dose group (50 mg/kg) but still within the control range for gestation length from the testing facility. The incidence of embryo-fetal losses (abortion, in-utero embryo-fetal death) and neonatal deaths was comparable among the groups. The incidence of stillbirths was slightly higher in the high-dose group but still within the range of historical control data of facility.

Toxicokinetic parameters for this study are summarized in the tables below.

Table 3: ePPND study- group mean sarilumab serum concentrations in maternal and neonate monkeys

Day	Number of Infusions	TK Parameters	5 mg/kg/week (µg/mL)	15 mg/kg/week (µg/mL)	50 mg/kg/week (µg/mL)
Maternal Monkeys					
GD20	1	C_{max}	167 ± 29.3	495 ± 141	1624 ± 186
		C_{trough}	49.1 ± 8.16	160 ± 71.5	511 ± 112
GD41	4	C_{max}	225 ± 40.6	780 ± 180	2584 ± 338
		C_{trough}	81.4 ± 40.7	306 ± 67.6	1230 ± 191
GD97	12	C_{max}	296 ± 59.5	885 ± 92.6	2913 ± 523
		C_{trough}	157 ± 51.9	487 ± 144	1570 ± 300
GD146	19	C_{max}	310 ± 63.8	922 ± 112	3049 ± 493
		C_{trough}	152 ± 46.6	622 ± 221	1780 ± 293
LD7	-	-	66.9 ± 48.6	311 ± 54.4	1389 ± 389
LD30 (Nec)		-	15.7 ± 16.4	154 ± 121	482 ± 119
Neonates					
DB7	-	-	54.7 ± 40.9	521 ± 179	1435 ± 630
DB30 (Nec)		-	9.18 ± 7.58	129 ± 32.0	339 ± 215

Values are mean ± standard deviation; N = 7-12 maternal monkeys/group and 5-7 neonate monkeys/group. The lower limit of quantitation was 0.157 µg/mL

Table 4: ePPND study- group mean AUC0-168 h of sarilumab in maternal monkeys

Number of Infusions	5 mg/kg/week (µg.h/mL)	15 mg/kg/week (µg.h/mL)	50 mg/kg/week (µg.h/mL)
1	14 750 ± 2882	42 491 ± 11 712	141 864 ± 22 721
4	22 885 ± 7775	81 588 ± 19 764	287 524 ± 35 363
12	35 554 ± 8699	110 616 ± 17 991	354 389 ± 58 057
19	37 260 ± 7643	124 845 ± 30 236	396 455 ± 62 297

Values are mean ± standard deviation; N = 7-12 maternal monkeys/group

No TK determination on breast milk was performed. This is appropriately reflected in section 4.6 of the SmPC. "Use in pregnant and lactating patients" is listed as missing information in the RMP safety specifications.

According to the agreed PIP, juvenile animal toxicity studies have not been requested to support the future use of sarilumab in paediatric patients. Nevertheless, the applicant has conducted a juvenile toxicology study with the murine surrogate mAb REGN844 in juvenile mice, dosed from post-natal day 14 to 70. In addition to general toxicity endpoints, immunotoxicity was a focus of the study. REGN844 treatment had no major effect on lymphocyte populations in peripheral blood, spleen and mesenteric lymph nodes, also serum IgM and IgG levels in peripheral blood were not reduced. In response to immunization with KLH the T cell-dependent IgG response was slightly reduced in REGN844-treated males. However, this finding was reversible at the end of the recovery period. The study does not raise concern for the use of sarilumab in young children.

In addition to the juvenile study, the immunotoxic potential of sarilumab was evaluated as part of the 26-week chronic toxicity study. In this study, sarilumab had no effect on peripheral lymphocyte populations as determined by immunophenotyping. Upon immunization with KLH, sarilumab had no effect on the development of an IgM response. However, primary and secondary IgG titers were lower in sarilumab-treated animals than in controls, although it should be noted, that antibody responses were not completely blocked.

Toxicokinetic data

The main TK parameters and number of animals who developed ADA in the monkey repeated-dose toxicity studies are illustrated in the table below:

Table 5:

Study ID	Weekly Dose (mg/kg)	Animal AUC (µg.h/ml)							
		Day 1 (dose1)		**Day8 (dose3)**		**Day15(dose 5)**		**Day 22(dose7)**	
	10 (IV)	26200	27800	40300	43900	6000	46900	32500	46600
ILR-TX-06029[a]	**ADA**	Not determined							
	20 (SC)	7650	6920	19400	20900	26100	21700	28600	30100
	ADA	Not determined							
		Day 1 (dose1)		**Day8 (dose2)**		**Day22 (dose 4)**		**Day 29(dose5)**	
	5 (IV)	8420	9020	13300	11900	18400	12200	20000	13600
	ADA	-	-	-	-	-	**2**	**-**	-
REGN88-TX-06040[b]	10 (IV)	20000	20800	26000	26100	23700	27000	24900	31200
	ADA	-	-	-	-	**2** by day15	**1**	-	-
	40 (IV)	72600	77700	96100	117000	149000	173000	150000	169000
	ADA	-	-	-	-	-	-	-	-
		Day 1 dose1		**Day 28 dose5**		**Day 63 dose10**		**Day 84 dose13**	
	1 (IV)	1347	1622	362	284	293	336	393	384
	ADA	-	-	**5** by day15	**5** by day21	**1** by day49	-	-	-
REGN88-TX-06037[c]	10 (IV)	20833	23521	40024	53187	46794	57748	56448	66652
	ADA	-	-	-	-	-	-	-	-
	50 (IV)	112736	114978	205021	247834	238553	320117	263856	252770
	ADA	-	-	-	-	-	-	-	-
		Week 0 Dose 1		**Week 3 Dose 7**		**Week 7 Dose 15**		**Week 11 Dose 23**	
	2 (2x wk SC)	4.02	5.85	2.32	3.13	1.05	BLQ	1.8	BLQ
	ADA								**12/12** 4/12 RP
REGN88-TX-06038[d]	10 (2x wk SC)	33.7	30.5	114	75.1	195	97.7	204	95.4
	ADA								**4/12**
	30 (2x wk SC)	137	120	550	454	676	549	963	711
	ADA								0/12
	100 (2x wk SC)	410	360	1560	1540	2210	2350	2560	2360
	ADA								0/12

		Day 1 dose1		Day 49 Dose 8		Day 140 dose 21		Day 168 Dose 25	
REGN88-TX-06031[e]	0.5 (IV)	662	626	167	75	259	37.8	338	33.1
	ADA								**12/12** 3/3 RP
	5 (IV)	13026	11144	13074	27379	13581	28962	14685	31098
	ADA								**5/12** 1 /4 RP
	15 (IV)	33213	32324	90207	86012	106226	72903	109469	71272
	ADA								**1/12** 0/3 RP
	50 (IV)	122907	145587	339369	353578	343358	387392	371194	390886
	ADA								**0/12** 0/4 RP

ADA: serum Anti-drug (sarilumab) antibody
RP: Recovery Phase
[a]$AUC_{0\text{-}72h}$ (µg.h/mL) for SC Dose 1; $AUC_{24\text{-}72h}$ (µg.h/mL) for SC Doses 3, 5, and 7; $AUC_{0\text{-}168h}$ (µg.h/mL) for IV Doses 1 to
[b]$AUC_{0\text{-}168h}$ (µg.h/mL); N=5
[c]$AUC_{0\text{-}168h}$ (µg.h/mL); N=6
[d] The data represent C_{trough} (µg/mL) values corresponding to the trough concentrations at 96h following first biweekly dose; sampling time was at 24h of each week, AUC and Cmax were not calculated for this study; N=6
[E]$AUC_{0\text{-}168h}$ (µg.h/mL); N=6

In all monkey repeated-dose toxicology studies, animals were exposed to sarilumab. The highest dose used in IV (50 mg/kg/week) and SC (100 mg/kg/2xweek) studies was adequate to obtained multiple exposure levels compared to the ones used during clinical development. The dose of 50 mg/kg/week IV provided exposures that were approximately 80-fold higher than those achieved in humans administered 200 mg SC sarilumab Q2W (see interspecies comparison section).

Exposure in term of AUC0-168h after IV administration is consistent across the various studies at the same dose (see table below).

Table 6: Toxicokinetics - overview of toxicokinetics data (AUC) across species

Species/ Strain (Study No.)	**Monkey/cynomolgus** *a* **[REGN88-TX-06040], [REGN88-MX-14095]**				**Monkey/cynomolgus** *a* **[REGN88-TX-06037], [REGN88-MX-14095]**				**Monkey/cynomolgus** *a* **[REGN88-TX-08031], [REGN88-MX-14095]**				**Monkey / cynomolgus** *a* **[REGN88-TX-08030], [REGN88-MX-14095]**	
Dose (mg/kg/week)	**Day 1 (Dose 1)** *b*		**Day 29 (Dose 5)** *b*		**Day 0 (Dose 1)** *cd*		**Day 84 (Dose 13)** *c*		**Day 0 (Dose 1)** *cd*		**Day 168 (Dose 25)** *c*		**GD20 (Dose 1)** *e*	**GD146 (Dose 19)** *e*
	M:	F:	M:	F:	M:	F:	M:	F:	M:	F:	M:	F:	F:	F:
0.5 (IV)	-	-	-	-	-	-	-	-	662	626	338	33.1	-	-
1 (IV)	-	-	-	-	1347	1622	393	384	-	-	-	-	-	-
5 (IV)	8420	9020	20 000	13 600	-	-	-	-	13 026	11 144	14 685	31 098	14 750	37 260
10 (IV)	20 000	20 800	24 900	31 200	20 833	23 521	56 448	66 652	-	-	-	-	-	-
15 (IV)	-	-	-	-	-	-	-	-	33 213	32 324	109 469	71 272	42 491	124 845

Species/ Strain (Study No.)	Monkey/cynomolgus [a] [REGN88-TX-06040], [REGN88-MX-14095]				Monkey/cynomolgus [a] [REGN88-TX-06037], [REGN88-MX-14095]				Monkey/cynomolgus [a] [REGN88-TX-08031], [REGN88-MX-14095]				Monkey / cynomolgus [a] [REGN88-TX-08030], [REGN88-MX-14095]	
40 (IV)	72 600	77 700	150 000	169 000	-	-	-	-	-	-	-	-	-	-
50 (IV)	-	-	-	-	112 736	114 978	263 856	252 770	122 907	145 587	371 194	390 886	141 864	396 455

	Human
Dose (mg Q2W)	Population PK Data [f]
150 (SC)	5040
200 (SC)	9504

Abbreviations: M: male; F: female; AUC: area under the concentration-time curve; IV: intravenous; GD: gestation day

[a] For purposes of comparison across species, data from the 5-week, 13-week, 26-week, and ePPND IV toxicology studies (first and last timepoints) are presented here. [b] $AUC_{0\text{-}168h}$ (µg.h/mL); N=5 [c] $AUC_{0\text{-}168h}$ µg.h/mL; N=6 [d] Day 0 equals the first day of dosing [e] $AUC_{0\text{-}168h}$ (µg.h/mL); N=7 to 12

[f] Rheumatoid arthritis patient Population PK values for predicted $AUC_{0\text{-}\tau}$ (0-14 days) following SC administration of 150 mg Q2W and 200 mg Q2W are 210 and 396 mg.day/L, respectively (see 2.7.2 Summary of Clinical Pharmacology Studies). Values are presented as µg.h/mL; conversion to µg.h/mL = mg.day/L X 24

Formation of anti-sarilumab antibodies was measured in each of the monkey toxicology studies. ADAs were present in monkeys at doses of ≤ 15 mg/kg/week. The lack of an ADA response at the doses >15 g/kg/week may reflect the potential for the high circulating sarilumab concentrations causing immune tolerance because ADA was not observed in recovery animals even after sarilumab concentrations reached low levels at the end of the recovery period. Alternately, the lack of an ADA response may reflect the potential for the high circulating drug concentrations to interfere in the ADA assay. The presence of ADAs was associated with lower exposure to sarilumab, but was not associated with any adverse effects.

Local Tolerance

No classical local tolerance studies were performed. Local tolerance was assessed in repeat-dose toxicology studies by evaluating IV infusion and SC injection sites from treated animals (visual, macro- and microscopic observations).

Following SC administration, there were minimal to moderate mixed inflammatory infiltrates at the SC injection sites in all sarilumab-treated groups. The incidence and/or severity of the SC microscopic findings were not dose dependent, and were fully or partially reversible following the recovery period.

Other toxicity studies

The immunotoxic potential of sarilumab was evaluated as part of the 26-week chronic toxicity study. In this study, sarilumab had no effect on peripheral lymphocyte populations as determined by immunophenotyping. Upon immunization with KLH, sarilumab had no effect on the development of an IgM response. However,

primary and secondary IgG titers were lower in sarilumab-treated animals than in controls, although it should be noted, that antibody responses were not completely blocked.

2.3.5. Ecotoxicity/environmental risk assessment

Sarilumab is a monoclonal antibody consisting of natural amino acids, and is therefore not expected to pose a risk to the environment. As such, no ERA was performed.

This is in line with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (ERA Guideline).

2.3.6. Discussion on non-clinical aspects

The non-clinical in vitro data submitted demonstrates the pharmacological mode of action for sarilumab as an inhibitor of IL-6Rα. The studies provide adequate information on the binding affinity of sarilumab and its potency to inhibit IL-6-induced signal transduction and cellular responses. Importantly, the studies demonstrate a lack of Fc effector function such as ADCC and CDC.

In vivo, the ability of sarilumab and its murine surrogate in preventing the increase of circulating Serum Amyloid A (SAA) in the Tg and WT turpentine-induced acute inflammation model has been demonstrated. Sarilumab murine surrogate was able to mitigate disease signs and severity (swelling of the joints, bone erosion) of induced autoimmune rheumatoid arthritis in CIA model. These data provide a proof-of-concept for the blockade of IL-6Rα in arthritis.

The pharmacokinetic studies performed for this application are considered sufficient for the proposed indication. No specific non-clinical PK drug interaction studies were conducted. This is acceptable, since sarilumab as a monoclonal antibody is not metabolized via CYP450 enzymes. However, according to literature, the expression of hepatic CYP450 enzymes is suppressed by cytokines such as IL-6. Thus, CYP450 expression may be reversed when IL-6 signalling is inhibited by sarilumab. This issue is adequately addressed in the SmPC.

To support the safety of sarilumab, an extensive toxicology programme was presented, which is in accordance with current guidance and considered adequate. Selection of species for the toxicity studies is scientifically justified and accepted. Sarilumab-related findings in the repeated-dose toxicity studies were related to pharmacology and consisted of decreases in neutrophil counts, serum fibrinogen and CRP and increases in serum IL-6 (when measured). A total of 4 deaths occurred throughout the study programme. Cause of death in 1 animal was gastrointestinal amoebiasis. While the data from this animal indicate that the infection was pre-existing, sarilumab may have impaired the immune response against this intestinal pathogen. “Serious infection” is considered as an identified risk for sarilumab. In studies were sarilumab was given SC, there were microscopic findings (i.e. inflammatory infiltrates) at the SC injection sites. These are considered a reaction to injection of high concentration of human protein. In addition, severe diffuse subacute inflammation in the heart was detected in 1 female and minimal focal subacute inflammation was observed in the brain of 1 male. It is agreed, that these findings can be considered as not related to sarilumab, since they were identified only in individual animals and are known as background findings in cynomolgus. In the 13 week SC comparability study, a cortical adenoma in the adrenal gland was detected in 1 M in the 100 mg/kg/wk C1F1P1 group. Adrenal cortical adenomas are known as spontaneous neoplasms in cynomolgus monkeys. The finding was considered as incidental and not related to sarilumab. In summary, in these studies, no adverse effects were observed. The NOAEL was the highest dose administered and was associated with an AUC0-168h of 381,040 µg*h/ml at 50

mg/kg/week IV in the chronic toxicity study. This exposure provides an adequate margin to the exposure at the proposed clinical dose of sarilumab (200 mg; Q2W).

No carcinogenicity studies were conducted which is in line with ICH S6 (R1). However, an assessment of the carcinogenic potential of sarilumab was made based on literature data on the role of the IL-6 pathway in tumour development and on non-clinical data for sarilumab.The applied weight of evidence approach is in accordance with ICH S6(R1). Based on the evidence as discussed by the applicant, it can be agreed that chronic treatment with sarilumab is not associated with an increased risk of cancer. In contrast, blockade of IL-6Rα signalling may contribute to inhibition of tumour growth.

The effect of IL-6Rα blockade on reproductive and developmental toxicity was evaluated in a fertility study in mice using the surrogate mAb and in an ePPND study with sarilumab in cynomolgus. These studies have not revealed adverse effects on fertility and pregnancy outcome. In surviving neonates, no developmental defects were noted.

To support the use of sarilumab in paediatric patients, toxicity was evaluated with the surrogate mAb in juvenile mice, although such study was not considered necessary in the agreed PIP. The study, with a focus on the effect of IL-6Rα blockade on the immune system, did not raise concerns for use of sarilumab in young children.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data submitted is considered adequate.

2.4. Clinical aspects

2.4.1. Introduction

Kevzara in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate

The sarilumab clinical program was designed to demonstrate its efficacy in combination with conventional DMARDs or as monotherapy for the treatment of moderately to severely active RA in adult patients who responded inadequately to or were intolerant of DMARDs (DMARD-IR) or TNF-α antagonists (hereafter referred to as [TNFIR]).

The main studies include two placebo-controlled studies and one active-comparator controlled study.
Long-term efficacy and safety is investigated in one uncontrolled long-term extension study.

GCP

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

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

- Tabular overview of clinical studies: Core Phase 2 and Phase 3 clinical studies contributing to the evaluation of efficacy and safety of sarilumab in patients with RA

Study[a]	Concomitant therapy	Study Population	Study duration	Treatment (Number of patients)	Rescue[b]	Eligible for LTS11210
EFC11072[c] Efficacy and safety Part A (Phase 2)	MTX	RA, MTX-IR	12 weeks	Placebo (52) Sarilumab: 100 mg qw (50); 150 mg qw (50); 100 mg q2w (51); 150 mg q2w (51); 200 mg q2w (52)	No	Yes
EFC11072[c] Efficacy and safety Part B (Phase 3)	MTX	RA, MTX-IR	52 weeks	Cohort 1[d]: Placebo (30) Sarilumab: 100 mg qw (29); 150 mg qw (27); 100 mg q2w (28); 150 mg q2w (30); 200 mg q2w (28) / Cohort 2[d]: Placebo (398) Sarilumab: 150 mg q2w (400); 200 mg q2w (399)	From Week 16	Yes
EFC10832 (Phase 3) Efficacy and safety	DMARD	RA, TNF-IR or TNF intolerant	24 weeks	Placebo (181) Sarilumab: 150 mg q2w (181); 200 mg q2w (184)	From Week 12	Yes
EFC14092 (Phase 3) Efficacy and safety	None (monotherapy)	RA, MTX-IR, MTX inappropriate or MTX intolerant	Main: 24 weeks Extension: 24 weeks	Main study: Sarilumab: 200 mg q2w (184) Adalimumab 40 mg q2w (185)[e] Extension: Sarilumab: 200 mg q2w (154)[f]	No	No
LTS11210 (Phase 3)enrollment[f,g,h] Efficacy and safety	DMARD (EFC11072, EFC10832, SFY13370 or ACT11575) None (EFC13752)	See initial study criteria	~5 years	Sarilumab 200 mg q2w after Phase 3 dose selection (1912) (316 patients started treatment at 150 mg qw prior to Phase 3 dose selection) Sarilumab monotherapy (111)	NA	NA
SFY13370 (Phase 3) Safety	DMARD	RA, TNF-IR or TNF intolerant	24 weeks	Sarilumab: 150 mg q2w (49); 200 mg q2w (51) Tocilizumab: 4/8 mg/kg q4w (102)[i]	No	Yes
EFC13752 (Phase 3) Safety	None (monotherapy)	RA, non-biologic DMARD-IR or DMARD intolerant	24 weeks	OL sarilumab: 150 mg q2w (65); 200 mg q2w (67)	No	Yes
MSC12665 (Phase 3)	DMARD	RA	Main: 12 weeks Extension: 52 weeks	Main study: OL sarilumab PFS: 150 mg q2w (53); 200 mg q2w (56) OL sarilumab AI: 150 mg q2w (56); 200 mg q2w (52) Extension: OL sarilumab PFS: 150 mg q2w (192)[f]	No	No

AI=autoinjector; DMARD-IR: inadequate response to one or more DMARDs; MTX=methotrexate; MTX IR=inadequate response to MTX; TNF-IR=inadequate response to TNF antagonist; OL=open-label; PFS=pre-filled syringe; TNF =tumor necrosis factor ;ULN=upper limit of normal

a Two studies were terminated by the Applicant due to delays in recruitment and their impact on development timelines (ACT11575 [Phase 2] and EFC11574 [Phase 3]). The studies are not summarized in the table.

b Patients could be rescued with open-label sarilumab: 150 mg qw prior to Phase 3 dose selection and 200 mg q2w after Phase 3 dose selection.

c EFC11072 consisted of 2 parts, A and B. Part A was initiated prior to Part B.

d EFC11072 Part B Cohort 1 patients were randomized prior to dose selection to the same doses as in Part A. After selection of the Phase 3 doses based on results from all 6 dose groups from Part A, patients randomized to selected doses or to placebo continued in the 52-week trial and patients randomized to the 3 other treatment arms (ie, "non-selected" doses) were discontinued from the study and eligible to enroll into LTS11210; EFC11072 Part B Cohort 2 patients were randomized after dose selection for Phase 3.

e Adalimumab could be increased to weekly dosing after Week 16 for patients with an inadequate response.

f Study ongoing

g Enrollment as of 25 January 2016

h Dose reduction to 150 mg q2w permitted for safety reasons as defined in protocol. Reasons for dose reduction were the following laboratory abnormalities: ANC ≥0.5 to 1.0 Giga/L in the absence of infection, platelet count ≥50 to 100 Giga/L in the absence of bleeding, or ALT ≥3 to 5 × ULN.

i The starting dose was 4 mg/kg q4w and could be increased to 8 mg/kg q4w at the investigator's discretion at any time

2.4.2. Pharmacokinetics

Assays

Two PK assay formats have been developed in order to distinguish between functional and bound sarilumab forms. Both the revised and the original assay were used in several studies including large Phase 3 studies.

Immunogenicity assessment was supported by ELISA assays, *i.e.*, ADA determination and NAb detection methods. ADA determination method validation (REGN88-AV-10017-VA-O1V2) was based on an ECL bridging assay accounting for screening (5% false positive error rate), confirmation (0.1% false positive error rate) and titer steps. NAb detection method validation (REGN88-AV-12055-VA-01V3) was a competitive ligand binding assay, supporting NAb activity assessment on samples from phase 3 studies that tested positive in ADA assay.

Absorption

Sarilumab was absorbed well in patients with RA after a single SC administration, with the maximum serum concentration of functional sarilumab achieved at a median tmax of 2 to 4 days, with no apparent dose effect (Table 7).

Table 7: Pharmacokinetic parameters of serum functional sarilumab after a single (or first) subcutaneous dose of sarilumab to healthy subjects or patients with rheumatoid arthritis

Study identifier (Population)	Dose	N	C_{max} (mg/L)[a]	AUC_{last} (mg•day/L)[a]	AUC (mg•day/L)[a]	t_{max}[b] (days)	$t_{1/2z}$ (days)[a]
TDU11373 (Healthy subjects)	100 mg	14	7.77 (3.65)	45.0 (22.7)	55.0 (25.0)	2.50 (1.00 - 6.00)	2.23 (1.07)
TDU10809/6R88-RA-0801 (RA patients)	50 mg	4	1.16 (1.82)	2.36 (3.94)	NR	2.04(1.99 - 2.10)	NR
	100 mg	4	4.89 (4.53)	25.5 (36.2)	NR	3.05 (2.01 - 3.11)	NR
	200 mg	6	10.9 (2.38)	90.0 (15.3)	NR	3.01 (2.96 - 3.05)	NR
ACT10804/6R88-RA-0803 (RA patients)	50 mg	8	0.516 (0.745)	0 (0)	NR	2.91 (1.83 - 2.93)	NR
	100 mg	8	3.96 (2.70)	18.4 (10.5)	NR	4.41 (1.90 - 4.88)	NR
	200 mg	8	12.9 (4.81)	93.2 (48.9)	NR	3.85 (1.98 - 5.00)	NR
TDU13402 (Japanese RA patients)	50 mg	6	1.36 (0.411)	4.69 (2.43)	NR	3.00 (2.00 - 3.00)	NR
	100 mg	6	4.54 (2.97)	33.0 (30.4)	70.1 (NC)[d]	3.00 (3.00 - 7.00)	1.62 (NC)
	200 mg	6	27.7 (12.6)	339 (173)	409 (126)[e]	3.00 (2.00 - 7.00)	3.49 (1.35)
PKM12058 (RA patients)	200 mg	16	17.9 (9.98)	178 (146)	202 (152)[f]	4.00 (2.01 – 8.00)	3.59 (1.66)
6R88-RA-1309 (RA patients)	150 mg	26	13.9 (9.28)	106 (91.9)	108 (92.2)	3.02 (2.00 - 6.16)	1.70 (0.457)
	200 mg	26	21.6 (11.7)	169 (105)	173 (105)	3.99 (1.99 - 6.17)	1.96 (1.10)
MSC12665 (RA patients)	150 mg	51	16.7 (13.0)	152 (76.7)[c]	NR	2.88 (0.90 - 6.88)	NR
	200 mg	53	23.7 (12.7)	227 (94.9)[c]	NR	3.67 (1.71 - 10.9)	NR

a Mean (standard deviation) for observed values from noncompartmental analysis
b Median (minimum - maximum) for observed values from noncompartmental analysis
c $AUC_{0\text{-}14\ days}$ instead of AUC_{last}
d N = 1
e N = 5
f N = 15

AUC: area under the serum concentration versus time curve extrapolated to infinity; $AUC_{0\text{-}14\ days}$: area under the serum concentration versus time curve from 0 to 14 days; AUC_{last}: area under the serum concentration versus time curve from 0 to the time of last quantifiable concentration; C_{max}: maximum serum concentration; DMARD: disease modifying antirheumatic drug; IR: inadequate responder(s); N: total number of subjects or patients; NC: not calculated; NR: not reported; RA: rheumatoid arthritis; t_{max}: time to reach the maximum serum concentration; $t_{1/2z}$: mean terminal half life

- Bioavailability

Subcutaneous bioavailability (F) of sarilumab was estimated to 80% by the PopPK analysis using IV PK data from n=7 patients.

- Bioequivalence

Comparability Studies

Three formulations for sarilumab drug product were used for clinical studies during the clinical development program. The C2P1F3 drug product formulation that was used in the pivotal Phase 3 studies is the planned-to-be-marketed drug product. No formal bioequivalence studies between different drug formulations and application forms were conducted. However, in three clinical studies PK profiles were compared after administration of different drug formulations and application forms (prefilled syringe vs autoinjector). After intensive revision, the functional sarilumab exposure for the planned-to-be marketed C2P1F3 drug product, used in the Phase 3 studies, can be considered comparable to the exposure observed for the C1P2F2 drug product used in the Phase 2 dose-ranging study although bioequivalence was not proven statistically.

A higher exposure (up to >20%) after using the autoinjector (AI) compared to the prefilled syringe (PFS) is indicated by results from a Phase 3 usability study (MSC12665). After careful evaluation of the supplementary information that was requested, it was concluded that the AI-linked higher bioavailability may not impair the safety profile of sarilumab.

Distribution

Sarilumab volume of distribution at steady state after IV administration (Vss) was 0.0300 and 0.0359 L/kg (approximately 2.1 to 2.5 L in a 70 kg individual) at 0.6 and 2.0 mg/kg, respectively, based on observed data in 6 patients with RA after a single administration. Population PK analysis results (Study POH0490) were consistent with an estimated apparent central volume of distribution (Vc/F) of 2.09 L and an apparent peripheral volume of distribution (Vp/F) of 6.19 L, resulting in a total volume of distribution (the sum of Vc/F and Vp/F) of 8.28 L. This low value suggests that the distribution of sarilumab is primarily limited to the circulatory system.

Elimination

Because sarilumab is an antibody, its metabolism is expected to be limited to proteolytic catabolism to small peptides and individual amino acids; hence no metabolism or excretion studies were conducted.

Fast and slow elimination pathways result in an initial half-life of 8 to 10 days and a terminal concentration dependent half-life of 2 to 4 days. After the last steady state doses of 150 and 200 mg q2w sarilumab, the median times to non-detectable concentration are 30 and 49 days, respectively.

The metabolic pathway of sarilumab has not been characterized. As a monoclonal antibody, sarilumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG, and not eliminated via renal or hepatic pathways.

Sarilumab is a protein which is degraded to small peptides and amino acids, and is not expected to be metabolized via CYP isozymes. Therapeutic proteins are metabolized by the same catabolic pathways as endogenous proteins, and are typically broken down into small peptides and amino acids via proteolysis. As sarilumab is an antibody which is thus expected to be metabolized by proteolytic catabolism, no specific in vitro or in vivo metabolism or excretion studies were conducted for sarilumab.

Dose proportionality and time dependencies

Sarilumab PK data and non-compartmental analysis (NCA) of functional serum sarilumab after a single subcutaneous dose (50 mg – 200 mg) of sarilumab to healthy subjects or patients with rheumatoid arthritis indicate a nonlinear PK with target-mediated drug disposition.

Single and multiple-dose administration resulted in an increase in exposure in a greater than dose proportional manner. For single dose SC application, observed mean AUClast increased by 38.1- to 72.3-fold over a 4-fold increase in dose over the range of 50 to 200 mg and by about 1.6 -fold over the therapeutic dose range of 150 to 200 mg. In case of multiple-dose administration, exposure over the dosing interval measured by area under the serum concentration versus time curve at steady state (AUC0-14 days) increased 2-fold for an increase in SC sarilumab dose from 150 to 200 mg q2w (corresponding to 1.33-fold increase in dose).

Steady state was reached in 12 to 16 weeks following repeated q2w SC administration, with a 2- to 3-fold accumulation compared to single dose exposure for AUC0-14 days and 2.87 – 3.49 for Ctrough values in patients receiving 150 mg or 200 mg q2w with DMARDs therapy or by monotherapy. This is in the range of what is theoretically expected from a monoclonal antibody administered q2w with a common t1/2 of 21 days (theoretical accumulation factor: 2.7).

Special populations

Two population PK analyses were performed to assess the variability of sarilumab PK, and to identify covariates as potential sources of variability in sarilumab exposure.

Sarilumab exhibited moderate to high PK variability in patients with RA. Functional sarilumab steady state exposure (AUC0-14 days) stratified by covariates indicates that there is a huge variability in AUC within each covariate and covariate subgroups.

The main source of PK variability is body weight with a trend for lower exposure in patients with higher body weight which partly resulted from fixed dosing compared to body weight scaled dosing. This is indicated by an estimated body weight exponent on CL0/F of about 0.8 (>0.5).

Body weight, ADA-status, drug product, albumin, gender, creatinine clearance and baseline CRP were statistically significant covariates influencing sarilumab PK.

Sarilumab exposure increased with a decrease in body weight, creatinine clearance, or baseline CRP level. Sarilumab exposure decreased with a decrease in serum albumin concentration. Exposure looked lower in ADA positive patients than in ADA negative patients, in NAb positive patients than in NAb negative patients (based on graphical exploration of the post hoc predicted exposure data), for the C1P2F2 drug product when compared to other drug products (C1P1F1 and C2P1F3), or in male patients when compared to female patients.

The main source of intrinsic PK variability identified in the population PK analysis was body weight (range: 32-183 kg), with decreasing body weight resulting in an increase in sarilumab exposure. Information concerning the efficacy in patients with body weight >100kg is appropriately reflected in section 5.2 of the SmPC.

Other demographic characteristics such as age and race did not have a significant influence on the PK of sarilumab based on population PK analysis. Accordingly, no dose adjustments are recommended for any of these demographics. Only 14% of patients were older than 65 years. In total, age ranged from 18 – 88 years.

Table 8: Functional sarilumab steady state exposure by age category in patients with rheumatoid arthritis in Phase 3 studies (Study POH0490)

Age (year)	150 mg q2w N	150 mg q2w C_{max} (mg/L)	150 mg q2w $AUC_{0\text{-}14\ days}$ (mg•day/L)	150 mg q2w C_{trough} (mg/L)	200 mg q2w N	200 mg q2w C_{max} (mg/L)	200 mg q2w $AUC_{0\text{-}14\ days}$ (mg•day/L)	200 mg q2w C_{trough} (mg/L)
<65	421	20 (7.85) [18.1]	203 (110) [177]	6.56 (7.28) [3.47]	670	36 (14.5) [33.8]	405 (203) [373]	17.3 (14.2) [14.7]
65 to <75	62	22.5 (10.4) [18.8]	243 (140) [194]	9.14 (9.12) [5.71]	98	39.1 (14.4) [35.8]	448 (195) [412]	20 (14) [17.3]
75 to <85	6	25.7 (8.94) [23]	289 (126) [261]	12.2 (8.96) [11.2]	10	43.8 (11.6) [41.8]	518 (164) [477]	24.6 (13) [23]
≥85	1	32.2 (na) [32.2]	301 (na) [301]	5.35 (na) [5.35]	1	37.7 (na) [37.7]	399 (na) [399]	13.2 (na) [13.2]

Descriptive statistics are mean (standard deviation) [median] for post hoc predicted pharmacokinetic parameters for patients on sarilumab + DMARDs in Studies EFC11072 Part B and EFC10832 from population pharmacokinetic analysis.

AUC0 14 days: area under the serum concentration versus time curve at steady state; Cmax: maximum serum concentration; Ctrough: serum concentration observed before drug administration during repeated dose administration; q2w: every 2 weeks

Pharmacokinetic interaction studies

Administration of concomitant MTX, the most commonly prescribed DMARD for patients with RA, did not impact sarilumab clearance irrespective of MTX dose, as assessed by population PK analyses. Graphic exploration of post-hoc predicted exposure data showed no appreciable impact on sarilumab PK by prior use of biologics (for RA treatment) or in patients receiving sarilumab in combination with DMARDs versus monotherapy. Among patients receiving sarilumab + DMARD, there was no appreciable impact on sarilumab PK for patients who were inadequate responders to TNF antagonists, MTX, and/or DMARDs.

Sarilumab is not anticipated to interact directly with or modulate the expression of cytochrome P450 (CYP) enzymes, because it is an antibody. However, CYP enzymes are downregulated by infection and stimuli of inflammation, including cytokines such as IL-6. Hence, IL-6Rα inhibitors may restore CYP activity to that of the non-inflammatory state, leading to restored metabolism of CYP substrates. Elevated IL-6 concentrations may down-regulate CYP activity in patients with chronic inflammatory conditions such as RA. Interleukin-6 reduces mRNA expression of several CYP450 isoenzymes, including CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Indeed, CYP3A4 expression has been shown to be normalised by another anti-IL-6Rα mAb (tocilizumab) at clinically relevant concentrations both in vitro and in vivo. Blockade of IL-6 signaling by IL-6Rα antagonists such as sarilumab might reverse the inhibitory effect of IL-6 and restore CYP activity, leading to restored medicinal products concentrations.

The modulation of IL-6 effect on CYP enzymes by sarilumab may be clinically relevant for CYP substrates with a narrow therapeutic index, where the dose is individually adjusted. In particular, caution should be exercised in patients who start sarilumab treatment while on therapy with CYP3A substrates. Indeed, inflammation-dependent reduction of CYP3A4 activity, which reduces CYP3A4 substrate exposure, may normalize upon sarilumab administration. Detailed information, i.e., percentage of simvastatin exposure decrease, about results obtained from PK single dose interaction study between sarilumab (200mg SC) and simvastatin (40 mg PO), are included in the SmPC in section 5.2. Although specific clinical drug interaction studies to assess the influence of sarilumab on CYP2C9, CYP2C19 and CYP2D6 substrates have not been

conducted, it is expected that sarilumab would have a similar effect as that observed for IL-6 antagonists such as sirukumab and tocilizumab. This information is appropriately reflected in the SmPC in section 4.5.

2.4.3. Pharmacodynamics

Mechanism of action

Interleukin 6 (IL-6) is a pleiotropic cytokine that stimulates proliferation, differentiation, survival and apoptosis of immune cells (both B cells and T cells) and can activate hepatocytes to release acute-phase proteins, including C-reactive protein (CRP), serum amyloid A (SAA), and fibrinogen, biological markers which reflect disease activity in patients with rheumatoid arthritis (RA). Elevated levels of IL-6 are found in the synovial fluid of patients with RA and play an important role in both the pathologic inflammation and joint destruction that are hallmarks of RA.

Sarilumab is a recombinant human immunoglobulin (IgG)1 monoclonal antibody that binds specifically to both soluble and membrane-bound interleukin-6 (IL-6) receptors (sIL-6Rα and mIL-6Rα) and inhibits IL-6-mediated signaling. IL6 receptor is a known target with respect to the indication rheumatoid arthritis. By inhibiting both intra-articular and systemic IL-6 signaling sarilumab has the potential to alleviate many of the signs and symptoms of RA.

Primary and Secondary pharmacology

According to the mode of action, several PD biomarkers were assessed in clinical studies, including IL-6, sIL-6Rα, and several inflammatory markers (acute phase proteins CRP, SAA, and fibrinogen, and an indirect index of these proteins, the erythrocyte sedimentation rate [ESR]).

Immunogenicity

Persistent ADA response was found to be 4.0% (200 mg q2w group), 5.6% (150 mg q2w group), and 2.0% (placebo group). Neutralizing antibody responses were calculated to 1.0% in the 200 mg q2w group, 1.6% in the 150 mg q2w 0.2% in the placebo group. AUC0-14 day was lower in ADA positive patients compared to ADA negative patients by 20% and 24% at 150 mg q2w and 200 mg q2w, respectively. No correlation was observed between ADA being developed and either loss of efficacy or adverse events.

Secondary pharmacology

No data on secondary pharmacology were provided. No meaningful effects are expected from the monoclonal antibody sarilumab.

PK/PD relationships

Semi-mechanistic population PK/PD models were submitted in order to describe the relationship between sarilumab concentrations (derive from PopPK in study POH0428) and DAS28-CRP (Disease Activity Score 28-CRP) and ANC (absolute neutrophil count). These two PK/PD models are POH0446 and POH0429.

The empirical exposure-response evaluation for efficacy and safety was submitted through the population PK POH0455 that was an exposure/response analysis report in which the endpoints considered were both efficacy and safety.

Globally, a trend for lower efficacy response rates for patients with higher body weight treated with 150 mg q2w could be detected. Body weight was a covariate on the PD parameters in the semi-mechanistic population PK/PD modelling of DAS28-CRP (efficacy) and the ANC (safety). No statistically significant interaction of ADA status (positive or negative) was identified by trough serum concentration on either the efficacy or safety endpoints. The power of the interaction test was low due to the relatively low percentage of sarilumab treated patients with positive ADA status.

The efficacy endpoints considered in the POH0455 were American College of Rheumatology improvement scores (ACR20, ACR50, ACR70), the Disease Activity Score 28-CRP (DAS28-CRP), the Health Assessment Questionnaire Disability Index for Rheumatoid Arthritis (HAQ-DI), the van der Heijde modified total Sharp score (mTSS), and the clinical disease activity index (CDAI). Overall, for all key efficacy endpoints, except for the HAQ-DI, exposure-response relationships indicated that higher exposure resulted in better efficacy and suggested a consistent trend toward a greater therapeutic benefit of 200 mg q2w dose as compared to 150 mg q2w; for the HAQ-DI, there was a smaller difference in effect with the increase in exposure from 150 mg q2w to 200 mg q2w. An evaluation of the impact of exposure on ACR response rates stratified by body weight was requested, including the estimation of AUC50 and AUC90 values as well as Ctrough50 and Ctrough 90 values, respectively, which are needed to achieve 50% (90%) of the maximum effect for both envisaged dosing regimens.

Empirical exposure-safety analyses (Study POH0455) investigated the safety endpoints absolute neutrophil count (ANC), alanine transaminase (ALT) and low density lipoprotein (LDL) levels. For percent change in LDL concentration and change in ALT (x ULN) and ALT >3 x ULN, there was only a marginally increased risk at 200 mg q2w when compared to150 mg q2w. Both the empirical and semi-mechanistic PK/PD models showed that the decrease in the ANC reached a plateau over the observed sarilumab serum concentration range in the Phase 3 studies. There was an increase in risk of ANC <1.0 Giga/L in patients at the median concentration for 200 mg q2w as compared to 150 mg q2w, especially for patients at low body weight.

However, the long-term benefit of inhibition of irreversible joint damage demonstrated by sarilumab 200 mg q2w outweighs the short-term risk for decreased neutrophil counts, which is transient and probably manageable with dose reduction to 150 mg q2w.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Assays

Choice of screening assay format, acid dissociation step and addition of anti-sIL-6Ra-Ab (capture of dissociated ligand:drug) and exogenous IgG (capture of RF) are considered reasonable.

Concerning the immunogenicity assays, the Applicant was asked to consider a more appropriate error rate associated to the confirmatory cut points, *i.e.*, 1% instead of 0.1% error rate, and to present immunogenicity data according to the calculated 1% false positive rate for the confirmatory assays. The data requested were provided, showing a slight increase in ADA rate as compared to the original submission (0.1% error rate) within the all analysis sets (Study EFC10832, EFC13752 and EFC14092, Pool 1, 2 and 3). The impact on the incidence of persistent ADA, which are considered the clinically relevant ones, was limited. Importantly, no significant effect on sarilumab efficacy and safety profile was observed when a different cut point (1% error rate) was used (see safety section). Consequently, confirmatory cut point and immunogenicity data analysis according to either 0.1% or 1% error rate can be considered overall comparable.

The Applicant was asked to re-discuss the adequateness of the NAb assay. Despite the overall additional data submitted and the Applicant's justifications, the NAb assay remains unsuitable in terms of DTL for its intended use since the drug levels exceed the documented NAb assay DTL. Considering that immunogenicity characterization is a regulatory requirement for biological drug MA, an appropriate NAb test shall be developed as a post-authorization measure (recommendation, REC).

Pharmacokinetics and population PK

Functional sarilumab serum concentrations in healthy subjects were higher than in patients with RA at the same dose of 100 mg by approximately 1.8-fold. This is likely due to an elevated abundance of the target in patients with RA, as evidenced by about a 1000-fold higher sIL-6Rα serum concentration in patients with RA when compared to healthy subjects.

Subcutaneous bioavailability (F) of sarilumab was estimated by population PK analysis using IV PK data from n=7 patients. The Applicant confirmed that the limited number of subjects with IV data results in model instability and the failure to estimate the parameter F. Also, variability of F between patients may contribute to interindividual variability of PK profiles. Although it is not ideal to describe sarilumab PK following SC administration by the apparent parameters CL/F and V/F, the lack of IV data is accepted.

A higher bioavailability after using the autoinjector (AI) compared to the prefilled syringe (PFS) is indicated by results from a Phase 3 usability study (MSC12665). The Applicant presented further information to support the AI vs PFS comparability and it is further noted that study MSC12665 was not powered to demonstrate PK bioequivalence. A sensitivity analysis after outlier removal from PK data, showed that the overall difference between AI and PFS was only 6-7% for AUC0-τ at the 200 mg q2w dose (ratio: 1.07, IC: 0.87,1.31). ANC change from baseline was slightly worse upon sarilumab AI 200mg q2w compared to PFS 200 mg q2w administration (mean percent change from baseline was -35% and -31%, respectively). However, these differences could be most likely chance findings caused by limited sample size (n=45 for AI 200mg q2w vs n=53 for PFS 200mg q2w) and/or variability in exposure parameters. Additionally, the PK/PD simulations of ANC time-course profiles that were conducted taking into account up to 20% higher PK exposure for AI 200 mg q2w vs PFS 200 mg q2w, showed comparability between the two presentations. Of note, the incidence of patients with grade 3 or 4 neutropenia in MSC12665 was similar between AI and PFS at 200 mg q2w (7.7% - 7.1%). Regarding elevations of alanine aminotransferase (ALT), a greater change from baseline in ALT was reported in sarilumab 200 mg q2w/AI group than in the other groups. Moreover, in MSC12665 study, ALT elevation >3 x ULN was reported with a higher rate in the AI 200 mg group [4 patients (7.7%)] compared to the PFS 200 mg group [1 patient (1.1%)]. According to the Applicant, the observed differences could be driven by variability in mean values and small sample sizes. Importantly, the higher incidence of patients with an ALT elevation >3 x ULN in the AI 200 mg group compared to the PFS 200 mg group (7.7% vs 1.1%, respectively) lies within the variability range of the overall safety data in clinical studies. A slightly higher percentage of subjects experienced an increase of ALT levels >3 x ULN in the AI 200 mg q2w compared to the PFS 200 mg q2w, although the small sample size and associated variability cannot allow to draw firm conclusions. However, adequate management in case of liver enzyme abnormalities laboratory values is reported in the SmPC. In conclusion, the data submitted provides adequate support to the AI vs PFS comparability.

As exposure simulations have been simulated based on the prior population PK model, the Applicant was requested to conduct posthoc simulations based on the population PK model that has been built on the most comprehensive PK data base and compare results with the actual PK/PD analyses. The simulations indicate that no major deviations are expected.

There is an impact of covariates on PK parameter, especially regarding the impact of body weight on PK parameters for the 5th and 95th percentiles. A descriptive statistic analysis of body weight distribution within each level of renal impairment category, to better understand difference in sarilumab exposure among renal impairment groups has been provided. This analysis shows that patients with mild and moderate renal impairment had lower median body weight than patients with normal renal function. Considering the known effect of weight on exposure, it is reasonable that the effect of renal impairment on exposure is an indirect effect of weight.

Pharmacodynamics

PK/PD analyses of biomarkers show a dose-dependent effect, with sarilumab 200 mg q2w being superior in evoking PD responses as compared to sarilumab 150 mg q2w, which in turn shows effects greater than placebo. Thus, in general, dose recommendations are endorsed. However, the level of effective sarilumab concentrations may not be reached in about one quarter of patients with very low sarilumab exposure (e.g. Ctrough levels) following both dosing regimens.

Following report POH0455, it is of note that some covariates were not included in the final models of some efficacy/safety endpoints considered. In the description of model development, it is stated that a main effect and an interaction effect were considered for inclusion in the PK/PD model if they were highly significant (main effect p-value ~0.05 or less and interaction effect p value ~ 0.01 or less). However, in the tables reported in the appendixes and related to the estimation and p-value for testing the baseline covariate effect, it is of note that some covariates with a significant p-value were not included in the final model. An example is the case of RA duration that has been not included as a significant main effect for ACR20 in the final PK/PD model using data from EFC10832 (p-value 0.0354; see Appendix A1.6). Other similar cases were observed for the ACR70, CDAI, DAS28-CRP, HAQ-DI and ANC. The Applicant clarified this discrepancy sufficiently. There is a strong influence of body weight on exposure. In addition, there is a clear exposure-response relationship for efficacy endpoints ACR response rate and DAS28-CRP. Patients with higher bodyweight are expected to gain a less beneficial therapeutic effect. A statement regarding possibly impaired efficacy of sarilumab in overweight patients has been included in the SmPC.

In PK/PD analysis on POH0429, the Applicant was asked to justify the cut-off of maximal 60% maximal decrease in ANC. According to the data provided in this study, it seems that the ANC decrease with 150 mg q2w and 200 mg q2w dosing is essentially similar. As such, a recommendation to reduce sarilumab dose from 200 mg q2w to 150 mg q2w for management of laboratory abnormalities including decreased ANC has been included in section 5.2 of the SmPC.

2.4.5. Conclusions on clinical pharmacology

Overall, bioanalytical methods were adequately described and validated. The choice and performance of ADA assays are in general endorsed. While pending issues on the adequateness of the confirmatory cut point associated-error rates have been discussed and considered resolved, the NAb assay remains unsuitable for its intended use since the drug levels exceed the documented NAb assay DTL. The CHMP recommended that an appropriate NAb test is developed post-authorization (recommendation, REC).

Sarilumab exhibited moderate to high PK variability in patients with RA. The main source of PK variability is body weight with a trend for lower exposure in patients with higher body weight which partly resulted from fixed dosing compared to body weight scaled dosing. A statement regarding possibly impaired efficacy of sarilumab in overweight patients was included in the SmPC.

Body weight, ADA-status, drug product, albumin, gender, creatinine clearance and baseline CRP were statistically significant covariates influencing sarilumab PK.

2.5. Clinical efficacy

2.5.1. Dose response study

A randomized, double-blind, placebo-controlled, multicentre, two-part, dose ranging and confirmatory study with an operationally seamless design, evaluating efficacy and safety of SAR153191 (sarilumab) on top of methotrexate (MTX) in patients with active rheumatoid arthritis who are inadequate responders to MTX therapy (EFC11072 - Part A)

Methods

Study Participants

Patients with moderately to severely active RA who had an inadequate response to MTX were included in the study.

Inclusion criteria:

1. Diagnosis of Rheumatoid Arthritis (RA) as defined by the 1987 revised American College of Rheumatology (ACR) criteria with disease duration of no less than 3 months and ACRclass I-III

2. Patients must be on a stable dose of MTX (10 to 25 mg/week) for a minimum of 6 weeks prior to the Screening Visit and intend to continue for the duration of the study.

3. Patients must have been treated with, and tolerated, a minimum of 12 weeks treatment with methotrexate (MTX) prior to the inclusion visit.

4. Patient with moderate to severe active disease defined as:

- At least 8 out of 68 joints assessed as painful or tender on motion at both screening and baseline visits, and,

- At least 6 out of 66 joints assessed as swollen at both screening and baseline visits, and,

- hs C-Reactive Protein >10mg/L at screening visit

Treatments

Patients were randomly allocated to placebo or sarilumab 100 mg, 150 mg, 200 mg q2w, or 100 mg or 150 mg once weekly (qw).

Objectives

The primary objective in Part A was to demonstrate that sarilumab on top of MTX is effective on reduction of signs and symptoms of rheumatoid arthritis (RA) at 12 weeks (ACR20 at week 12) and to define the best dose/dosage regimen for further development.

The main secondary objectives were to:

• assess the safety of sarilumab on top of MTX;

• document the pharmacokinetic (PK) profile of sarilumab on top of MTX in patients with active RA who were inadequate responders to MTX therapy.

Outcomes / endpoints

The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12 and was assessed in the ITT patient population consisting of all patients who had been randomized.

In the primary approach to analysis of ACR20, patients who discontinued treatment for lack of efficacy were considered non-responders; response status for patients who were rescued or discontinued study due to other reasons were determined using their last observations prior to the rescue or discontinuation. Sensitivity analyses were performed for ACR20 using other missing data imputation approaches. Multiplicity for comparing 5 doses of sarilumab with placebo was controlled by the Hommel procedure. However, Phase 3 dose selection was based on the totality of the data, not merely on the analysis of ACR20 response rates.

Secondary endpoints:

- ACR50, ACR70 at Week 12
- Change from baseline in each of the seven ACR components at Week 12
- Change from baseline in DAS28 at Week 12
- DAS28 remission at Week 12
- EULAR response (nonresponders versus responders) at Week 12
- ACRn at Week 12

Statistical methods

Sample size determination: Anticipating response rates of 40% for placebo and 75% in at least 1 active sarilumab group, with 50 patients per group, the study had approximately 80% power to detect a difference of 35% between any dose of sarilumab and placebo using a 2-sided test with alpha = 0.01 (0.01 chosen to adjust for multiplicity)

Efficacy analysis: Efficacy analyses were based on the intent-to-treat (ITT) patient population consisting of all patients who were randomized. ACR20 response at week 12 was the primary efficacy parameter. The primary hypothesis was whether there was at least one dose in the dose range of sarilumab tested that was different from placebo in terms of the primary efficacy endpoint.

ACR20 at week 12 was analyzed using the two-sided Cochran-Mantel-Haenszel test stratified by prior biologic use and geographic region. Pairwise comparisons of the response rates between each dose of sarilumab and placebo were performed. Treatment effects were described by the odds ratio including the corresponding 95%. To account for multiplicity resulting from testing multiple doses of sarilumab against placebo the Hommel procedure was applied.

Categorical secondary efficacy variables were analyzed by the same method as ACR20 at week 12. For the continuous efficacy variables e.g. individual components of the ACR20, changes from baseline were analyzed using an ANCOVA model which included terms for baseline, treatment, region, and prior biologic use. The 95% confidence intervals for comparisons of each dose of sarilumab against placebo were derived from this model. ACRn was analyzed using an ANOVA model that included terms for treatment, region, and prior biologic use.

Safety data were analyzed descriptively on the basis of the safety population, i.e. all patients receiving at least one dose of study treatment.

Results

Participant flow

Table 9: Patients disposition - randomized population_Part A

		SAR153191					
	Placebo (N=52)	100mg q2w (N=51)	150mg q2w (N=51)	100mg qw (N=50)	200mg q2w (N=52)	150mg qw (N=50)	All (N=306)
Randomized and not treated	0	0	0	0	1 (1.9%)	0	1 (0.3%)
Randomized and treated	52 (100%)	51 (100%)	51 (100%)	50 (100%)	51 (98.1%)	50 (100%)	305 (99.7%)
Did not complete the study treatment period	3 (5.8%)	6 (11.8%)	3 (5.9%)	13 (26.0%)	6 (11.5%)	4 (8.0%)	35 (11.4%)
Subject's request for treatment discontinuation	1 (1.9%)	3 (5.9%)	2 (3.9%)	4 (8.0%)	2 (3.8%)	1 (2.0%)	13 (4.2%)
Reason for treatment discontinuation							
Adverse event	1 (1.9%)	3 (5.9%)	2 (3.9%)	13 (26.0%)	4 (7.7%)	1 (2.0%)	24 (7.8%)
Lack of efficacy	2 (3.8%)	1 (2.0%)	1 (2.0%)	0	1 (1.9%)	2 (4.0%)	7 (2.3%)
Poor compliance to protocol	0	0	0	0	0	0	0
Other reasons	0	2 (3.9%)	0	0	1 (1.9%)	1 (2.0%)	4 (1.3%)
Status at last study contact							
Alive	52 (100%)	50 (98.0%)	51 (100%)	50 (100%)	52 (100%)	50 (100%)	305 (99.7%)
Dead	0	1 (2.0%)	0	0	0	0	1 (0.3%)
Rolled over to LTS study							
Yes	46 (88.5%)	42 (82.4%)	39 (76.5%)	36 (72.0%)	39 (75.0%)	41 (82.0%)	243 (79.4%)
No	6 (11.5%)	9 (17.6%)	12 (23.5%)	14 (28.0%)	13 (25.0%)	9 (18.0%)	63 (20.6%)

Note: Percentages are calculated using the number of patients randomized as denominator

A total of 243 (79.4%) patients completing the EFC11072 Part A study entered the long-term safety study, LTS11210 (a multi-center, uncontrolled extension study evaluating efficacy and safety of sarilumab on top of DMARDs in patients with active RA. The percentages of patients who entered the LTS11210 study were comparable across all 6 treatment groups.

Recruitment

A total of 306 patients were randomized to receive placebo (N = 52) or sarilumab 100 mg q2w (N = 51), 150 mg q2w (N = 51), 100 mg qw (N = 50), 200 mg q2w (N = 52), or 150 mg qw (N = 50). One patient was randomized to the sarilumab 200 mg q2w treatment group but did not receive treatment.

305 patients were treated.

Evaluated: Efficacy 306, Safety 305, Pharmacokinetics 305

Date first patient enrolled: 22/Mar/2010

Date last patient completed: 31/May/2011

Baseline data

Baseline demographic and disease characteristics were well balanced among the treatment groups.

Table 10: Demographics and patient characteristics at baseline - randomized population, Part A of EFC11072

		SAR153191					
	Placebo (N=52)	100mg q2w (N=51)	150mg q2w (N=51)	100mg qw (N=50)	200mg q2w (N=52)	150mg qw (N=50)	All (N=306)
Age (years)							
Number	52	51	51	50	52	50	306
Mean (SD)	55.2 (12.5)	53.5 (11.8)	51.2 (12.9)	53.9 (12.3)	48.7 (12.4)	50.9 (11.1)	52.2 (12.3)
Median	58.5	57.0	53.0	56.0	50.5	51.0	54.0
Min : Max	23 : 74	19 : 68	23 : 73	22 : 73	21 : 71	24 : 71	19 : 74
Age Group (years) [n (%)]							
Number	52	51	51	50	52	50	306
<65	40 (76.9%)	42 (82.4%)	43 (84.3%)	38 (76.0%)	47 (90.4%)	45 (90.0%)	255 (83.3%)
≥65-75	12 (23.1%)	9 (17.6%)	8 (15.7%)	12 (24.0%)	5 (9.6%)	5 (10.0%)	51 (16.7%)
≥75	0	0	0	0	0	0	0
Sex [n (%)]							
Number	52	51	51	50	52	50	306
Male	14 (26.9%)	13 (25.5%)	9 (17.6%)	9 (18.0%)	10 (19.2%)	8 (16.0%)	63 (20.6%)
Female	38 (73.1%)	38 (74.5%)	42 (82.4%)	41 (82.0%)	42 (80.8%)	42 (84.0%)	243 (79.4%)
Race [n (%)]							
Number	52	51	51	50	52	50	306
Caucasian/White	49 (94.2%)	49 (96.1%)	49 (96.1%)	47 (94.0%)	47 (90.4%)	46 (92.0%)	287 (93.8%)
Black	0	1 (2.0%)	2 (3.9%)	1 (2.0%)	3 (5.8%)	1 (2.0%)	8 (2.6%)
Asian/Oriental	2 (3.8%)	0	0	1 (2.0%)	2 (3.8%)	1 (2.0%)	6 (2.0%)
Other	1 (1.9%)	1 (2.0%)	0	1 (2.0%)	0	2 (4.0%)	5 (1.6%)

		SAR153191					
	Placebo (N=52)	100mg q2w (N=51)	150mg q2w (N=51)	100mg qw (N=50)	200mg q2w (N=52)	150mg qw (N=50)	All (N=306)
Ethnicity [n (%)]							
Number	52	51	51	50	52	50	306
Hispanic	14 (26.9%)	16 (31.4%)	16 (31.4%)	14 (28.0%)	15 (28.8%)	14 (28.0%)	89 (29.1%)
Non Hispanic	38 (73.1%)	35 (68.6%)	35 (68.6%)	36 (72.0%)	37 (71.2%)	36 (72.0%)	217 (70.9%)
Weight (kg)							
Number	52	51	51	50	51	50	305
Mean (SD)	75.37 (15.49)	75.86 (15.55)	73.90 (15.25)	74.08 (16.28)	77.49 (15.38)	72.37 (13.78)	74.86 (15.27)
Median	77.90	77.60	73.00	71.50	77.00	69.65	74.10
Min : Max	46.0 : 108.4	46.5 : 109.0	46.0 : 108.0	50.5 : 107.0	46.2 : 110.0	48.5 : 109.1	46.0 : 110.0
Height (cm)							
Number	52	51	51	50	50	49	303
Mean (SD)	163.60 (10.24)	163.12 (10.47)	162.91 (7.77)	162.29 (8.79)	163.21 (10.16)	161.58 (9.44)	162.80 (9.47)
Median	162.75	162.80	162.60	163.00	162.50	160.00	162.50
Min : Max	137.0 : 182.0	144.0 : 193.0	142.0 : 178.0	135.0 : 183.0	140.0 : 186.0	139.0 : 187.0	135.0 : 193.0
BMI(kg/m^2)							
Number	52	51	51	50	50	49	303
Mean (SD)	28.32 (6.53)	28.51 (5.41)	27.82 (5.35)	28.20 (6.19)	29.13 (5.52)	27.69 (4.81)	28.28 (5.64)
Median	27.29	27.74	27.36	27.61	29.31	27.26	27.65
Min : Max	18.0 : 51.6	20.1 : 43.8	17.5 : 44.0	18.8 : 46.3	19.1 : 39.6	20.0 : 38.1	17.5 : 51.6

		SAR153191					
	Placebo (N=52)	100mg q2w (N=51)	150mg q2w (N=51)	100mg qw (N=50)	200mg q2w (N=52)	150mg qw (N=50)	All (N=306)
BMI group(kg/m²) [n (%)]							
Number	52	51	51	50	50	49	303
<25	16 (30.8%)	17 (33.3%)	14 (27.5%)	16 (32.0%)	13 (26.0%)	17 (34.7%)	93 (30.7%)
≥25-30	20 (38.5%)	14 (27.5%)	23 (45.1%)	17 (34.0%)	13 (26.0%)	16 (32.7%)	103 (34.0%)
≥30	16 (30.8%)	20 (39.2%)	14 (27.5%)	17 (34.0%)	24 (48.0%)	16 (32.7%)	107 (35.3%)
Region [n(%)]							
Number	52	51	51	50	52	50	306
Western Countries	16 (30.8%)	15 (29.4%)	16 (31.4%)	14 (28.0%)	16 (30.8%)	17 (34.0%)	94 (30.7%)
South America	13 (25.0%)	14 (27.5%)	13 (25.5%)	13 (26.0%)	14 (26.9%)	13 (26.0%)	80 (26.1%)
Rest of the World	23 (44.2%)	22 (43.1%)	22 (43.1%)	23 (46.0%)	22 (42.3%)	20 (40.0%)	132 (43.1%)

Note: Number = Number of patients assessed
% calculated using number of patients assessed as denominator

Table 11: Disease characteristics at baseline

		SAR153191					
	Placebo (N=52)	100mg q2w (N=51)	150mg q2w (N=51)	100mg qw (N=50)	200mg q2w (N=52)	150mg qw (N=50)	All (N=306)
Duration of RA (Years)							
Number	52	51	51	50	52	50	306
Mean (SD)	8.07 (8.62)	9.76 (9.08)	7.74 (7.20)	8.07 (8.68)	5.95 (6.18)	7.30 (8.28)	7.81 (8.08)
Median	4.92	7.36	5.50	5.36	4.10	4.29	5.15
Min : Max	0.4 : 43.3	0.6 : 36.9	0.4 : 28.9	0.3 : 38.1	0.4 : 33.1	0.5 : 38.7	0.3 : 43.3
RA functional class [n(%)]							
Number	52	51	51	50	52	50	306
I	3 (5.8%)	2 (3.9%)	4 (7.8%)	2 (4.0%)	8 (15.4%)	0	19 (6.2%)
II	37 (71.2%)	35 (68.6%)	36 (70.6%)	31 (62.0%)	34 (65.4%)	42 (84.0%)	215 (70.3%)
III	12 (23.1%)	14 (27.5%)	11 (21.6%)	17 (34.0%)	10 (19.2%)	8 (16.0%)	72 (23.5%)
IV	0	0	0	0	0	0	0
Prior biologic use [n(%)]							
Number	52	51	51	50	52	50	306
Yes	12 (23.1%)	13 (25.5%)	12 (23.5%)	12 (24.0%)	14 (26.9%)	12 (24.0%)	75 (24.5%)
No	40 (76.9%)	38 (74.5%)	39 (76.5%)	38 (76.0%)	38 (73.1%)	38 (76.0%)	231 (75.5%)
Rheumatoid factor [n(%)]							
Number	52	51	51	50	51	50	305
Positive	35 (67.3%)	42 (82.4%)	44 (86.3%)	35 (70.0%)	44 (86.3%)	43 (86.0%)	243 (79.7%)
Negative	17 (32.7%)	9 (17.6%)	7 (13.7%)	15 (30.0%)	7 (13.7%)	7 (14.0%)	62 (20.3%)

	Placebo (N=52)	SAR153191 100mg q2w (N=51)	SAR153191 150mg q2w (N=51)	SAR153191 100mg qw (N=50)	SAR153191 200mg q2w (N=52)	SAR153191 150mg qw (N=50)	All (N=306)
Anti CCP antibody [n(%)]							
Number	22	20	22	20	23	21	128
Positive	16 (72.7%)	16 (80.0%)	21 (95.5%)	14 (70.0%)	20 (87.0%)	18 (85.7%)	105 (82.0%)
Negative	6 (27.3%)	4 (20.0%)	1 (4.5%)	6 (30.0%)	3 (13.0%)	3 (14.3%)	23 (18.0%)
Number of prior DMARD							
Number	52	51	51	50	52	50	306
Mean (SD)	0.04 (0.28)	0.06 (0.31)	0.18 (0.52)	0.12 (0.39)	0.08 (0.27)	0.10 (0.36)	0.09 (0.36)
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Min : Max	0.0 : 2.0	0.0 : 2.0	0.0 : 2.0	0.0 : 2.0	0.0 : 1.0	0.0 : 2.0	0.0 : 2.0
Number of prior DMARD [n(%)]							
Number	52	51	51	50	52	50	306
None	51 (98.1%)	49 (96.1%)	45 (88.2%)	45 (90.0%)	48 (92.3%)	46 (92.0%)	284 (92.8%)
1	0	1 (2.0%)	3 (5.9%)	4 (8.0%)	4 (7.7%)	3 (6.0%)	15 (4.9%)
2	1 (1.9%)	1 (2.0%)	3 (5.9%)	1 (2.0%)	0	1 (2.0%)	7 (2.3%)
≥3	0	0	0	0	0	0	0
Smoking history [n(%)]							
Number	52	51	51	50	52	50	306
Yes	14 (26.9%)	14 (27.5%)	16 (31.4%)	18 (36.0%)	17 (32.7%)	17 (34.0%)	96 (31.4%)
No	38 (73.1%)	37 (72.5%)	35 (68.6%)	32 (64.0%)	35 (67.3%)	33 (66.0%)	210 (68.6%)
Alcohol use [n(%)]							
Number	52	50	51	49	52	49	303
Yes	9 (17.3%)	12 (24.0%)	15 (29.4%)	13 (26.5%)	8 (15.4%)	11 (22.4%)	68 (22.4%)
No	43 (82.7%)	38 (76.0%)	36 (70.6%)	36 (73.5%)	44 (84.6%)	38 (77.6%)	235 (77.6%)

	Placebo (N=52)	SAR153191 100mg q2w (N=51)	SAR153191 150mg q2w (N=51)	SAR153191 100mg qw (N=50)	SAR153191 200mg q2w (N=52)	SAR153191 150mg qw (N=50)	All (N=306)
Tender joint count (0-68)							
Number	52	51	51	50	52	50	306
Mean (SD)	27.09 (16.12)	30.31 (14.68)	26.94 (16.79)	29.12 (15.36)	25.52 (14.21)	25.36 (11.97)	27.39 (14.93)
Median	21.50	28.00	21.00	26.50	20.50	23.50	24.00
Min : Max	6.0 : 64.0	10.0 : 66.0	8.0 : 68.0	5.0 : 68.0	8.0 : 62.0	8.0 : 50.0	5.0 : 68.0
Swollen joint count (0-66)							
Number	52	51	51	50	52	50	306
Mean (SD)	17.45 (11.68)	19.53 (9.46)	17.59 (10.60)	16.76 (9.05)	16.63 (8.94)	16.29 (8.33)	17.38 (9.73)
Median	14.00	18.00	14.00	14.50	12.50	13.50	14.00
Min : Max	6.0 : 56.0	6.0 : 39.0	6.0 : 54.0	5.0 : 45.0	6.0 : 41.0	7.0 : 44.0	5.0 : 56.0
Patient global VAS (0-100)							
Number	52	51	51	50	52	50	306
Mean (SD)	66.23 (19.51)	69.18 (20.65)	66.10 (19.41)	68.26 (18.76)	66.92 (19.49)	68.54 (19.14)	67.53 (19.38)
Median	67.50	74.00	70.00	68.50	66.50	70.00	69.50
Min : Max	7.0 : 98.0	24.0 : 100.0	12.0 : 98.0	15.0 : 100.0	10.0 : 100.0	26.0 : 100.0	7.0 : 100.0
Physician global VAS (0-100)							
Number	52	51	51	50	52	50	306
Mean (SD)	62.73 (17.24)	68.57 (17.85)	63.25 (19.86)	61.78 (16.48)	63.31 (14.71)	67.30 (14.80)	64.48 (16.97)
Median	63.00	71.00	64.00	61.50	64.00	66.50	65.00
Min : Max	27.0 : 94.0	25.0 : 95.0	8.0 : 100.0	24.0 : 98.0	20.0 : 92.0	35.0 : 96.0	8.0 : 100.0

	Placebo (N=52)	SAR153191 100mg q2w (N=51)	SAR153191 150mg q2w (N=51)	SAR153191 100mg qw (N=50)	SAR153191 200mg q2w (N=52)	SAR153191 150mg qw (N=50)	All (N=306)
Pain VAS (0-100)							
Number	52	51	51	50	52	50	306
Mean (SD)	64.92 (21.78)	68.45 (21.90)	67.86 (19.83)	69.12 (20.54)	66.56 (19.86)	67.58 (21.33)	67.40 (20.77)
Median	70.00	70.00	71.00	72.00	67.50	72.00	70.00
Min : Max	4.0 : 99.0	18.0 : 100.0	12.0 : 98.0	6.0 : 100.0	10.0 : 100.0	21.0 : 98.0	4.0 : 100.0
CRP (mg/dL)							
Number	52	51	51	50	52	50	306
Mean (SD)	2.97 (2.78)	2.69 (2.62)	2.75 (2.79)	2.57 (3.00)	3.23 (4.15)	2.47 (2.09)	2.78 (2.96)
Median	2.18	1.98	1.76	1.70	1.90	1.71	1.92
Min : Max	0.2 : 14.4	0.1 : 13.9	0.0 : 13.0	0.1 : 17.3	0.0 : 21.8	0.1 : 8.7	0.0 : 21.8
HAQ-DI							
Number	52	51	51	50	52	50	306
Mean (SD)	1.57 (0.57)	1.67 (0.60)	1.54 (0.73)	1.69 (0.58)	1.50 (0.57)	1.57 (0.64)	1.59 (0.62)
Median	1.50	1.50	1.63	1.56	1.50	1.63	1.60
Min : Max	0.5 : 2.9	0.6 : 2.9	0.0 : 3.0	0.4 : 3.0	0.0 : 2.8	0.1 : 2.9	0.0 : 3.0
DAS28							
Number	52	51	51	50	52	50	306
Mean (SD)	6.08 (0.86)	6.28 (0.92)	6.11 (0.91)	6.05 (0.79)	6.06 (0.90)	6.07 (0.65)	6.11 (0.84)
Median	5.99	6.25	6.03	6.10	5.85	6.07	6.02
Min : Max	4.1 : 7.9	4.8 : 8.0	4.4 : 8.1	4.0 : 8.0	4.4 : 8.1	4.8 : 8.0	4.0 : 8.1

	Placebo (N=52)	SAR153191 100mg q2w (N=51)	SAR153191 150mg q2w (N=51)	SAR153191 100mg qw (N=50)	SAR153191 200mg q2w (N=52)	SAR153191 150mg qw (N=50)	All (N=306)
CRP group [n(%)]							
Number	52	51	51	50	52	50	306
≤1.5 mg/dL	18 (34.6%)	20 (39.2%)	22 (43.1%)	20 (40.0%)	18 (34.6%)	20 (40.0%)	118 (38.6%)
> 1.5 mg/dL	34 (65.4%)	31 (60.8%)	29 (56.9%)	30 (60.0%)	34 (65.4%)	30 (60.0%)	188 (61.4%)
FACIT-Fatigue (0-52)							
Number	52	51	51	50	52	50	306
Mean (SD)	23.31 (11.59)	23.73 (9.61)	25.39 (10.03)	24.13 (11.18)	24.71 (10.65)	24.26 (9.91)	24.26 (10.46)
Median	22.38	23.00	26.00	22.00	22.00	24.00	23.00
Min : Max	5.0 : 46.0	6.0 : 50.0	8.0 : 48.0	4.0 : 50.0	5.0 : 45.0	7.0 : 51.0	4.0 : 51.0
Sleep VAS (0-100)							
Number	52	50	51	50	50	50	303
Mean (SD)	56.65 (27.80)	60.64 (28.76)	54.45 (26.58)	48.50 (29.44)	55.64 (25.95)	53.14 (26.18)	54.85 (27.50)
Median	63.50	64.00	54.00	50.00	61.00	59.50	60.00
Min : Max	1.0 : 97.0	0.0 : 100.0	0.0 : 98.0	0.0 : 100.0	0.0 : 100.0	0.0 : 96.0	0.0 : 100.0
WPAI (% work time missed)							
Number	13	11	18	15	16	12	85
Mean (SD)	27.51 (28.49)	19.90 (30.39)	10.06 (18.19)	4.19 (10.72)	10.56 (16.26)	24.53 (21.87)	15.10 (22.18)
Median	21.05	0.00	0.00	0.00	0.00	18.33	0.00
Min : Max	0.0 : 100.0	0.0 : 100.0	0.0 : 53.3	0.0 : 40.0	0.0 : 42.9	0.0 : 62.5	0.0 : 100.0

	Placebo (N=52)	SAR153191 100mg q2w (N=51)	SAR153191 150mg q2w (N=51)	SAR153191 100mg qw (N=50)	SAR153191 200mg q2w (N=52)	SAR153191 150mg qw (N=50)	All (N=306)
WPAI (% impairment while working)							
Number	12	11	20	15	18	12	88
Mean (SD)	57.50 (20.50)	52.73 (19.02)	50.00 (23.62)	50.67 (27.12)	57.78 (19.57)	63.33 (19.69)	54.89 (21.92)
Median	60.00	60.00	50.00	50.00	50.00	70.00	60.00
Min : Max	20.0 : 90.0	20.0 : 80.0	10.0 : 80.0	0.0 : 80.0	30.0 : 100.0	30.0 : 90.0	0.0 : 100.0
WPAI (% activity impairment)							
Number	52	49	51	50	51	49	302
Mean (SD)	66.54 (23.92)	65.31 (22.18)	60.39 (24.90)	66.60 (22.00)	62.94 (21.10)	67.76 (18.96)	64.90 (22.25)
Median	70.00	70.00	60.00	70.00	70.00	70.00	70.00
Min : Max	0.0 : 100.0	20.0 : 100.0	0.0 : 100.0	10.0 : 100.0	10.0 : 100.0	20.0 : 100.0	0.0 : 100.0
WPAI (% overall work impairment)							
Number	12	10	18	15	16	12	83
Mean (SD)	64.72 (22.41)	58.33 (18.01)	51.88 (26.01)	52.46 (27.91)	60.95 (21.07)	71.28 (18.86)	59.17 (23.49)
Median	70.26	56.67	54.17	70.00	65.00	75.50	70.00
Min : Max	20.0 : 95.0	20.0 : 80.0	10.0 : 90.0	0.0 : 80.0	30.0 : 100.0	30.0 : 95.8	0.0 : 100.0

Note: Number = Number of patients assessed
% calculated using number of patients assessed as denominator

Outcomes and estimation

The highest ACR20 response rate occurred in the 150 mg qw treatment group, and was statistically significant compared with placebo (Hommel-adjusted p-value = 0.0203). Hommel-adjusted statistically significant ACR20 responses were not demonstrated in the other sarilumab dose regimen groups although a trend for treatment effect and nominal statistical significance was evident in the 150 mg q2w, 100 mg qw, and 200 mg q2w sarilumab treatment arms. The sarilumab 100 mg q2w dose regimen did not show a statistical difference versus the placebo for the primary endpoint and was assessed as the no effect dose. With respect to the other endpoints, the 150 mg once weekly dose was not more effective than some of the lower doses evaluated. The ACR50 response rates were highest for the 100 mg qw (nominal p = 0.0062) and 200 mg q2w (nominal p = 0.0038) groups. The response rate of patients achieving ACR70 at Week 12 was also highest in the 200 mg q2w group with nominal p = 0.0078 compared with placebo.

Table 12: Percentage of patients with ACR20, 50. And 70 responses at week 12 in EFC11072 Part A (dose ranging)

	Placebo + MTX (N=52)	Sarilumab 100 mg q2w + MTX (N=51)	Sarilumab 150 mg q2w + MTX (N=51)	Sarilumab 100 mg qw + MTX (N=50)	Sarilumab 200 mg q2w + MTX (N=52)	Sarilumab 150 mg qw + MTX (N=50)
ACR20	46.2%	49.0%	66.7%	62.0%	65.4%	72.0%
Nominal p-values[a]		p=0.7119	p=0.0363	p=0.1155	p=0.0426	p=0.0041
Hommel p-values[b]		0.7119	0.1090	0.2311	0.1277	p=0.0203
ACR50	15.4%	21.6%	35.3%	40.0%	40.4%	30.0%
Nominal p-values[a]		p=0.4002	p=0.0163	p=0.0062	p=0.0038	p=0.0734
ACR70	1.9%	5.9%	11.8%	16.0%	17.3%	16.0%
Nominal p-values[a]		p=0.3046	p=0.0574	p=0.0128	p=0.0078	p=0.0144

ACR = American College of Rheumatology; MTX = methotrexate
Source: 5.3.5.1 Study EFC11072 Part A [Table 16], [Tables 21], and [Table 23].
a Nominal p-values versus placebo based on CMH test stratified by prior biologic use and region.
b Hommel adjusted p-values

The 200 mg dose had numerically superior response rates for ACR50 and ACR70, as well as notably larger effects on certain components of the ACR score, specifically Pain and physician global assessment.

Table 13 shows the change from baseline in pain VAS at Week 12 for the ITT population. The change in mean was comparable for all treatment groups.

Table 13: Change from baseline in ACR components at week 12 - pain VAS - ITT population

		SAR153191				
	Placebo (N=52)	100mg q2w (N=51)	150mg q2w (N=51)	100mg qw (N=50)	200mg q2w (N=52)	150mg qw (N=50)
Pain VAS						
Number	52	51	51	49	50	50
Baseline Mean (SD)	64.9 (21.8)	68.5 (21.9)	67.9 (19.8)	69.1 (20.8)	67.9 (19.0)	67.6 (21.3)
Week 12 Mean (SD)	43.4 (23.9)	46.1 (29.6)	37.8 (24.0)	38.1 (25.4)	34.5 (22.1)	41.6 (25.2)
Change Mean (SD)	-21.50 (26.16)	-22.35 (31.58)	-30.06 (26.57)	-31.04 (24.91)	-33.36 (24.71)	-26.02 (28.04)
LS Mean (SE)	-22.28 (3.46)	-21.02 (3.47)	-29.05 (3.49)	-29.19 (3.55)	-32.46 (3.48)	-25.26 (3.51)
LS Mean Diff, 95% CI	-	1.26 (-8.05, 10.57)	-6.77 (-16.07, 2.53)	-6.90 (-16.31, 2.51)	-10.17 (-19.53, -0.82)	-2.98 (-12.33, 6.37)
P-value vs placebo [1]	-	0.7899	0.1531	0.1499	0.0332	0.5312

LOCF used for all seven ACR components.
All assessments are set to missing from the time a patient receives rescue medication or discontinue treatment early. Only pre-rescue/pre-discontinuation scores are carried forward.
Note: Number = Number of patients with assessment at both baseline and Week 12
[1] Type III sum of squares ANCOVA with PROC GLM: model = baseline, treatment, prior biological use, region.

Table 14 shows the change from baseline in physician global VAS at Week 12 for the ITT population. The results were comparable among treatment groups with the exception of the 200 mg q2w group.

Table 14: Change from baseline in ACR components at week 12 - physician global VAS - ITT population

		SAR153191				
	Placebo (N=52)	100mg q2w (N=51)	150mg q2w (N=51)	100mg qw (N=50)	200mg q2w (N=52)	150mg qw (N=50)
Physician global VAS						
Number	52	51	51	49	50	50
Baseline Mean (SD)	62.7 (17.2)	68.6 (17.9)	63.3 (19.9)	61.5 (16.5)	64.6 (13.3)	67.3 (14.8)
Week 12 Mean (SD)	37.5 (19.9)	36.6 (21.7)	30.1 (20.4)	28.5 (17.7)	24.9 (20.9)	30.6 (22.8)
Change Mean (SD)	-25.19 (23.21)	-31.94 (25.79)	-33.12 (24.76)	-32.96 (24.15)	-39.66 (25.08)	-36.70 (23.68)
LS Mean (SE)	-26.79 (2.88)	-28.85 (2.89)	-34.32 (2.90)	-35.20 (2.95)	-39.66 (2.89)	-34.91 (2.92)
LS Mean Diff, 95% CI	-	-2.06 (-9.82, 5.70)	-7.53 (-15.24, 0.19)	-8.41 (-16.21, -0.61)	-12.87 (-20.63, -5.10)	-8.12 (-15.90, -0.33)
P-value vs placebo [1]	-	0.6021	0.0559	0.0347	0.0012	0.0410

LOCF used for all seven ACR components.
All assessments are set to missing from the time a patient receives rescue medication or discontinue treatment early. Only pre-rescue/pre-discontinuation scores are carried forward.
Note: Number = Number of patients with assessment at both baseline and Week 12
[1] Type III sum of squares ANCOVA with PROC GLM: model = baseline, treatment, prior biological use, region.

2.5.2. Main studies

A randomized, double-blind, placebo-controlled, multicenter, two-part, dose ranging and confirmatory study with an operationally seamless design, evaluating efficacy and safety of SAR153191 (sarilumab) on top of methotrexate (MTX) in patients with active rheumatoid arthritis who are inadequate responders to MTX therapy (EFC11072 - Part B)

Methods

Study Participants

Main Inclusion criteria in addition to part A:

- Bone erosion based on documented X-ray prior to first study drug dosing

- Or Cyclic Citrullinated Peptide CCP positive

- Or Rheumatoid Factor (RF) positive.

Main Exclusion Criteria:

1. Presence of any of the following laboratory abnormalities (for the central laboratory conducting the test) at the screening visit:

- Hemoglobin <8.5 g/dL (<85 g/L)

- WBC <3000/µL

- Platelet count <150 000/µL. Prior to Amendment 4, this value was <100,000/µL.

- Neutrophils <2000/µL

- AST or ALT >1.5x ULN

- Bilirubin (total) above the ULN, unless the patient had been diagnosed with Gilbert disease by genetic testing and documented. Prior to Amendment 4, the cutoff for the bilirubin value was >1.5x ULN.

- Creatinine clearance <30 mL/min (<0.5 mL/s) (according to the Cockroft formula).

2. Current treatment with DMARDs/immunosuppressive agents other than MTX:

cyclosporine, mycophenolate, tacrolimus, gold, penicillamine, sulfasalazine or hydroxychloroquine within 4 weeks prior to the screening visit or azathioprine, cyclophosphamide within 12 weeks prior to the screening visit or leflunomide within 12 weeks prior to the screening visit (or 4 weeks after 11 days of standard cholestyramine washout).

Treatments

• Cohort 1: 6 dose regimens including placebo (sarilumab 100 mg weekly [qw], sarilumab 150 mg qw, sarilumab 100 mg every other week [q2w] alternating with placebo, sarilumab 150 mg q2w alternating with placebo, sarilumab 200 mg q2w alternating with placebo, or placebo qw)

• Cohort 2: 3 dose regimens including placebo (sarilumab 150 mg q2w, sarilumab 200 mg q2w, or placebo q2w)

• Open-label rescue: highest dose of sarilumab available at the time of transfer into the rescue arm; 150 mg qw until a site was approved to enroll patients in Cohort 2.

Route of administration: SC in abdomen

Objectives

Primary objectives: To demonstrate that sarilumab added to MTX is effective in:

• Reduction of signs and symptoms of rheumatoid arthritis at 24 weeks

• Inhibition of progression of structural damage at 52 weeks

• Improvement in physical function at 16 weeks

Secondary objectives: To demonstrate that sarilumab added to MTX is effective in induction of a major clinical response at 52 weeks, to assess the safety of sarilumab added to MTX, and to document the pharmacological profile of sarilumab added to MTX in patients with active rheumatoid arthritis who are inadequate responders to MTX therapy.

Exploratory objectives:

The objective was to collect DNA, RNA, and other biomarkers for future use for the purpose of discovery of predictive biomarkers.

Outcomes / endpoints

Co-primary endpoints:

• ACR20 response at Week 24

• Change in physical function as measured by the change from baseline in the Health Assessment Question-Disability (HAQ-DI) at Week 16

• Change in van der Heijde modified total Sharp score at Week 52

Main secondary endpoint: Major clinical response defined as the event of achieving and maintaining an ACR 70 response for at least 24 consecutive weeks during the 52week treatment period.

Other secondary endpoints: ACR 20 at Weeks 36 and 52; ACR50 and ACR70 responses at Weeks 24, 36, and 52; ACR20/50/70 at each visit; change from baseline in each of the 7 ACR components at each visit, ACRn at each visit, standardized AUC for change from baseline in HAQ-DI up to Week 52; HAQ-DI response over 52 weeks; change from baseline in disease activity score 28 C-reactive protein (DAS28-CRP) at each visit; DAS28-CRP remission at Weeks 24 and 52; European League Against Rheumatism (EULAR) response at Weeks 24 and 52; clinical disease activity index (CDAI) remission at Weeks 24 and 52; SDAI remission at Weeks 24 and 52; change from baseline in CDAI and SDAI at Weeks 24 and 52; Boolean-based ACR/EULAR remission at Weeks 24 and 52; change from baseline in erosion score and joint space narrowing (JSN) score at Week 52; change from baseline in modified total Sharp score (mTSS), ES, and JSN at Week 24; radiographic progression of the mTSS/erosion score/JSN at Week 52.

• Quality of life and health economics observations: short form-36 survey (SF-36) at Weeks 24 and 52, Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-Fatigue) at Weeks 24 and 52, Sleep visual analog scale (VAS) at Weeks 24 and 52, and work productivity activity impairment (WPAI) at Weeks 12 and 52

Sample size

Sample size calculation was based on the change in mTSS. A 2-sided Wilcoxon test for alpha = 0.025 (to address the multiplicity across the 2 active dose regimens), 90% power, a week 52 mean change of 1.10 and 0.35 in the placebo and active groups, a standard deviation (SD) of 2.6 (Lithe study) and a missing data rate of 15% resulted in a requirement of 372 patients per group.

It was calculated that with 372 subjects per group the power for testing week ACR20 (anticipating ARC20 response rates of 27% for placebo and 51% for each of the active treatment groups) and change in HAQ-DI at week 16 (anticipating 0.3 week 16 treatment difference and common SD of 0.79) would exceed 90%.

Randomisation

Patients in part B of the study were initially randomized at a ratio of 1:1:1:1:1:1 (5 dose regimens of sarilumab: placebo) (cohort 1). Following dose selection in part A of the study subjects were randomized at a randomization ratio of 1:1:1 (placebo: sarilumab 150 mg q2w: sarilumab 200 mg q2w) (cohort 2). Randomisation was done via an IVR system. Randomization was stratified for to prior biologic use and region. Permuted block randomisation (block length: 6) was applied

Blinding (masking)

Double-blind.

Statistical methods

In general data were summarized by statistical characteristics (continuous data: n, mean, SD, median, minimum, and maximum; qualitative data: absolute and relative frequencies) stratified by treatment and visit (if applicable).

The primary efficacy analyses were based on the ITT population of all patients randomised in part B of the trial after the dose selection based on part A was done (cohort 2).

The study had 3 co-primary endpoints: ACR20 response at week 24, change from baseline in HAQ-DI at week 16 and change from baseline in the van der Heijde mTSS at week 52.

ACR20 response rate at week 24 was analysed by means of a Cochran-Mantel-Haenszel (CMH) test stratified by prior biologic use and region. For the primary analysis patients with missing ACR20 at week 24 for any reason including patients who dropped out or required rescue medication were considered non-responders. In a sensitivity analysis responder status following treatment discontinuation or rescue was determined using LOCF to impute missing data (patients with still insufficient information were considered non-responders).

Change from baseline in HAQ-DI at week 16, was analysed by means of a MMRM approach assuming an unstructured covariance structure to model the within-subject errors. The model included treatment, region, prior biologic use, visit, and treatment-by-visit interaction as fixed effects and baseline as a covariate. For the primary analysis data collected after treatment discontinuation or rescue were set to missing. For a sensitivity analysis an LOCF approach was used to impute missing HAQ-DI values beyond the time of treatment discontinuation or initiation of rescue medication (rescue allowed from week 16 onwards). A supportive analysis compared the proportion of HAQ-DI responder at week 16 for each active group vs. placebo using the same approach as for ACR20 applying non-responder imputation for missing data. Additionally the standardized AUC for change from baseline in HAQ-DI up to week 52 was compared between each active treatment group and placebo by means of an ANCOVA model with baseline as covariate and factors for treatment, region and prior biologic use.

Change from baseline in the van der Heijde mTSS at week 52, was analysed by fitting a 2-sided rank-based analysis of covariance (rank ANCOVA) model adjusted for baseline with factors for treatment, prior biologic use and region. This was done separately for each dose versus placebo. Standardized ranks were computed by prior biologic use and region for the covariate baseline and the response change in van der Heijde mTSS. For the primary analysis missing or post-rescue week 52 mTSS score was imputed by means of linear extrapolation. To assess the robustness of the analysis several sensitivity analyses for imputing missing data were pre-planned (mean rank imputation, LOCF, linear extrapolation including post treatment discontinuation and rescue data, observed cases).

Subgroup analyses for each of the co-primary efficacy endpoints were conducted with respect to the following subgroups in the ITT population: gender, Race, Region, Age, baseline weight, BMI, prior biologic use, rheumatoid factor, anti-CCP antibody, baseline CRP, duration of RA, number of prior DMARDs, smoking history.

Binary secondary variables, including the key secondary efficacy endpoint, major clinical response during 52 weeks (with non-responder imputation for missing endpoint data), were analysed in the same way as ACR20. Change from baseline for continuous secondary efficacy variables was analysed via a MMRM approach.

For each sarilumab group treatment effects (vs. placebo) were described by point estimates from the respective analysis model including the corresponding 95%-CIs.

To control the type I error for the 3 co-primary endpoints and the 1 key secondary endpoint across part B for each dose (at alpha = 0.025) separately a hierarchical testing procedure was defined:

1. ACR20 response at week 24
2. Change from baseline in HAQ-DI at week 16
3. Change from baseline in mTSS at week 52
4. Incidence of achieving major clinical response during the 52-week period.

The study was considered positive if ACR20 response achieved statistical significance at least 1 dose.

For other secondary endpoints each selected dose regimen of sarilumab was tested versus placebo at the 0.025 level according to a hierarchical testing order pre-specified in the SAP.

For the co-primary efficacy parameter the same analyses as mentioned above were performed on the ITT population of all randomized patients in part B (i.e. patients randomized to either sarilumab 150 mg q2w, sarilumab 200 mg q2w or placebo prior and after dose selection in part A). For this population no sensitivity or subgroup analyses were performed.

Results

Participant flow

Figure 1: Diagram of patient disposition - all patients

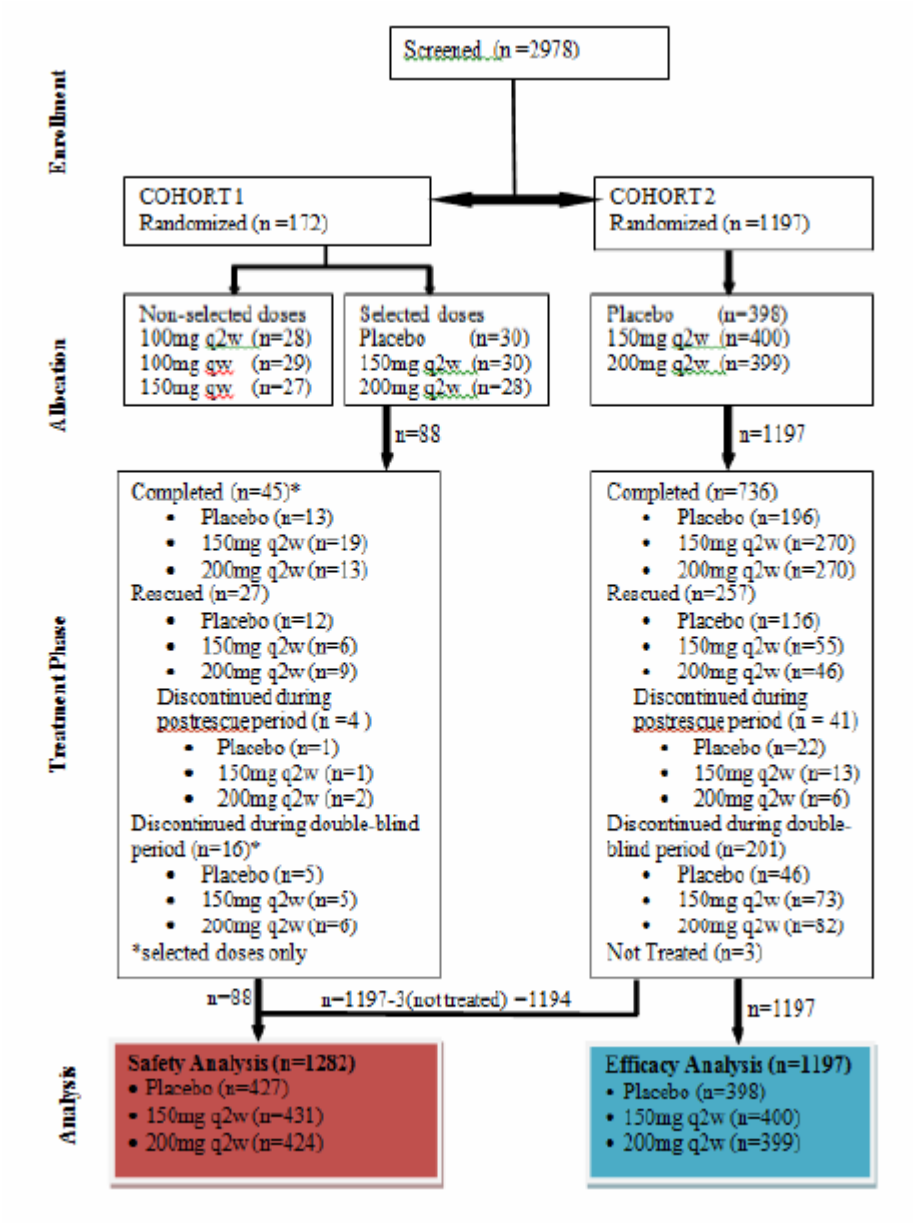


Table 15: Important protocol deviations potentially impacting efficacy analyses - Part B Cohort 2 - Randomized population

	Placebo + MTX (N=398)	Sarilumab 150mg q2w + MTX (N=400)	Sarilumab 200mg q2w + MTX (N=399)
Any important deviations potentially impacting efficacy analyses	15 (3.8%)	8 (2.0%)	12 (3.0%)
Patient with at least 8 of 68 joints assessed as painful or tender on motion and at least 6 of 66 as swollen at both screening and baseline visits, and hsCRP>10mg/L for B1 and >6 for B2 at screening.	6 (1.5%)	4 (1.0%)	6 (1.5%)
History of or current acute inflammatory joint disease other than RA, or RA diagnosed before the age of 16.	1 (0.3%)	1 (0.3%)	2 (0.5%)
Part B only: At least one locally documented bone erosions (on X-ray) prior to first dosing; Or, anti CCP antibody positive or positive rheumatoid factor according to screening laboratory tests.	5 (1.3%)	0	2 (0.5%)
Patients must have been treated with, and tolerated, a minimum of 12 weeks treatment with methotrexate (MTX) prior to the randomization visit.	2 (0.5%)	0	2 (0.5%)
Treatment with oral prednisone or equivalent >10mg/day within 4 weeks prior to randomization visit or use of parenteral or intra-articular glucocortisteroids within 4 weeks prior to screening visit.	0	0	2 (0.5%)
Patients must be on a stable dose of MTX (10 to 25 mg/week) for a minimum of 6 weeks prior to the Screening Visit (6 to 25 mg/week in Asia-Pacific) and must intend to continue MTX during the study.	2 (0.5%)	3 (0.8%)	1 (0.3%)

Note: Percentages are calculated using the number of patients randomized as denominator.

Recruitment

Date first patient enrolled: 07 March 2011, date last patient completed: 08 October 2013.

Conduct of the study

Seven amendments were implemented during the conduct of the study. Amendment No. 1 (dated 09 February 2010) and Amendment No. 2 (dated 01 June 2010) were implemented prior to enrolment of the first patient in Cohort 1. Amendment No. 3 (dated 04 April 2011) was implemented prior to enrolment of the first patient in Cohort 2.

Baseline data

For Cohort 2 and Cohort 1 selected doses, the randomized population was comprised of 1285 patients.

Table 16: Demographics and patient characteristics at baseline - Part B Cohort 2 + Cohort 1 selected doses - Randomized population

		Sarilumab		
	Placebo + MTX (N=428)	150mg q2w + MTX (N=430)	200mg q2w + MTX (N=427)	All (N=1285)
Age (years)				
Number	428	430	427	1285
Mean (SD)	51.1 (11.2)	50.3 (11.9)	50.8 (12.0)	50.8 (11.7)
Median	52.0	52.0	52.0	52.0
Min : Max	19 : 75	18 : 74	19 : 75	18 : 75
Age Group (years) [n (%)]				
Number	428	430	427	1285
<65	381 (89.0%)	383 (89.1%)	370 (86.7%)	1134 (88.2%)
≥65-75	46 (10.7%)	47 (10.9%)	56 (13.1%)	149 (11.6%)
≥75	1 (0.2%)	0	1 (0.2%)	2 (0.2%)
Sex [n (%)]				
Number	428	430	427	1285
Male	82 (19.2%)	85 (19.8%)	68 (15.9%)	235 (18.3%)
Female	346 (80.8%)	345 (80.2%)	359 (84.1%)	1050 (81.7%)
Race [n (%)]				
Number	428	430	427	1285
Caucasian/White	370 (86.4%)	371 (86.3%)	369 (86.4%)	1110 (86.4%)
Black	10 (2.3%)	11 (2.6%)	10 (2.3%)	31 (2.4%)
Asian/Oriental	35 (8.2%)	35 (8.1%)	33 (7.7%)	103 (8.0%)
Other	13 (3.0%)	13 (3.0%)	15 (3.5%)	41 (3.2%)

	Placebo + MTX (N=428)	Sarilumab 150mg q2w + MTX (N=430)	Sarilumab 200mg q2w + MTX (N=427)	All (N=1285)
Ethnicity [n (%)]				
Number	428	430	427	1285
Hispanic	147 (34.3%)	162 (37.7%)	161 (37.7%)	470 (36.6%)
Non Hispanic	281 (65.7%)	268 (62.3%)	266 (62.3%)	815 (63.4%)
Weight (kg)				
Number	428	428	426	1282
Mean (SD)	74.31 (17.25)	73.91 (18.27)	74.94 (19.98)	74.39 (18.52)
Median	72.00	70.20	72.00	71.95
Min : Max	42.0 : 164.8	31.5 : 151.0	36.7 : 173.1	31.5 : 173.1
Height (cm)				
Number	427	426	426	1279
Mean (SD)	162.17 (9.18)	162.46 (9.17)	161.56 (8.92)	162.06 (9.09)
Median	162.00	162.00	160.00	161.00
Min : Max	131.0 : 200.0	142.0 : 194.0	136.0 : 190.0	131.0 : 200.0
Body mass index (BMI)(kg/m^2)				
Number	427	426	426	1279
Mean (SD)	28.19 (5.81)	27.98 (6.51)	28.61 (6.68)	28.26 (6.34)
Median	27.14	26.86	28.03	27.27
Min : Max	16.4 : 54.0	15.0 : 65.2	16.4 : 55.2	15.0 : 65.2
BMI group(kg/m^2) [n (%)]				
Number	427	426	426	1279
<25	132 (30.9%)	156 (36.6%)	135 (31.7%)	423 (33.1%)
≥25-30	161 (37.7%)	143 (33.6%)	136 (31.9%)	440 (34.4%)
≥30	134 (31.4%)	127 (29.8%)	155 (36.4%)	416 (32.5%)

	Placebo + MTX (N=428)	Sarilumab 150mg q2w + MTX (N=430)	Sarilumab 200mg q2w + MTX (N=427)	All (N=1285)
Region [n(%)]				
Number	428	430	427	1285
Region 1	81 (18.9%)	82 (19.1%)	82 (19.2%)	245 (19.1%)
Region 2	162 (37.9%)	163 (37.9%)	162 (37.9%)	487 (37.9%)
Region 3	185 (43.2%)	185 (43.0%)	183 (42.9%)	553 (43.0%)

Note: Number = Number of patients assessed.
Region 1: Austria, Australia, Belgium, Canada, Finland, Germany, Greece, Hungary, New Zealand, Norway, Portugal, Spain, USA
Region 2: Argentina, Brazil, Chile, Colombia, Mexico
Region 3: Belarus, Estonia, India, Malaysia, Philippines, Poland, Romania, Russia, South Africa, South Korea, Ukraine, Taiwan, Thailand
Percentages are calculated using number of patients assessed as denominator.

Table 17: Disease characteristics at baseline- Part B Cohort 2 + Cohort 1 selected doses - Randomized population

	Placebo + MTX (N=428)	Sarilumab 150mg q2w + MTX (N=430)	Sarilumab 200mg q2w + MTX (N=427)	All (N=1285)
Duration of RA since diagnosis (Years)				
Number	428	430	427	1285
Mean (SD)	9.02 (8.10)	9.41 (8.40)	8.66 (6.98)	9.03 (7.85)
Median	6.65	6.91	7.36	7.06
Min : Max	0.3 : 44.0	0.3 : 44.7	0.3 : 34.2	0.3 : 44.7
RA functional class [n(%)]				
Number	428	430	427	1285
I	52 (12.1%)	53 (12.3%)	45 (10.5%)	150 (11.7%)
II	293 (68.5%)	275 (64.0%)	295 (69.1%)	863 (67.2%)
III	83 (19.4%)	102 (23.7%)	87 (20.4%)	272 (21.2%)
IV	0	0	0	0
Prior biologic use [n(%)]				
Number	428	430	427	1285
Yes	120 (28.0%)	119 (27.7%)	119 (27.9%)	358 (27.9%)
No	308 (72.0%)	311 (72.3%)	308 (72.1%)	927 (72.1%)
Rheumatoid factor [n(%)]				
Number	428	426	425	1279
Positive	359 (83.9%)	373 (87.6%)	354 (83.3%)	1086 (84.9%)
Negative	69 (16.1%)	53 (12.4%)	71 (16.7%)	193 (15.1%)
Anti CCP antibody [n(%)]				
Number	428	428	425	1281
Positive	366 (85.5%)	386 (90.2%)	361 (84.9%)	1113 (86.9%)
Negative	62 (14.5%)	42 (9.8%)	64 (15.1%)	168 (13.1%)
Tender joint count (0-68)				
Number	428	430	427	1285
Mean (SD)	26.41 (13.72)	27.49 (14.12)	26.64 (14.39)	26.85 (14.07)
Median	23.00	25.00	23.00	24.00
Min : Max	5.0 : 68.0	8.0 : 68.0	3.0 : 68.0	3.0 : 68.0
Swollen joint count (0-66)				
Number	428	430	427	1285
Mean (SD)	16.51 (9.33)	17.02 (9.42)	16.92 (9.73)	16.82 (9.49)
Median	14.00	14.00	14.00	14.00
Min : Max	3.0 : 56.0	2.0 : 64.0	3.0 : 66.0	2.0 : 66.0
CRP (mg/L)				
Number	428	430	427	1285
Mean (SD)	20.72 (22.82)	23.59 (24.69)	22.38 (23.49)	22.23 (23.69)
Median	13.15	14.85	15.60	14.70
Min : Max	0.3 : 169.0	0.2 : 209.0	0.2 : 203.0	0.2 : 209.0
HAQ-DI (0-3)				
Number	428	430	427	1285
Mean (SD)	1.59 (0.66)	1.64 (0.62)	1.70 (0.64)	1.64 (0.64)
Median	1.63	1.75	1.75	1.75
Min : Max	0.0 : 3.0	0.0 : 3.0	0.0 : 3.0	0.0 : 3.0
DAS28-CRP (>5.1: high disease activity)				
Number	428	429	427	1284
Mean (SD)	5.90 (0.90)	5.98 (0.92)	6.00 (0.87)	5.96 (0.90)
Median	5.90	5.94	5.97	5.93
Min : Max	3.1 : 8.1	2.8 : 8.5	3.4 : 8.0	2.8 : 8.5

Note: Number = Number of patients assessed.
Percentages are calculated using number of patients assessed as denominator.

Numbers analysed

Table 18: Patient disposition Part B Cohort 2 - Randomized population

	Placebo + MTX (N=398)	Sarilumab 150mg q2w + MTX (N=400)	Sarilumab 200mg q2w + MTX (N=399)	All (N=1197)
Randomized and not treated	0	2 (0.5%)	1 (0.3%)	3 (0.3%)
Randomized and treated	398 (100%)	398 (99.5%)	398 (99.7%)	1194 (99.7%)
Complete the study treatment period	330 (82.9%)	312 (78.0%)	310 (77.7%)	952 (79.5%)
Were rescued	134 (33.7%)	42 (10.5%)	40 (10.0%)	216 (18.0%)
Were not rescued	196 (49.2%)	270 (67.5%)	270 (67.7%)	736 (61.5%)
Did not complete the study treatment period	68 (17.1%)	86 (21.5%)	88 (22.1%)	242 (20.2%)
Were rescued	22 (5.5%)	13 (3.3%)	6 (1.5%)	41 (3.4%)
Were not rescued	46 (11.6%)	73 (18.3%)	82 (20.6%)	201 (16.8%)
Discontinued during double-blind period	46 (11.6%)	73 (18.3%)	82 (20.6%)	201 (16.8%)
Subject's request for treatment discontinuation	19 (4.8%)	39 (9.8%)	33 (8.3%)	91 (7.6%)
Reason for treatment discontinuation				
Adverse event	21 (5.3%)	50 (12.5%)	57 (14.3%)	128 (10.7%)
Lack of efficacy	3 (0.8%)	5 (1.3%)	6 (1.5%)	14 (1.2%)
Poor compliance to protocol	6 (1.5%)	2 (0.5%)	5 (1.3%)	13 (1.1%)
Other reasons	16 (4.0%)	16 (4.0%)	14 (3.5%)	46 (3.8%)
Discontinued during open label rescue period	22 (5.5%)	13 (3.3%)	6 (1.5%)	41 (3.4%)
Subject's request for treatment discontinuation	13 (3.3%)	7 (1.8%)	4 (1.0%)	24 (2.0%)
Reason for treatment discontinuation				
Adverse event	12 (3.0%)	9 (2.3%)	3 (0.8%)	24 (2.0%)
Lack of efficacy	4 (1.0%)	3 (0.8%)	2 (0.5%)	9 (0.8%)
Poor compliance to protocol	2 (0.5%)	0	0	2 (0.2%)
Other reasons	4 (1.0%)	1 (0.3%)	1 (0.3%)	6 (0.5%)
Status at last study contact				
Alive	396 (99.5%)	396 (99.0%)	396 (99.2%)	1188 (99.2%)
Dead	2 (0.5%)	2 (0.5%)	2 (0.5%)	6 (0.5%)
Rolled over to LTS study				
Yes	307 (77.1%)	300 (75.0%)	294 (73.7%)	901 (75.3%)
No	91 (22.9%)	98 (24.5%)	104 (26.1%)	293 (24.5%)

Outcomes and estimation

ACR20

The proportion of patients achieving an ACR20 response at Week 24 was higher in patients treated with sarilumab (58.0% for the 150 mg q2w and 66.4% for the 200 mg q2w groups) than in patients treated with placebo (33.4%), with p-values <0.0001 demonstrating a statistically significant reduction in signs and symptoms of RA in favor of both sarilumab doses compared with placebo.

Similar results were obtained in the primary analysis of Cohort 2 and Cohort 1 selected doses.

The ACR20 response rate increased at each visit from Week 2 through Week 16 for all treatment groups. The response rate was maintained up to Week 52, with a slight decrease in response rates due to patients discontinuing study treatment and being assigned as non-responders (Figure 2).

Figure 2: Incidence of ACR20 response at each visit (observed cases) - Part B Cohort 2 – ITT population

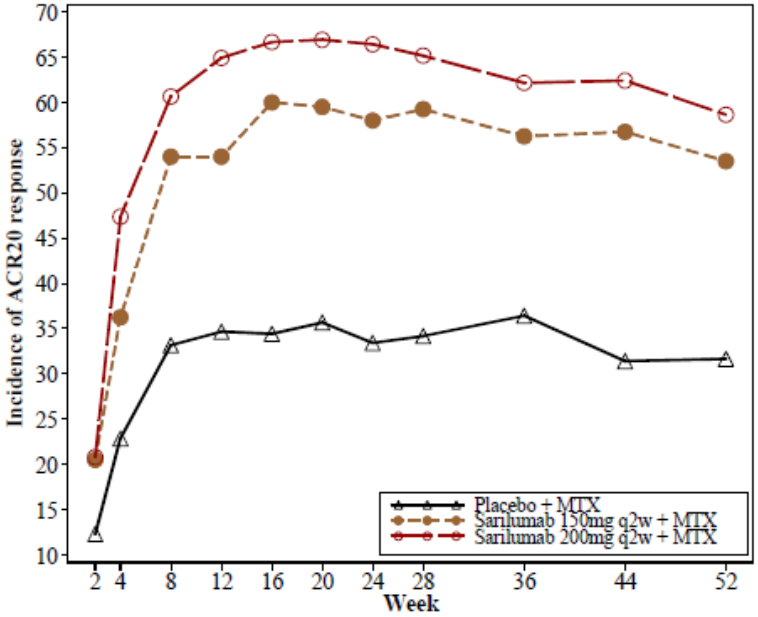


Table 19: Incidence of ACR20 response at Week 52 - Part B Cohort 2 - ITT population

		Sarilumab	
ACR20 at Week 52 n(%)	Placebo + MTX (N=398)	150mg q2w + MTX (N=400)	200mg q2w + MTX (N=399)
Responders	126 (31.7%)	214 (53.5%)	234 (58.6%)
Non-responders	272 (68.3%)	186 (46.5%)	165 (41.4%)
P-value vs placebo[a]	-	<0.0001	<0.0001
OR, CI vs placebo[b]	-	2.487 (1.863, 3.320)	3.086 (2.305, 4.131)

OR: Odds ratio.
ACR20 response = at least 20% improvement from baseline in both TJC and SJC, and in at least three of the HAQ score, CRP and three VAS assessments.
Patients are considered non-responders from the time they started rescue medication or discontinued study medication.
Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group within each subgroup as denominator.

HAQ-DI

The mean change from baseline in the HAQ-DI score at Week 16 was greater in patients treated with sarilumab (-0.54 for the150 mg q2w and -0.58 for the 200 mg q2w groups) than in patients treated with placebo (-0.30).

The results demonstrated a statistically significant difference (p-values <0.0001) in improvement of physical function in favor of both sarilumab doses compared with placebo.

Similar results were obtained in the primary analysis of Cohort 2 and Cohort 1 selected doses.

Supportive analyses

For the analysis of clinically meaningful HAQ-DI response, 2 different definitions were used: >0.3 and >0.22 units of improvement in the change from baseline. For both definitions, the proportion of patients who were HAQ-DI responders at Week 16 was higher in the sarilumab 150 mg q2w and 200 mg q2w treatment groups than in the placebo group:

• HAQ-DI response >0.3 units of improvement: 42.5% for placebo, 53.8% for 150 mg q2w and 57.4% for 200 mg q2w

• HAQ-DI response >0.22 units of improvement: 51.3% for placebo, 63.3% for 150 mg q2w and 64.9% for 200 mg q2w

The proportion of patients who were HAQ-DI responders at Weeks 24 and 52 was higher in the sarilumab 150 mg q2w and 200 mg q2w treatment groups than in the placebo group:

• HAQ-DI response >0.3 units of improvement: 33.4% for placebo, 51.0% for 150 mg q2w and 51.4% for 200 mg q2w at Week 24; 26.1% for placebo, 47.0% for 150 mg q2w and 47.6% for 200 mg q2w at Week 52;

• HAQ-DI response >0.22 units of improvement: 39.2% for placebo, 57.5% for 150 mg q2w and 57.9% for 200 mg q2w at Week 24; 32.9% for placebo, 53.3% for 150 mg q2w and 53.1% for 200 mg q2w at Week 52.

For both definitions of clinically meaningful HAQ-DI response, sarilumab doses had nominal p-values <0.0001 at Weeks 16, 24, and 52, indicating a clinically meaningful effect on improvement of physical function.

HAQ-DI response over 52 weeks is defined as the standardized AUC for change from baseline in HAQ-DI up to Week 52 with >0.22 or >0.3 units of improvement. For both definitions, the proportion of patients who were HAQ-DI responders was higher in the sarilumab 150 mg q2w and sarilumab 200 mg q2w groups than in the placebo group (nominal p-values <0.0001 for both comparisons):

• HAQ-DI response >0.3 units of improvement: 43.7% for placebo, 59.0% for sarilumab 150 mg q2w and 59.9% for sarilumab 200 mg q2w

• HAQ-DI response >0.22 units of improvement: 49.7 % for placebo, 65% for sarilumab 150 mg q2w and 67.7% for sarilumab 200 mg q2w

The effect was maintained up to Week 52.

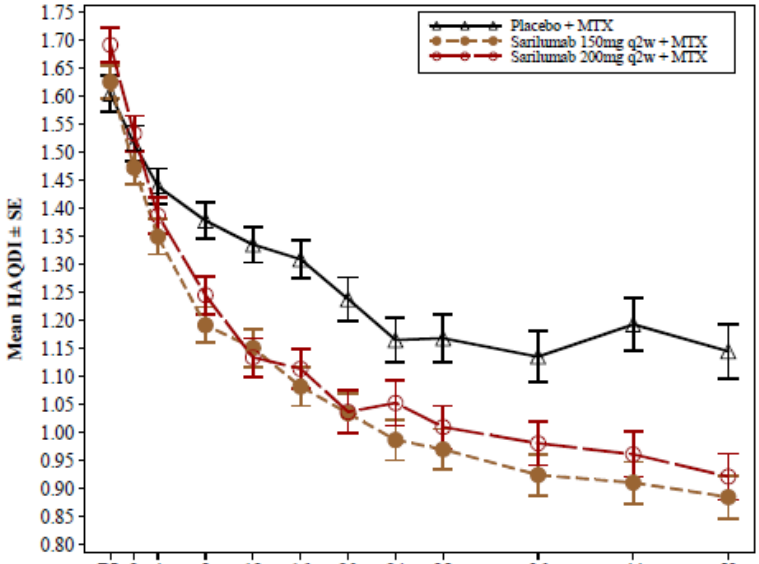
Standardized AUC for the change from baseline in HAQ-DI up to Week 52

The change in LS mean in the standardized AUC for change from baseline in HAQ-DI score up to Week 52 was numerically greater in patients treated with sarilumab (-0.48 for the 150 mg q2w and -0.50 for the 200 mg q2w groups) than in patients treated with placebo (-0.26). The difference in LS means between each of the sarilumab groups and the placebo group was statistically significant (p-value <0.0001)

HAQ-DI response at each visit

Improvement in physical function was maintained up to Week 52 (Figure 4). The improvement in physical function was greater for both sarilumab groups compared with the placebo group (nominal p-values <0.0001) at Weeks 24 and 52.

Figure 3: HAQ-DI at each visit (observed cases) - Part B Cohort 2 - ITT population



# subjects											
Placebo + MTX	398	395	388	383	378	283	253	230	216	204	195
Sarilumab 150mg q2w + MTX	400	391	385	374	362	334	313	307	289	280	272
Sarilumab 200mg q2w + MTX	399	394	385	378	365	328	316	307	292	286	270

Van der Heijde modified total Sharp score

Smaller increases from baseline in the mTSS at Week 52 were observed in patients treated with sarilumab (0.90 for the150 mg q2w and 0.25 for the 200 mg q2w groups) than in patients treated with placebo (2.78), indicating inhibition of progression of structural damage by sarilumab.

Differences compared with placebo were statistically significant (p-value <0.0001) in favor of both sarilumab doses.

Similar results were obtained in the primary analysis of Cohort 2 and Cohort 1 selected doses.

Supportive analyses

At Week 52, treatment with sarilumab was associated with significantly less radiographic progression of structural damage as compared with placebo (Table 20).

Table 20: Rates of no progression from baseline to Week 52 in the modified total Sharp score (supportive analysis) - Part B Cohort 2 - ITT population

		Sarilumab	
	Placebo + MTX (N=398)	150mg q2w + MTX (N=400)	200mg q2w + MTX (N=399)
Modified total Sharp score (0-448)			
Number	398	400	399
No progression	154 (38.7%)	191 (47.8%)	222 (55.6%)
Progression	244 (61.3%)	209 (52.3%)	177 (44.4%)
P-value vs placebo[a]	-	0.0094	<0.0001
OR, CI vs placebo[b]	-	1.453 (1.095, 1.926)	2.001 (1.506, 2.660)

OR: Odds ratio.
Modified total Sharp score = the sum of bone erosion scores from 44 joints and joint space narrowing scores from 42 joints, with a maximum score 448.
The linear extrapolation method is used to impute missing or postrescue Week 52 modified total Sharp scores.
Patients with missing Week 52 modified total Sharp scores after the imputation are considered as progression.
Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.
[a] CMH test stratified by prior biologic use and region. [b] Mantel-Haenszel estimate.

Secondary Endpoints:

Main secondary efficacy endpoint

Major clinical response is defined as the event of achieving and maintaining ACR70 for at least 24 consecutive weeks during the 52-week period. A larger proportion of patients in the sarilumab groups achieved major clinical response compared to the placebo group, and the differences between each sarilumab group and placebo were statistically significant (p <0.0001). There were no subgroup interactions, all nominal p-values >0.1

Table 21: Summary of results for co-primary and key secondary endpoints in EFC11072 Part B, Cohort 2

	Placebo + MTX (N=398)	Sarilumab 150 mg q2w + MTX (N=400)	Sarilumab 200 mg q2w + MTX (N=399)
Co-primary endpoints			
ACR20 responders at Week 24	133 (33.4%)	232 (58.0%)	265 (66.4%)
OR, 95% CI versus placebo[a]		2.773 (2.077, 3.703)	3.975 (2.957, 5.344)
p-value versus placebo[b]		<0.0001	<0.0001
Change from baseline in HAQ-DI at Week 16			
Mean change (SD)	-0.30 (0.58)	-0.54 (0.55)	-0.58 (0.63)
p-value versus placebo[c]		<0.0001	<0.0001
Change from baseline in mTSS at Week 52			
Mean change (SD)	2.78 (7.73)	0.90 (4.66)	0.25 (4.61)
p-value versus placebo[d]		<0.0001	<0.0001
Main secondary endpoint			
Major clinical response[e]			
Responders	12 (3.0%)	51 (12.8%)	59 (14.8%)
p-value versus placebo[b]		<0.0001	<0.0001

ACR = American College of Rheumatology; ANCOVA = analysis of covariance; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; HAQ-DI = Health Assessment Questionnaire – Disability Index; mTSS = modified total Sharp score; MMRM = mixed model for repeated measures; MTX = methotrexate; SD = standard deviation

Source: 5.3.5.1 Study EFC11072 Part B [Table 17], [Table 18], [Table 19], and [Table 23].

a Mantel-Haenszel estimate

b CMH test stratified by prior biologic use and region

c Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, prior biological use, region, visit, and treatment-by-visit interaction.

d Rank ANCOVA model stratified by prior biologic use and region

e Major clinical response = Achieving ACR70 for at least 24 consecutive weeks during the 52-week period.

Other Secondary endpoints

Table 22 shows the results for the pre-specified hierarchy of primary and secondary efficacy endpoints including assessments of quality of life and work productivity. The results that are in bold font are statistically significant according to the procedure of analysis.

Table 22: Nominal p-values for comparing sarilumab 150 mg q2w and 200 mg q2w versus placebo for the primary and secondary endpoints

	Placebo + MTX (N = 398)	Sarilumab 150mg q2w + MTX (N = 400)		Sarilumab 200mg q2w + MTX (N = 399)	
Parameter[a]		Estimate[b]	P-value[c]	Estimate[b]	P-value[c]
Primary endpoints					
ACR20 – Week 24	133 (33.4%)	232 (58.0%)	**< 0.0001**	265 (66.4%)	**< 0.0001**
HAQ-DI – Week 16	-0.29(0.028)	-0.53(0.029)	**< 0.0001**	-0.55(0.029)	**< 0.0001**
mTSS – Week 52	2.78 (7.73)	0.90 (4.66)	**< 0.0001**	0.25 (4.61)	**< 0.0001**
Secondary endpoints					
Major Clinical Response – Week 52	12 (3.0%)	51(12.8%)	**< 0.0001**	59 (14.8%)	**< 0.0001**
DAS28-CRP – Week 24	-1.17(0.079)	-2.45(0.076)	**< 0.0001**	-2.82(0.075)	**< 0.0001**
ACR50 – Week 24	66 (16.6%)	148 (37.0%)	**< 0.0001**	182 (45.6%)	**< 0.0001**
ACR70 – Week 24	29 (7.3%)	79 (19.8%)	**< 0.0001**	99 (24.8%)	**< 0.0001**
DAS28-CRP remission – Week 24	40 (10.1%)	111 (27.8%)	**< 0.0001**	136 (34.1%)	**< 0.0001**
HAQ-DI AUC up to Week 52	-0.25(0.024)	-0.47(0.024)	**< 0.0001**	-0.50(0.024)	**< 0.0001**
mTSS no progression – Week 52	154 (38.7%)	191 (47.8%)	**0.0081**	222 (55.6%)	**< 0.0001**
CDAI – Week 24	-14.47(0.811)	-23.89(0.774)	**< 0.0001**	-25.79(0.770)	**< 0.0001**
FACIT – Fatigue – Week 24	5.80(0.482)	8.61(0.453)	**< 0.0001**	9.15(0.449)	**< 0.0001**
SF-36 Physical – Week 24	5.15(0.496)	8.01(0.449)	**< 0.0001**	8.35(0.446)	**< 0.0001**
SF-36 Mental – Week 24	3.90(0.614)	5.70(0.557)	**0.0215**	8.17(0.552)	**< 0.0001**
WPAI percent overall work impairment – Week 12	-10.01(2.843)	-19.61(2.731)	**0.0127**	-17.24(2.829)	0.0631
Sleep – Week 24	-14.30(1.441)	-21.79(1.340)	**0.0001**	-22.29(1.328)	< 0.0001
FACIT- Fatigue – Week 52	6.06(0.544)	9.09(0.489)	**< 0.0001**	9.20(0.487)	< 0.0001
SF-36 Physical – Week 52	5.55(0.554)	9.21(0.479)	**< 0.0001**	9.08(0.477)	< 0.0001
SF-36 Mental – Week 52	5.50(0.688)	7.10(0.597)	0.0659	8.40(0.593)	0.0008
Sleep – Week 52	-17.55(1.595)	-23.76(1.404)	0.0030	-24.17(1.413)	0.0016
WPAI percent overall work impairment – Week 52	-16.83(3.829)	-21.79(3.245)	0.3156	-25.60(3.008)	0.0679

[a] For further details of the endpoint definition and analysis method see the SAP 16-1-9-sap.

[b] Values presented are number and percent of responders for binary variables and LS mean change from baseline with standard error for continuous variables, except for mTSS where mean change from baseline with standard deviation is reported.

[c] Nominal p-values. All values in bold font are significant according to the hierarchical testing procedure.

ACR50

The ACR50 response increased, indicating greater improvement, at each visit up to Week 24 in both sarilumab groups (Figure 4). The incidence of ACR50 response at Week 24 was statistically significant in patients treated with sarilumab compared with patients treated with placebo (p <0.0001). The results at Week 52, which were not part of the hierarchy, were consistent with the results at Week 24 (nominal p-value <0.0001) (Table 23).

Figure 4: Incidence of ACR50 response at each visit - Part B Cohort 2 - ITT population

Source: efc11072-1-5-body p.115

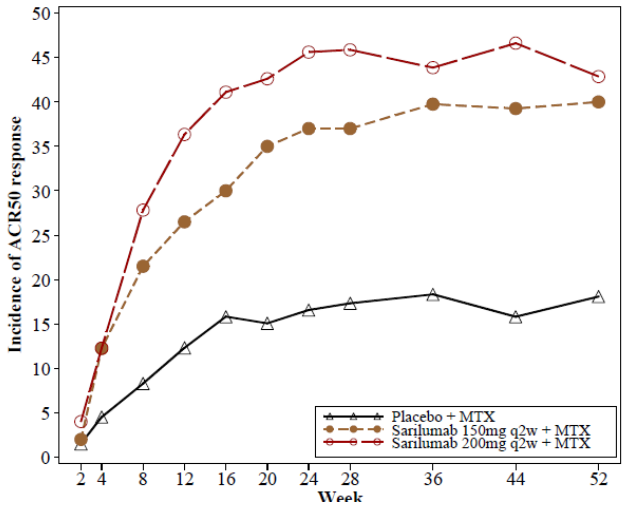


Table 23: Incidence of ACR50 response at Week 24 - Part B Cohort 2 - ITT population

Source: efc11072-1-5-body p.116

ACR50 at Week 24 n(%)	Placebo + MTX (N=398)	Sarilumab 150mg q2w + MTX (N=400)	Sarilumab 200mg q2w + MTX (N=399)
Responders	66 (16.6%)	148 (37.0%)	182 (45.6%)
Non-responders	332 (83.4%)	252 (63.0%)	217 (54.4%)
P-value vs placebo[a]	-	<0.0001	<0.0001
OR, CI vs placebo[b]	-	2.966 (2.125, 4.140)	4.269 (3.064, 5.948)

OR: Odds ratio.
ACR50 response = at least 50% improvement from baseline in both TJC and SJC, and in at least three of the HAQ score, CRP and three VAS assessments.
Patients are considered non-responders from the time they started rescue medication or discontinued study medication.
Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.
[a] CMH test stratified by prior biologic use and region. [b] Mantel-Haenszel estimate.

Table 24: Incidence of ACR50 response at Week 52 - Part B Cohort 2 - ITT population
Source: efc11072-1-5-body p.117

		Sarilumab	
ACR50 at Week 52 n(%)	Placebo + MTX (N=398)	150mg q2w + MTX (N=400)	200mg q2w + MTX (N=399)
Responders	72 (18.1%)	160 (40.0%)	171 (42.9%)
Non-responders	326 (81.9%)	240 (60.0%)	228 (57.1%)
P-value vs placebo[a]	-	<0.0001	<0.0001
OR, CI vs placebo[b]	-	3.023 (2.185, 4.183)	3.377 (2.446, 4.663)

OR: Odds ratio.
ACR50 response = at least 50% improvement from baseline in both TJC and SJC, and in at least three of the HAQ score, CRP and three VAS assessments.
Patients are considered non-responders from the time they started rescue medication or discontinued study medication.
Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.

ACR70:

The ACR70 response showed an increasing trend across all visits for both sarilumab treatment groups (Figure 5). The incidence of ACR70 response at Week 24 was statistically significant in patients treated with sarilumab compared with patients treated with placebo (p <0.0001) (Table 29). The results at Week 52, which were not part of the hierarchy, were consistent with the results at Week 24 (nominal p-value <0.0001) (Table 25).

Figure 5: Incidence of ACR70 response at each visit (observed cases) - Part B Cohort 2 – ITT Population

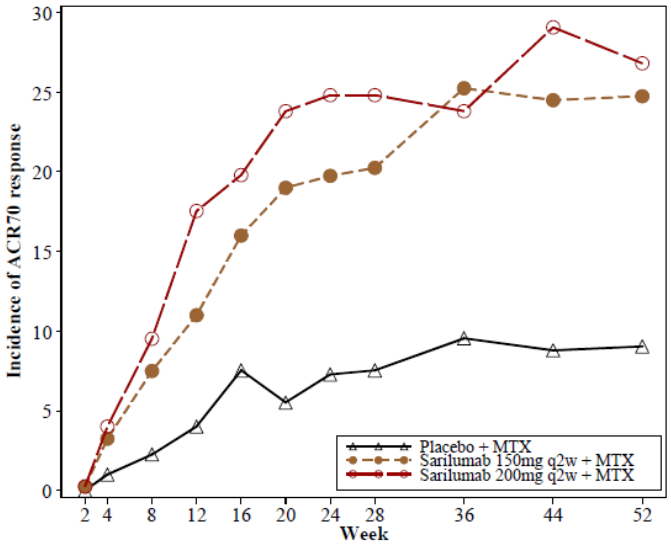


Table 25: Incidence of ACR70 response at Week 24 - Part B Cohort 2 - ITT population

Source: efc11072-1-5-body p.118

		Sarilumab	
ACR70 at Week 24 n(%)	Placebo + MTX (N=398)	150mg q2w + MTX (N=400)	200mg q2w + MTX (N=399)
Responders	29 (7.3%)	79 (19.8%)	99 (24.8%)
Non-responders	369 (92.7%)	321 (80.3%)	300 (75.2%)
P-value vs placebo[a]	-	<0.0001	<0.0001
OR, CI vs placebo[b]	-	3.174 (2.016, 4.996)	4.280 (2.743, 6.678)

OR: Odds ratio.
ACR70 response = at least 70% improvement from baseline in both TJC and SJC, and in at least three of the HAQ score, CRP and three VAS assessments.
Patients are considered non-responders from the time they started rescue medication or discontinued study medication.
Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.
[a] CMH test stratified by prior biologic use and region. [b] Mantel-Haenszel estimate.

Table 26: Incidence of ACR70 response at Week 52 - Part B Cohort 2 - ITT population

Source: efc11072-1-5-body p.118

		Sarilumab	
ACR70 at Week 52 n(%)	Placebo + MTX (N=398)	150mg q2w + MTX (N=400)	200mg q2w + MTX (N=399)
Responders	36 (9.0%)	99 (24.8%)	107 (26.8%)
Non-responders	362 (91.0%)	301 (75.3%)	292 (73.2%)
P-value vs placebo[a]	-	<0.0001	<0.0001
OR, CI vs placebo[b]	-	3.323 (2.200, 5.020)	3.691 (2.453, 5.554)

OR: Odds ratio.
ACR70 response = at least 70% improvement from baseline in both TJC and SJC, and in at least three of the HAQ score, CRP and three VAS assessments.
Patients are considered non-responders from the time they started rescue medication or discontinued study medication.
Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.
[a] CMH test stratified by prior biologic use and region. [b] Mantel-Haenszel estimate.

ACR components

There were 7 ACR components: TJC, SJC, physician global VAS, patient global VAS, pain VAS, HAQ-DI, and CRP.

Tender joint count

At Weeks 24 and 52, the difference in the decrease from baseline in TJC was greater in both sarilumab groups compared with placebo (all nominal p-values <0.0001).

Swollen joint count

Baseline mean SJC were similar across the treatment groups, ranging from 15.96 to 16.95. At Weeks 24 and 52, the difference in the decrease from baseline in SJC was greater in both sarilumab groups compared with placebo (all nominal p-values <0.0001).

Pain VAS

Baseline pain VAS values were similar across the treatment groups, ranging from 62.12 to 65.72. At Weeks 24 and 52, the difference in the decrease from baseline in pain was greater in both sarilumab groups compared with placebo (all nominal p-values <0.0001).

CRP

Baseline CRP values were similar across the treatment groups, ranging from 17.40 to 22.49. Both sarilumab treatment groups showed a decrease from baseline in CRP compared with placebo. At Weeks 24 and 52, the difference in the decrease from baseline in CRP was greater in both sarilumab groups compared with placebo (all nominal p-values <0.0001).

Physician global VAS

Baseline physician global VAS values were similar across the treatment groups, ranging from 62.58 to 62.88. At Weeks 24 and 52, the difference in the decrease from baseline in physician global VAS was greater in both sarilumab groups compared with placebo (all nominal p-values <0.0001).

Patient global VAS

Baseline patient global VAS values were similar across the treatment groups, ranging from 61.85 to 65.45. At Weeks 24 and 52, the difference in the decrease from baseline in patient global VAS was greater in both sarilumab groups compared with placebo (all nominal p-values <0.0001).

ACRn

All treatment groups showed an improvement in the ACRn. At Week 24, the change in LS mean was 6.13 for the placebo group, 34.18 for the sarilumab 150 mg q2w group, and 42.45 for the sarilumab 200 mg q2w group (nominal p-value <0.0001). At Week 52, the change in LS mean was 11.96 for the placebo group and 43.82 for the sarilumab 150 mg q2w group, and 48.17 for the sarilumab 200 mg q2w group (nominal p-value <0.0001).

DAS28-CRP

Baseline DAS-28 CRP values were similar across the treatment groups, ranging from 5.87 to 5.97.

All treatment groups showed a decrease in the DAS28-CRP score when compared to baseline. At Week 24, the change in LS mean was -1.17 for the placebo group, -2.45 for the sarilumab150 mg q2w group, and -2.82 for the sarilumab 200 mg q2w group. At Week 24 the differences between each of the sarilumab groups and the placebo group were statistically significant (p-values <0.0001), in favor of sarilumab.

At Week 52, the change in LS mean was -1.36 for the placebo group, -2.78 for the sarilumab 150 mg q2w group, and -2.95 for the sarilumab 200 mg q2w group. At Week 52 the change in LS mean was greater in the sarilumab groups compared with the placebo group (nominal p-values <0.0001).

The proportion of patients achieving DAS28-CRP remission (DAS28-CRP <2.6) at Week 24 was higher in patients treated with sarilumab than in patients treated with placebo (10.1% for placebo, 27.8% for sarilumab

150 mg q2w, and 34.1% for sarilumab 200 mg q2w). At Week 24 the differences between each sarilumab treatment group and placebo were statistically significant (p-values <0.0001), in favor of sarilumab.

At Week 52 the proportion of patients achieving DAS28-CRP remission was higher in patients treated with sarilumab than in patients treated with placebo (8.5% for placebo, 31% for sarilumab 150 mg q2w, and 34.1% for sarilumab 200 mg q2w). At Week 52 the proportion of patients achieving DAS28-CRP remission was greater in the sarilumab groups compared with the placebo group (nominal p-values <0.0001).

EULAR response

A larger proportion of patients in the sarilumab treatment groups achieved a good to moderate EULAR response compared to the placebo group at Weeks 24 and 52: Good response: 16.8% for placebo, 39.5% for 150 mg q2w and 49.1% for 200 mg q2w at Week 24 and 13.8% for placebo, 44.5% for 150 mg q2w and 45.9% for 200 mg q2w at Week 52; Moderate response: 24.6% for placebo, 31.5% for 150 mg q2w and 26.3% for 200 mg q2w at Week 24 and 26.4% for placebo, 19.5% for 150 mg q2w and 19.3% for 200 mg q2w at Week 52.The nominal p-value for testing the difference in the EULAR response between each of the sarilumab groups and the placebo group was p <0.0001 for both comparisons at Weeks 24 and 52.

Simplified disease activity index

Baseline SDAI values were similar across the treatment groups, ranging from 42.17 to 42.70.

All treatment groups showed a decrease from baseline in the SDAI. At Week 24, the change in LS mean was -14.36 for the placebo group, -25.26 for the sarilumab 150 mg q2w group, and -27.54 for the sarilumab 200 mg q2w group. At Week 52, the change in LS mean was -17.10 for the placebo group, -28.23 for the sarilumab 150 mg q2w group, and -28.95 for the sarilumab 200 mg q2w group. At Weeks 24 and 52, the difference in the decrease from baseline was greater in both sarilumab groups compared with the placebo group (nominal p-values <0.0001.

The proportion of patients achieving SDAI remission (ie, SDAI $\leq$ 3.3) was numerically higher in patients in the sarilumab groups at Weeks 24 and 52 when compared with placebo (4.8% for placebo, 10.3% for sarilumab 150 mg q2w, and 13.0% for sarilumab 200 mg q2w at Week 24 and 4.0% for placebo, 15.0% for sarilumab 150 mg q2w, and 18.5% for sarilumab 200 mg q2w at Week 52). The nominal p-value at Week 24 for the sarilumab 150 mg q2w group was 0.004 and all other nominal p-values <0.0001 at Weeks 24 and 52.

Clinical disease activity index

Baseline CDAI values were similar across the treatment groups, ranging from 40.34 to 40.39.

All treatment groups showed a decrease from baseline in the CDAI. At Week 24, the change in LS mean was -14.50 for the placebo group, -23.90 for the sarilumab 150 mg q2w group, and -25.79 for the sarilumab 200 mg q2w group. At Week 24 the differences between each of the sarilumab groups and the placebo group were statistically significant (p-values <0.0001), in favor of sarilumab.

At Week 52, the change in LS mean was -17.53 for the placebo group, -26.97 for the sarilumab 150 mg q2w group, and -27.25 for the sarilumab 200 mg q2w group. At Week 52 the change in LS mean was greater in the sarilumab groups compared with the placebo group (nominal p-values <0.0001)

The proportion of patients achieving CDAI remission (i.e., CDAI $\leq$ 2.8) was higher in patients in the sarilumab groups at Weeks 24 and 52 when compared with placebo (5.0% for placebo, 10.3% for sarilumab 150 mg q2w, and 13.8% for sarilumab 200 mg q2w at Week 24 and 4.8% for placebo, 14.8% for sarilumab 150 mg q2w, and 18.0% for sarilumab 200 mg q2w at Week 52).

The nominal p-value for testing the difference in incidence of CDAI remission between each of the sarilumab groups and the placebo group was p <0.001 for both comparisons at Weeks 24 and 52.

Boolean-based ACR/EULAR remission

The proportion of patients achieving Boolean-based ACR/EULAR remission at Weeks 24 and 52 was numerically higher in patients treated with sarilumab than in patients treated with placebo (3.8% for placebo, 6.5% for sarilumab 150 mg q2w, and 10.5% for sarilumab 200 mg q2w at Week 24 and 3% for placebo, 10.5% for sarilumab 150 mg q2w, and 14.0% for sarilumab 200 mg q2w at Week 52). At Week 24, nominal p-values for testing the difference in increase in Boolean-based ACR/EULAR response between each of the sarilumab groups and the placebo group were p=0.09 for sarilumab 150 mg q2w dose and p=0.0002 for sarilumab 200 mg q2w group. At Week 52, nominal p-values were p <0.0001 for both comparisons.

Erosion score

At Week 24, smaller increases from baseline in ES were observed in patients treated with sarilumab than in patients treated with placebo (nominal p-value=0.0074 for the sarilumab 150 mg q2w group and nominal p-value <0.0001 for the sarilumab 200 mg q2w group). At Week 52, the differences in the increases from baseline between the sarilumab groups and the placebo group were much greater than the differences at Week 24, in favor of sarilumab (nominal p-values <0.0001).

At Week 52, the proportion of patients who had no progression in ES was higher in the sarilumab groups compared with placebo. The nominal p-values for testing the difference between each of the sarilumab groups and the placebo group were p=0.0013 for sarilumab 150 mg q2w group and p-value <0.0001 for sarilumab 200 mg q2w group.

Joint space narrowing score

At Week 24, smaller increases from baseline in the JSN score were observed in patients treated with sarilumab than in patients treated with placebo (nominal p-value=0.1514 for the sarilumab 150 mg q2w group and nominal p-value=0.0003 for the sarilumab 200 mg q2w group). At Week 52, the differences in the increases from baseline between the sarilumab groups and the placebo group were much greater than the differences at Week 24, in favor of sarilumab (nominal p-value =0.0005 for the sarilumab 150 mg q2w and p <0.0001 for the sarilumab 200 mg q2w groups

At Week 52, the proportion of patients who had no progression in JSN score was higher in sarilumab groups compared with placebo. The nominal p-values for testing the difference between each of the sarilumab groups and the placebo group were p=0.0619 for the sarilumab 150 mg q2w group and p <0.0001 for the sarilumab 200 mg q2w group.

QUALITY OF LIFE AND HEALTH ECONOMICS OBSERVATIONS

SF-36 Physical component summary and Physical Health Domain scores at Week 24

The differences in SF-36 PCS scores were statistically significant and clinically meaningful for both sarilumab treatment groups as compared with placebo (p-values of <0.0001). At Week 24, both sarilumab treatment groups had clinically meaningful changes from baseline on all 4 SF-36 physical health domain scores.

SF-36 Mental component summary and Mental Health Domains scores at Week 24

The differences in SF-36 PCS scores were statistically significant as compared to placebo and showed clinically meaningful changes from baseline for both sarilumab treatment groups as compared with placebo (p-values of <0.0001).

At Week 24, both sarilumab treatments had clinically meaningful changes from baseline on all 4 SF-36 mental health domain scores.

SF-36 Physical component summary and Physical Health Domains scores at Week 52

The differences in SF-36 MCS scores were between the sarilumab 150 mg q2w group and placebo group was statistically significant as compared to placebo and showed clinically meaningful changes from baseline for both sarilumab treatment groups (p-value of 0.0200 for 150 mg group and p <0.0001 for 200 mg group).

At Week 52, both sarilumab treatments had a clinically meaningful change from baseline on all 4 SF-36 physical health domain scores.

SF-36 Mental component summary and Mental Health Domains scores at Week 52

At Week 52, the difference in SF-36 MCS score between the sarilumab 150 mg q2w group and the placebo group was not statistically significant (p=0.0659). The SF-36 MCS score for the sarilumab 200 mg q2w The SF-36 MCS score for the sarilumab 200 mg q2w group showed a clinically meaningful change from baseline at Week 52 (nominal p-value =0.0008), but statistical significance is not claimed due to a break in the hierarchy.

At Week 52, both sarilumab treatments had clinically meaningful changes from baseline on all 4 SF-36 mental health domain scores.

FACIT-Fatigue

At Week 24, both sarilumab treatment groups demonstrated a statistically significant difference compared to placebo and clinically meaningful change from baseline in FACIT-Fatigue scores (p <0.0001).

At Week 52, the sarilumab 150 mg q2w group demonstrated statistically significant difference compared to placebo and a clinically meaningful difference from baseline in FACIT-Fatigue score (p <0.0001). The difference in FACIT-Fatigue score for the placebo group was clinically meaningful at Week 52 (nominal p-value <0.0001), but statistical significance compared to placebo is not claimed due to a break in the hierarchy.

Sleep VAS

At Week 24, the difference in Sleep VAS score was statistically significant compared to placebo and showed a clinically meaningful difference from baseline for the sarilumab 150 mg q2w group (nominal p-value =0.0008). For sarilumab 200mg q2w group, the change from baseline in Sleep VAS score was clinically meaningful (nominal p-value =0.0006), but statistical significance is not claimed due to a break in the hierarchy.

At Week 52, both sarilumab treatment groups demonstrated clinically meaningful improvements from baseline in the Sleep VAS scores (nominal p-values =0.0059 and 0.0036, respectively), but statistical significance is not claimed due to a break in the hierarchy.

Work productivity activity impairment

About 25% of the efficacy population (90 of 398 placebo patients, 90 of 400 sarilumab 150 mg q2w patients, and 85 of 399 sarilumab 200 mg q2w patients) were working. At baseline, all 4 WPAI percentage scores were comparable among the treatment groups Work productivity activity impairment domain scores at Week 12. At Week 12, both sarilumab groups showed less overall work impairment due to RA compared with placebo. The difference in WPAI percentage of overall work impairment was statistically significant between the sarilumab 150 mg q2w and placebo groups (p =0.0127). The difference in WPAI percentage of overall work impairment was not statistically significant between the sarilumab 200 mg q2w group and the placebo group (nominal p-value =0.0631).

The difference in WPAI percentage work time missed (Absenteeism) at Week 12 did not improve for the sarilumab 150 mg q2w and sarilumab 200 mg q2w groups (nominal p-values =0.4596 and 0.1798, respectively). The difference in WPAI percentage of impairment while working (Presenteeism) improved at Week 12 for the sarilumab 150 mg q2w and sarilumab 200 mg q2w groups (nominal p-values =0.0028 and 0.0139, respectively). The difference between each sarilumab group the placebo group in WPAI percentage of activity impairment improved at Week 12 (nominal p-values <0.0001)

Work productivity activity impairment domain scores at Week 52

At Week 52, the difference in WPAI percentage of overall work impairment was not statistically significant for both the sarilumab 150 mg q2w and sarilumab 200 mg q2w groups (nominal p-values =0.3156 and 0.0679, respectively).

The difference in WPAI percentage work time missed (absenteeism) did not improve for the sarilumab 150 mg q2w and sarilumab 200 mg q2w groups (nominal p-values of 0.7409 and 0.6042, respectively). The difference in WPAI percentage impairment while working (presenteeism) between the sarilumab 150 mg q2w group and the placebo group did not improve (nominal p-value =0.2429). The difference in WPAI percentage of impairment while working (presenteeism) between the sarilumab 200 mg q2w group and the placebo group improved (nominal p-value =0.0114). The differences in WPAI percentage of activity impairment improved for both the sarilumab 150 mg q2w group and sarilumab 200 mg q2w group (nominal p-values =0.0002 and <0.0001, respectively).

Subgroup analyses

ACR20

An analysis of the proportion of patients achieving an ACR20 response was also conducted for subgroups based on gender, race, region, age group, baseline weight, BMI, prior biologic use, RF, anti-CCP antibody, baseline CRP, duration of RA, number of prior DMARDs, and smoking history.

The subgroup interaction analysis for the anti-CCP antibody subgroup (anti-CCP antibody positive versus negative patients) showed a lower ACR20 response in anti-CCP antibody negative patients than in anti-CCP positive patients (nominal p-value=0.001). No evidence of interaction was observed for other subgroups (nominal p-values >0.05).

HAQ-DI:

The subgroup interaction analyses for the anti-CCP antibody and RF subgroups (anti-CCP antibody positive versus negative and RF positive versus negative patients) showed a lower HAQ-DI response in anti-CCP antibody negative patients and in RF negative patients (nominal p-value =0.0028 and nominal p-value =0.0417, respectively). No evidence of interaction was observed for other subgroups (nominal p-values >0.05).

mTSS:

The subgroup interaction analysis for the smoking history subgroup (self-reported positive smoking history, current or former, versus negative smoking history) indicated an increase in progression in patients with a history of smoking (nominal p-value =0.0386). No evidence of (electronic 5.0) interaction was observed for other subgroups (nominal p-values >0.05).

Ancillary analyses

Immunogenicity

The incidence of patients with any positive ADA assay result during the TEAE period (ie, having at least 1 sample positive in the ADA assay during the study) was 5.9% in placebo, 22.6% in 150 mg q2w, and 16.0% in 200 mg q2w.

The incidence of positive ADA assay results during the treatment period (ie, ADA negative at baseline and became ADA positive on treatment or ADA positive at baseline with at least a 4-fold increase in ADA titer on treatment) was 4.2% in the placebo group, 19.8% in the sarilumab 150 mg q2w group, and 14.6% in the sarilumab 200 mg q2w group.

The incidence of neutralizing antibodies was 0.2% in the placebo group, 3.5% in the sarilumab 150 mg q2w group, and 2.4% in the sarilumab 200 mg q2w group.

A persistent positive ADA assay result (ie, at least 2 consecutive post-baseline samples were positive or the last post-baseline sample collected was positive) was observed in 2.3% of patients in the placebo group, 7.9% of patients in the sarilumab 150 mg q2w group, and 6.1% of patients in the sarilumab 200 mg q2w group. A transient result (ie, any treatment-emergent positive ADA assay result that was not considered persistent) was observed in 1.9% of placebo patients, 11.9% of patients in the sarilumab 150mg q2w group, and 8.5% of patients in the sarilumab 200 mg q2w group.

Patients were grouped by ADA status (positive or negative), regardless of sarilumab treatment group, for assessment of lack or loss of efficacy and treatment-emergent hypersensitivity. Lack of efficacy was defined as permanent discontinuation of IMP due to lack of efficacy or switching to open-label rescue treatment. Loss of efficacy was defined as permanent discontinuation of IMP or switching to open-label rescue treatment after achieving an ACR50 or good EULAR response.

The incidence of lack of efficacy was 14.8% and 16.3% and loss of efficacy was 3.8% and 6.8% in ADA negative and ADA positive patients, respectively. The incidence of hypersensitivity, both local and systemic reactions, was 7.5% in ADA negative patients and 6.1% in ADA positive patients. The incidences in the placebo group were 40.7% for lack of efficacy, 4.0% for loss of efficacy, and 4.7% for hypersensitivity.

A randomized, double-blind, parallel, placebo-controlled study assessing the efficacy and safety of sarilumab added to non-biologic DMARD therapy in patients with rheumatoid arthritis (RA) who are inadequate responders to or intolerant of TNF-α antagonists (EFC 10832)

Methods

Study Participants

Study participants

Inclusion criteria:

1. Diagnosis of RA ≥ 6 months duration, according to the American College of Rheumatology (ACR)/ EULAR 2010 RA Classification Criteria

2. ACR Class I-III functional status, based on 1991 revised criteria

3. Anti-TNF-α therapy failures, defined as patients with an inadequate clinical response defined by the investigator, after being treated for at least 3 consecutive months, and/or intolerance to at least 1 anti-TNF-α blocker(s), resulting in or requiring their discontinuation

   - TNF-α-blockers may include, but are not limited to: etanercept, infliximab, adalimumab, golimumab and/or certolizumab

4. Moderate-to-severely active RA, defined as:

- at least 8 of 68 tender joints and 6 of 66 swollen joints at screening and baseline visits and

- Hypersensitive CRP (hs-CRP) ≥ 8 mg/L at screening

5. Continuous treatment with 1 or a combination of non-biologic DMARDs (except for simultaneous combination use of LEF and MTX) for at least 12 consecutive weeks prior to randomization and on a stable dose(s) for at least 6 consecutive weeks prior to screening:

- Methotrexate – 10 to 25 mg/week PO or intra muscular (or per local labeling requirements for the treatment of RA if the dose range differs)

- Leflunomide – 10 to 20 mg PO daily

- Sulfasalazine – 1000 to 3000 mg PO daily

- Hydroxychloroquine – 200 to 400 mg PO daily

Exclusion criteria (shortened by assessor):

1. Treatment with anti-TNF-α agents, as follows:

- Etanercept: within 28 days prior to randomization

- Infliximab, adalimumab, golimumab, certolizumab pegol: within 42 days prior to randomization

2. Treatment with previous RA-directed biologic agents with other than TNF-α antagonist mechanisms:

- Anakinra: within 28 days prior to randomization

- Abatacept: within 42 days prior to randomization

- Rituximab or other cell depleting agent: Within 6 months prior to randomization or until total lymphocyte count and CD-19+ lymphocyte count are normalized, whichever is longer

3. Prior treatment with anti-IL-6 or IL-6R antagonist therapies, including tocilizumab or sarilumab, participation in a prior study of sarilumab, irrespective of treatment arm Patients with any of the following laboratory abnormalities at the screening visit (identified by the central laboratory):

- Hemoglobin <8.5 g/dL

- White blood cells <3000/mm3

- Neutrophils <2000/mm3

- Platelet count <150 000 cells/mm3

- AST or ALT >1.5 X ULN

- Bilirubin (total) >ULN, unless Gilbert's disease has been determined by genetic testing and has been documented

4. Presence of severe uncontrolled hypercholesterolemia (>350 mg/dL, 9.1 mmol/L) or hypertriglyceridemia (>500 mg/dL, 5.6 mmol/L) at screening or baseline.

Treatments

Dose regimen: sarilumab 150 mg or sarilumab 200 mg or placebo q2w.

Route(s) of administration: subcutaneous (SC) in the abdomen, or thigh, or upper arm.

All patients continued to receive regular treatment with one or a combination of the non-biologic DMARDs, MTX, SSZ, LEF, and HCQ which should have been started at least 12 weeks prior to baseline and patients should have been on a stable dose(s) for at least 6 weeks prior to screening and during the study treatment period.However, at any time, the DMARD dose could be reduced for a safety or tolerability reason, and the dose was not to be increased any time during the study.

Non-investigational medicinal products (eg, DMARDs) were dispensed according to the local practice. All patients taking MTX received folic/folinic acid according to local recommendation in the country where the study was conducted.

Background medication as monotherapy or in combination, oral or parenteral, included:

• Methotrexate (MTX) – 10 to 25 mg/wk (or per local labeling requirements if the dose range differs)

• Folic/folinic acid per country guidelines

• Leflunomide (LEF) – 10 to 20 mg daily

• Sulfasalazine (SSZ) – 1000 to 3000 mg daily

• Hydroxychloroquine (HCQ) - 200 to 400 mg daily

Objectives

Primary objectives

To demonstrate that sarilumab added to non-biologic DMARDs is effective in reducing the signs and symptoms at Week 24 and improving physical function at Week 12 in patients with active RA who are inadequate responders to or intolerant of TNF-α antagonists.

Secondary objectives

To demonstrate that sarilumab added to non-biologic DMARD therapy in patients with active RA who are inadequate responders or intolerant to TNF-α antagonists, is effective in the:

• reduction of signs and symptoms at Week 12

• improvement in physical function at Week 24

• improvement of disease activity score at Weeks 12 and 24, and

• improvement of quality of life as measured by patient reported outcomes (PROs) at intermediate visits and at Week 24

To assess the exposure to sarilumab added to non-biologic DMARD therapy in this population.

To assess the safety of sarilumab in this population.

Exploratory objectives

To collect DNA, RNA, and other biomarkers for future use for the purpose of discovery of predictive biomarker.

Outcomes / endpoints

The co-primary endpoints in the study were the ACR20 response rate at Week 24 and the change from baseline in HAQ-DI at Week 12.

Secondary efficacy variables

• ACR20/50/70 at Week 12 and ACR50/70 at Week 24

• ACR-N at Week 12 and Week 24

• Change from baseline in the ACR components at Weeks 12 and 24

• Disease activity score (DAS28)/EULAR Response at Week 12 and Week 24

• DAS28 -CRP <2.6 (“remission”) at Week 12 and Week 24

• EULAR Response at Week 12 and Week 24

• ACR/EULAR Remission (Boolean-based) at Week 12 and Week 24

• Simplified disease activity index/clinical disease activity index

Patient reported outcomes (PRO) were also recorded (Short-Form-36, EQ-5D-3L, functional assessment of chronic illness therapy fatigue scale, morning stiffness visual analogue scale, rheumatoid arthritis-work productivity survey, and rheumatoid arthritis impact of disease).

Sample size

From the tocilizumab program changes of -0.05 and -0.35 in the placebo and sarilumab groups, respectively as well as a common standard deviation (SD) of 0.79 were anticipated for the initial primary endpoint change from baseline in HAQ-DI at week 24. Applying a 2 group t-test, alpha = 0.025 (2-sided, to account for comparing 2 active groups to placebo) 174 patients per treatment group (i.e. 522 patients in total) were to be randomized in order to achieve 90% power.

With amendment 3 the timing of the HAQ primary endpoint was changed from 24 weeks to 12 weeks. Under the following assumptions for HAQ-DI at week 12 (as seen in study EFC11072 part B) SD = 0.52 and treatment difference to placebo equals 0.2 (low dose) and 0.28 (high dose) respectively, with 174 subjects per group, the power for HAQ-DI at week 12 was calculated to 90% for the low dose group and >90% for the high dose group.

With 174 patients per group, ACR20 week 24 response rates of 20% (placebo) and 50% (active treatment) respectively and a type I error of 0.025 (2-sided), a $\chi 2$ test comparing each active treatment to placebo has about 99% power.

Randomisation

Subjects were randomized at a ratio of 1:1:1 (sarilumab 150 mg q2w: sarilumab 200 mg q2w: placebo q2w). Randomization was stratified by region and number of previous anti-TNFs (1 versus >1). Permuted block randomisation (block length: 6) was applied.

Blinding (masking)

Double blind.

Statistical methods

In general data were summarized by statistical characteristics (continuous data: n, mean, SD, median, minimum, and maximum; qualitative data: absolute and relative frequencies) stratified by treatment and visit (if applicable).

The primary efficacy analysis population was the intent-to-treat (ITT) population consisting of all randomized patients.

ACR20 response rate at week 24 was analyzed by means of a Cochran-Mantel-Haenszel (CMH) test stratified by number of previous anti-TNFs (1 versus >1) and region. Each dose group of sarilumab was compared to placebo separately. In the primary analysis patients with missing ACR20 at week 24 information for any reason including patients who dropped out or required rescue medication (rescue medication permitted from week 12 on) were considered non-responders. In a sensitivity analysis responder status following treatment discontinuation or rescue was determined using LOCF to impute missing data (patients with insufficient information were considered non-responders).

Change from baseline in HAQ-DI at week 12, was analyzed using a MMRM approach assuming an unstructured covariance structure to model the within-subject errors. The model included treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects and baseline as a covariate. The difference between each active treatment group versus placebo in the change from baseline in HAQ-DI at week 12 was tested. For the primary analysis data collected after treatment discontinuation or rescue were set to missing. Two sensitivity analyses were performed. The first sensitivity analysis applied an LOCF procedure to impute missing HAQ-DI values beyond the time of treatment discontinuation or initiation of rescue medication. The second sensitivity analysis of the HAQ-DI at Week 12 used multiple imputations for handling missing data.

Subgroup analyses were conducted for ACR20 as well as change from baseline in HAQ-DI with respect to subgroups defined by gender, race, region, age, baseline weight, BMI, number of previous anti-TNF-α, rheumatoid factor, anti-CCP antibody, baseline CRP, duration of RA, number of prior DMARDs, background DMARDs use, and smoking history. For each subgroup and each active dose group the MH estimate of the odds ratio vs. placebo and the corresponding 95% CI were calculated.

Treatment effects were described by point estimates and the corresponding 95%-CI derived from the analyses models mentioned above.

Binary secondary efficacy variables were analyzed using the same approach as for ACR20 at week 24. Continuous secondary endpoints were analysed using the same method used to analyse HAQ-DI.

The study was declared successful if any dose regimen achieved statistical significance in ACR20. A hierarchical testing procedure was used for the multiple endpoints at $\alpha=0.025$ for each dose regimen separately. The hierarchy was:

- Incidence of ACR20 response at Week 24
- Change from baseline in HAQ-DI at Week 12.

For secondary efficacy endpoints, each selected dose regimen was tested versus placebo at the 0.025 level in a pre-specified hierarchical order.

Results

Participant flow

Of the 1224 patients that were screened, 678 patients were screen failures (55.4%) and 1 patient was not randomized but treated (this patient was treated mistakenly with one dose of sarilumab 200 mg by the study staff during the screening period and no associated adverse event was reported).

Screen failures were mainly due to failure to meet the inclusion criterion for the severity of the disease (53%) or not having high sensitivity C-reactive protein (CRP) above or equal to 8 mg/L, or were excluded due to tuberculosis (21%).

A total of 546 patients were randomized and treated. These patients represent the ITT/efficacy population and the safety population.

Figure 6: Disposition diagram

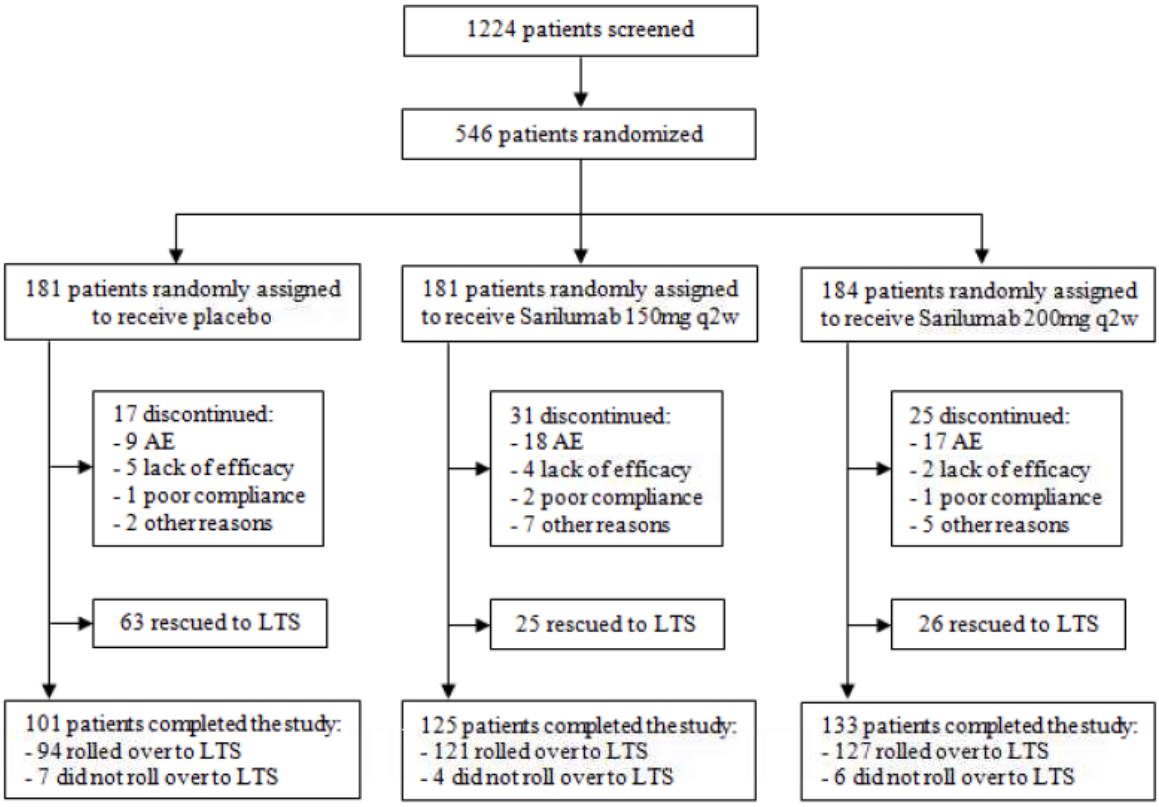


Table 27 provides details of overall patient disposition, with details of all patients who withdrew from the study after enrollment, together with the specific reasons for discontinuation, and the duration of treatment before discontinuation. All “other” reasons for withdrawals were reviewed and were mostly due to withdrawal of consent and were not related to safety or lack of efficacy.

Table 27: Patients disposition - Randomized population

	Placebo + DMARD (N=181)	Sarilumab 150mg q2w + DMARD (N=181)	Sarilumab 200mg q2w + DMARD (N=184)	All (N=546)
Randomized and not treated	0	0	0	0
Randomized and treated	181 (100%)	181 (100%)	184 (100%)	546 (100%)
Completed the study treatment period	101 (55.8%)	125 (69.1%)	133 (72.3%)	359 (65.8%)
Rolled over to LTS	94 (51.9%)	121 (66.9%)	127 (69.0%)	342 (62.6%)
Did not roll over to LTS	7 (3.9%)	4 (2.2%)	6 (3.3%)	17 (3.1%)
Rescued due to lack of efficacy and entered LTS	63 (34.8%)	25 (13.8%)	26 (14.1%)	114 (20.9%)
Discontinued from the study (not entering LTS)	17 (9.4%)	31 (17.1%)	25 (13.6%)	73 (13.4%)
Subject's request for treatment discontinuation	9 (5.0%)	11 (6.1%)	9 (4.9%)	29 (5.3%)
Reason for treatment discontinuation				
Adverse event	9 (5.0%)	18 (9.9%)	17 (9.2%)	44 (8.1%)
Lack of efficacy	5 (2.8%)	4 (2.2%)	2 (1.1%)	11 (2.0%)
Poor compliance to protocol	1 (0.6%)	2 (1.1%)	1 (0.5%)	4 (0.7%)
Other reasons	2 (1.1%)	7 (3.9%)	5 (2.7%)	14 (2.6%)
Status at last study contact				
Alive	180 (99.4%)	181 (100%)	184 (100%)	545 (99.8%)
Dead	1 (0.6%)	0	0	1 (0.2%)

Note: Percentages are calculated using the number of patients randomized as denominator.

Subject's request for treatment discontinuation is a separate category and is not additive with the reasons for discontinuation

Recruitment

Date first patient enrolled: 29 October 2012, date last patient completed: 23 March 2015.

Conduct of the study

There were 3 amendments to the protocol, of which 1 was introduced before the inclusion of any patients. The changes introduced by the first amendment were applied to all patients (the first patient was screened on 29 October 2012).Following changes were made:

Amendment 1:

To implement new safety measures to prevent the administration of sarilumab to patients at risk for development of severe thrombocytopenia (< 100,000/mm3) and grade 3/grade 4 neutropenia (based on NCI CTCAE).

• To remove the open-label rescue therapy arm within this study (EFC10832) and give patient qualifying for rescue therapy the opportunity to directly enroll into the parallel ongoing long-term safety study (LTS11210).

To replace the partial EQ-5D-3L (EuroQol) instrument with the original complete instrument.

To clarify instructions that for any occurrence of a serious adverse event (SAE) and for any occurrence of an adverse event of special interest (AESI).

Amendment 2:

• To update Section 8.8.4 relating to treatment for dyslipidemia.

• To remove text related to description of an open treatment arm with sarilumab.

• To update text related to handling of patient for temporary and permanent treatment .discontinuation.

• To update safety reporting instructions.

Amendment 3:

• To modify the analyses for the co-primary endpoint. (HAQ-DI).

• To remove references to the bioanalytical assay and related analyses.

• To clarify safety instructions related to the management of alanine aminotransferase (ALT) elevations.

Baseline data

Table 28: Demographic and patient characteristics at baseline – Randomized population

		Sarilumab		
	Placebo + DMARD (N=181)	150mg q2w + DMARD (N=181)	200mg q2w + DMARD (N=184)	All (N=546)
Age (years)				
Number	181	181	184	546
Mean (SD)	51.9 (12.4)	54.0 (11.7)	52.9 (12.9)	52.9 (12.4)
Median	53.0	54.0	54.0	54.0
Min : Max	24 : 79	23 : 88	19 : 87	19 : 88
Age Group (years) [n (%)]				
Number	181	181	184	546
<65	152 (84.0%)	150 (82.9%)	154 (83.7%)	456 (83.5%)
≥65 and <75	26 (14.4%)	24 (13.3%)	21 (11.4%)	71 (13.0%)
≥75	3 (1.7%)	7 (3.9%)	9 (4.9%)	19 (3.5%)

Note: Number = Number of patients assessed.
Region 1 (Western countries): Australia, Canada, Czech Republic, Germany, Greece, Hungary, Israel, Italy, New Zealand, Portugal, Spain, USA
Region 2 (South American): Argentina, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Peru.
Region 3 (Rest of the world): South Korea, Lithuania, Poland, Russia,Taiwan, Turkey, Ukraine.
Percentages are calculated using number of patients assessed as denominator.
[a]Alcohol habits: how often subject has a drink containing alcohol in the last 12 month.

		Sarilumab		
	Placebo + DMARD (N=181)	150mg q2w + DMARD (N=181)	200mg q2w + DMARD (N=184)	All (N=546)
Sex [n (%)]				
Number	181	181	184	546
Male	27 (14.9%)	39 (21.5%)	33 (17.9%)	99 (18.1%)
Female	154 (85.1%)	142 (78.5%)	151 (82.1%)	447 (81.9%)
Race [n (%)]				
Number	181	181	184	546
Caucasian/White	124 (68.5%)	134 (74.0%)	130 (70.7%)	388 (71.1%)
Black	7 (3.9%)	8 (4.4%)	5 (2.7%)	20 (3.7%)
Asian/Oriental	1 (0.6%)	3 (1.7%)	1 (0.5%)	5 (0.9%)
Other	49 (27.1%)	36 (19.9%)	48 (26.1%)	133 (24.4%)

Note: Number = Number of patients assessed.
Region 1 (Western countries): Australia, Canada, Czech Republic, Germany, Greece, Hungary, Israel, Italy, New Zealand, Portugal, Spain, USA
Region 2 (South American): Argentina, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Peru.
Region 3 (Rest of the world): South Korea, Lithuania, Poland, Russia,Taiwan, Turkey, Ukraine.
Percentages are calculated using number of patients assessed as denominator.
[a]Alcohol habits: how often subject has a drink containing alcohol in the last 12 month.

	Placebo + DMARD (N=181)	Sarilumab 150mg q2w + DMARD (N=181)	Sarilumab 200mg q2w + DMARD (N=184)	All (N=546)
Ethnicity [n (%)]				
Number	181	181	184	546
Hispanic	77 (42.5%)	77 (42.5%)	88 (47.8%)	242 (44.3%)
Not Hispanic	104 (57.5%)	104 (57.5%)	96 (52.2%)	304 (55.7%)
Weight (kg)				
Number	181	181	184	546
Mean (SD)	79.41 (21.30)	78.59 (22.04)	76.68 (21.25)	78.22 (21.52)
Median	76.00	74.00	73.25	74.25
Min : Max	44.5 : 149.6	39.7 : 183.2	46.3 : 146.3	39.7 : 183.2

	Placebo + DMARD (N=181)	Sarilumab 150mg q2w + DMARD (N=181)	Sarilumab 200mg q2w + DMARD (N=184)	All (N=546)
Weight group(kg) [n (%)]				
Number	181	181	184	546
<60	36 (19.9%)	29 (16.0%)	45 (24.5%)	110 (20.1%)
≥60 and <100	112 (61.9%)	132 (72.9%)	109 (59.2%)	353 (64.7%)
≥100	33 (18.2%)	20 (11.0%)	30 (16.3%)	83 (15.2%)
Body mass index (BMI)(kg/m^2)				
Number	181	181	184	546
Mean (SD)	30.24 (7.78)	29.14 (6.92)	29.21 (6.75)	29.53 (7.17)
Median	28.37	28.26	28.02	28.18
Min : Max	18.4 : 58.3	16.3 : 63.4	18.8 : 51.8	16.3 : 63.4

Table 29: Disease characteristics at baseline – Randomized population

	Placebo + DMARD (N=181)	Sarilumab 150mg q2w + DMARD (N=181)	Sarilumab 200mg q2w + DMARD (N=184)	All (N=546)
Duration of RA since diagnosis (Years)				
Number	181	181	184	546
Mean (SD)	12.04 (9.99)	11.55 (8.55)	12.68 (9.63)	12.09 (9.40)
Median	9.53	10.20	10.34	9.90
Min : Max	0.6 : 54.0	0.7 : 45.6	0.6 : 46.2	0.6 : 54.0
RA functional class [n(%)]				
Number	181	181	184	546
I	13 (7.2%)	20 (11.0%)	19 (10.3%)	52 (9.5%)
II	110 (60.8%)	100 (55.2%)	105 (57.1%)	315 (57.7%)
III	58 (32.0%)	61 (33.7%)	60 (32.6%)	179 (32.8%)
IV	0	0	0	0
Rheumatoid factor [n(%)]				
Number	180	181	181	542
Positive	142 (78.9%)	135 (74.6%)	132 (72.9%)	409 (75.5%)
Negative	38 (21.1%)	46 (25.4%)	49 (27.1%)	133 (24.5%)

	Placebo + DMARD (N=181)	Sarilumab 150mg q2w + DMARD (N=181)	Sarilumab 200mg q2w + DMARD (N=184)	All (N=546)
Anti CCP antibody [n(%)]				
Number	180	180	180	540
Positive	150 (83.3%)	135 (75.0%)	137 (76.1%)	422 (78.1%)
Negative	30 (16.7%)	45 (25.0%)	43 (23.9%)	118 (21.9%)
Number of non-biological DMARDs [n(%)]				
Number	181	181	184	546
None	0	0	0	0
1	98 (54.1%)	93 (51.4%)	101 (54.9%)	292 (53.5%)
2	50 (27.6%)	50 (27.6%)	50 (27.2%)	150 (27.5%)
≥3	33 (18.2%)	38 (21.0%)	33 (17.9%)	104 (19.0%)
Number of Previous Anti-TNFs [n(%)]				
Number	181	180	183	544
1	135 (74.6%)	143 (79.4%)	140 (76.5%)	418 (76.8%)
>1	46 (25.4%)	37 (20.6%)	43 (23.5%)	126 (23.2%)

	Placebo + DMARD (N=181)	Sarilumab 150mg q2w + DMARD (N=181)	Sarilumab 200mg q2w + DMARD (N=184)	All (N=546)
Tender joint count (0-68)				
Number	181	181	184	546
Mean (SD)	29.42 (14.54)	27.66 (15.57)	29.55 (15.54)	28.88 (15.22)
Median	29.00	24.00	26.50	26.00
Min : Max	8.0 : 68.0	5.0 : 68.0	4.0 : 68.0	4.0 : 68.0
Swollen joint count (0-66)				
Number	181	181	184	546
Mean (SD)	20.21 (11.34)	19.60 (11.23)	19.97 (11.94)	19.93 (11.49)
Median	17.00	16.00	17.00	17.00
Min : Max	6.0 : 60.0	6.0 : 66.0	3.0 : 62.0	3.0 : 66.0
CRP (mg/L)				
Number	181	181	184	546
Mean (SD)	26.02 (25.20)	23.60 (23.44)	30.77 (28.35)	26.82 (25.89)
Median	17.00	16.80	21.70	17.75
Min : Max	1.2 : 147.0	0.2 : 148.0	0.3 : 142.0	0.2 : 148.0

	Placebo + DMARD (N=181)	Sarilumab 150mg q2w + DMARD (N=181)	Sarilumab 200mg q2w + DMARD (N=184)	All (N=546)
CRP group (≤15 mg/L, > 15 mg/L) [n(%)]				
Number	181	181	184	546
≤15 mg/L	82 (45.3%)	83 (45.9%)	68 (37.0%)	233 (42.7%)
> 15 mg/L	99 (54.7%)	98 (54.1%)	116 (63.0%)	313 (57.3%)
HAQ-DI (0-3)				
Number	181	181	184	546
Mean (SD)	1.80 (0.64)	1.72 (0.62)	1.82 (0.62)	1.78 (0.63)
Median	1.88	1.75	1.88	1.88
Min : Max	0.0 : 2.9	0.0 : 3.0	0.0 : 3.0	0.0 : 3.0
DAS28-CRP				
Number	181	181	184	546
Mean (SD)	6.23 (0.86)	6.09 (0.90)	6.29 (0.98)	6.20 (0.91)
Median	6.14	6.13	6.27	6.17
Min : Max	4.4 : 8.1	3.3 : 8.0	3.9 : 8.3	3.3 : 8.3

Numbers analysed

Of the 1224 patients that were screened, 678 patients were screen failures (55.4%) and 1 patient was not randomized but treated (this patient was treated mistakenly with one dose of sarilumab 200 mg by the study staff during the screening period and no associated adverse event was reported).

Screen failures were mainly due to failure to meet the inclusion criterion for the severity of the disease (53%) or not having high sensitivity C-reactive protein (CRP) above or equal to 8 mg/L, or were excluded due to tuberculosis (21%).

A total of 546 patients were randomized and treated. These patients represent the ITT/efficacy population and the safety population.

Table 30: Patients disposition

	Placebo + DMARD (N=181)	Sarilumab 150mg q2w + DMARD (N=181)	Sarilumab 200mg q2w + DMARD (N=184)	All (N=546)
Randomized and not treated	0	0	0	0
Randomized and treated	181 (100%)	181 (100%)	184 (100%)	546 (100%)
Completed the study treatment period	101 (55.8%)	125 (69.1%)	133 (72.3%)	359 (65.8%)
Rolled over to LTS	94 (51.9%)	121 (66.9%)	127 (69.0%)	342 (62.6%)
Did not roll over to LTS	7 (3.9%)	4 (2.2%)	6 (3.3%)	17 (3.1%)
Rescued due to lack of efficacy and entered LTS	63 (34.8%)	25 (13.8%)	26 (14.1%)	114 (20.9%)
Discontinued from the study (not entering LTS)	17 (9.4%)	31 (17.1%)	25 (13.6%)	73 (13.4%)
Subject's request for treatment discontinuation	9 (5.0%)	11 (6.1%)	9 (4.9%)	29 (5.3%)
Reason for treatment discontinuation				
Adverse event	9 (5.0%)	18 (9.9%)	17 (9.2%)	44 (8.1%)
Lack of efficacy	5 (2.8%)	4 (2.2%)	2 (1.1%)	11 (2.0%)
Poor compliance to protocol	1 (0.6%)	2 (1.1%)	1 (0.5%)	4 (0.7%)
Other reasons	2 (1.1%)	7 (3.9%)	5 (2.7%)	14 (2.6%)
Status at last study contact				
Alive	180 (99.4%)	181 (100%)	184 (100%)	545 (99.8%)
Dead	1 (0.6%)	0	0	1 (0.2%)

Note: Percentages are calculated using the number of patients randomized as denominator.

Subject's request for treatment discontinuation is a separate category and is not additive with the reasons for discontinuation.

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There were approximately 30% dropouts/rescued patients at week 24.

Outcomes and estimation

ACR20

Table 31: Incidence of ACR20 response at week 24 – ITT population

ACR20 at Week 24 n(%)	Placebo + DMARD (N=181)	Sarilumab 150mg q2w + DMARD (N=181)	Sarilumab 200mg q2w + DMARD (N=184)
Responders	61 (33.7%)	101 (55.8%)	112 (60.9%)
Non-responders	120 (66.3%)	80 (44.2%)	72 (39.1%)
P-value vs placebo[a]	-	<0.0001	<0.0001
OR, CI vs placebo[b]	-	2.711 (1.730, 4.247)	3.284 (2.108, 5.115)

OR: Odds ratio.

ACR20 response = at least 20% improvement from baseline in both TJC and SJC, and in at least three of the HAQ score, CRP and three VAS assessments.

Patients are considered non-responders from the time they started rescue medication or discontinued study medication.

Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.

[a] CMH test stratified by number of previous anti-TNFs and region. [b] Mantel-Haenszel estimate.

HAQ-DI

Table 32: Change from baseline in HAQ-DI at week 12 – ITT population

		Sarilumab	
	Placebo + DMARD (N=181)	150mg q2w + DMARD (N=181)	200mg q2w + DMARD (N=184)
HAQ-DI (0-3)			
Number	170	165	171
Baseline Mean (SD)	1.78 (0.64)	1.73 (0.62)	1.82 (0.62)
Week12 Mean (SD)	1.49 (0.73)	1.23 (0.70)	1.33 (0.69)
Change Mean (SD)	-0.29 (0.54)	-0.50 (0.64)	-0.49 (0.56)
LS mean (SE)	-0.26 (0.043)	-0.46 (0.044)	-0.47 (0.043)
LS mean diff, 95% CI	-	-0.202 (-0.318,-0.086)	-0.210 (-0.325,-0.095)
P-value vs placebo[a]	-	0.0007	0.0004

All assessments are set to missing from the time a patient receives rescue medication or discontinues study medication early.
Missing HAQ-DI measurements are not imputed.
Note: Number = Number of patients with assessment at both baseline and Week 12.
[a] Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, number of previous anti-TNFs, region, visit, and treatment-by-visit interaction.

Proportion of HAQ-DI responder

For the analysis of clinically meaningful HAQ-DI response, 2 different definitions were used:

≥ 0.3 and ≥ 0.22 units of improvement in the change from baseline. At Week 12, there was no difference between the 2 sarilumab dose groups and placebo for the definition using an improvement of ≥ 0.22 units, which may be explained by the regional differences.

Using an improvement of ≥ 0.3 units as the definition, however both sarilumab doses were numerically higher compared to placebo (51.1% for the sarilumab 200 mg q2w group, 47.0% for the sarilumab 150 mg q2w group and 35.9% for the placebo group). The nominal p-values were 0.0025 and 0.0297, respectively.

At Week 24, and for an improvement of ≥ 0.22 units, the proportion of patients who were HAQ-D responders was higher in both of the sarilumab treated groups (150 mg q2w group [47.5%] and 200 mg q2w group [56.0%]) than in the placebo group (35.4%) (nominal p-values=0.0137 for 150 mg q2w and p<0.0001 for 200 mg q2w group).

At Week 24, and for an improvement of ≥ 0.3 units, the proportion of patients who were HAQ-DI responders was higher in both of the sarilumab treated groups (150 mg q2w group [43.1%] and 200 mg q2w group [47.3%]) than in the placebo group (31.5%) (nominal p-values=0.0165 for 150 mg q2w and p=0.0014 for 200 mg q2w group).

Secondary analyses of ACR20 and HAQ-DI

Sensitivity analysis

Sensitivity analysis of the incidence of ACR20 response at Week 24 used the LOCF method for handling missing data are presented in table 37. These results were similar to those of the primary analysis and the proportion of patients achieving an ACR 20 response at Week 24 was significantly higher in patients treated with sarilumab than in patients treated with placebo.

Table 33: Incidence of ACR20 response at week 34 (sensitivity) – ITTpopulation

ACR20 at Week 24 n(%)	Placebo + DMARD (N=181)	Sarilumab 150mg q2w + DMARD (N=181)	Sarilumab 200mg q2w + DMARD (N=184)
Responders	67 (37.0%)	109 (60.2%)	123 (66.8%)
Non-responders	114 (63.0%)	72 (39.8%)	61 (33.2%)
P-value vs placebo[a]	-	<0.0001	<0.0001
OR, CI vs placebo[b]	-	2.835 (1.809, 4.443)	3.720 (2.378, 5.819)

OR: Odds ratio.

ACR20 response = at least 20% improvement from baseline in both TJC and SJC, and in at least three of the HAQ score, CRP and three VAS assessments.

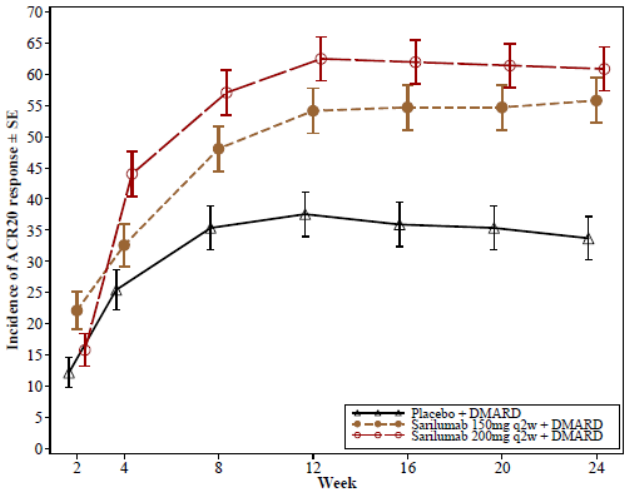
LOCF used for all seven ACR components. All assessments are set to missing from the time a patient receives rescue medication or discontinues study medication early. Only pre-rescue/pre-discontinuation scores are carried forward.

Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.

Response over time

The ACR20 response rate increased at each visit from Week 2 through Week 12 for the sarilumab treatment groups. The response rate was maintained up to Week 24. The placebo effect increased for the first 8 weeks and reached a plateau until Week 24.

Figure 7: Incidence of ACR20 response at each visit – ITT population



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OUT=REPORT/OUTPUT/eff_resp_acr20_byvis_i_g_i.rtf (19MAY2015 - 7:42)

Secondary efficacy endpoints

Each selected dose regimen was tested versus placebo at 0.025 level (simple Bonferroni adjustment) on the hierarchical order for the primary and secondary efficacy endpoints shown in Table 38. The results that are in bold font are statistically significant according to the procedure of analysis. The last statistically significant endpoint in the testing hierarchy was the PCS of SF-36 at Week 24 for both sarilumab dose groups. Significance is not claimed for those parameters lower in the testing hierarchy; ie, for the MCS of SF-36, FACIT-Fatigue, Morning Stiffness, WPS-RA, RAID, and EQ-5D-3L.

Week 24 is presented prior to Week 12 for these endpoints as it was the week included in the hierarchy.

Table 34: Hierarchical order for the secondary efficacy endpoints

	Placebo + MTX (N = 181)	Sarilumab 150mg q2w + DMARD (N = 181)		Sarilumab 200mg q2w + DMARD (N = 184)	
Parameter[a]		Estimate[b]	P-value[c]	Estimate[b]	P-value[c]
Primary endpoints					
ACR20 – Week 24	61(33.7%)	101(55.8%)	**< 0.0001**	112(60.9%)	**< 0.0001**
HAQ-DI – Week 12	-0.26(0.043)	-0.46(0.04)	**0.0007**	-0.47(0.043)	**0.0004**
Secondary endpoints					
DAS28-CRP – Week 24	-1.38(0.119)	-2.35(0.111)	**< 0.0001**	-2.82(0.108)	**< 0.0001**
ACR50 – Week 24	33 (18.2%)	67 (37.0%)	**< 0.0001**	75 (40.8%)	**< 0.0001**
ACR70 – Week 24	13 (7.2%)	36 (19.9%)	**0.0002**	30 (16.3%)	**0.0056**
DAS28-CRP<2.6 – Week 24	13 (7.2%)	45 (24.9%)	**< 0.0001**	53 (28.8%)	**< 0.0001**
CDAI – Week 24	-16.35(1.195)	-23.65(1.136)	**< 0.0001**	-26.08(1.109)	**< 0.0001**
HAQ-DI – Week 24	-0.34(0.051)	-0.52(0.049)	**0.0078**	-0.58(0.048)	**0.0004**
SF-36 Physical – Week 24	4.40(0.692)	7.65(0.653)	**0.0004**	8.48(0.630)	**< 0.0001**
SF-36 Mental – Week 24	4.74(0.902)	6.26(0.848)	0.2026	6.76(0.817)	0.0854
FACIT – Fatigue – Week 24	6.82(0.863)	9.86(0.802)	0.0078	10.06(0.778)	0.0040
Morning Stiffness – Week 24	-21.66(2.390)	-32.30(2.231)	0.0008	-33.79(2.148)	0.0001
WPS-RA– Week 24			0.0004		0.0003
RAID – Week 24	-1.8(0.203)	-2.55(0.189)	0.0057	-2.80(0.183)	0.0002
EQ-5D-3L – Week 24	0.19(0.024)	0.29(0.023)	0.0034	0.34(0.022)	< 0.0001

a For further details of the endpoint definition and analysis method see the SAP (16-1-9-sap).
b Values presented are number and percent of responders for binary variables and LS mean change from baseline with standard error for continuous variables
c Nominal p-values. All values in bold font are significant according to the hierarchical testing procedure.

Incidence of ACR50 at Weeks 12 and 24

The ACR50 response increased at each visit up to Week 24 in both sarilumab groups.

The incidence of ACR50 response at Week 24 was statistically significant in patients treated with sarilumab compared with patients treated with placebo (Table 34).

Figure 8: Figure of incidence of ACR50 response at each visit - ITT population

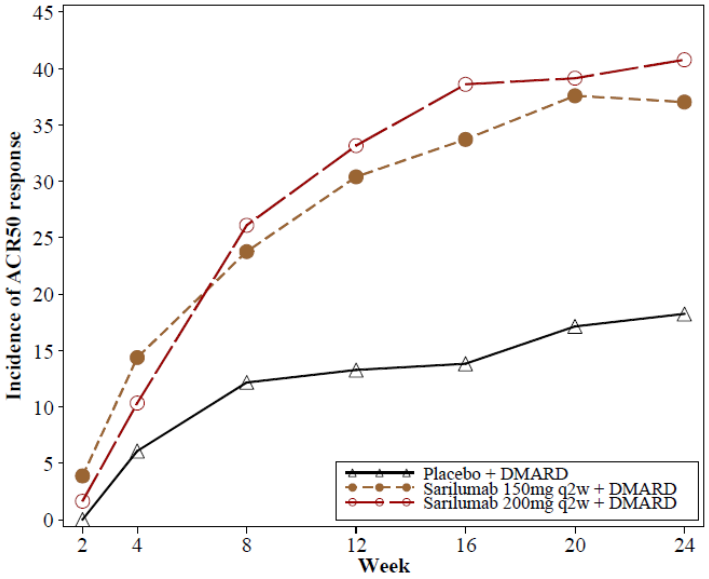


Table 35: Incidence of ACR50 response at Week 24 - ITT population

		Sarilumab	
ACR50 at Week 24 n(%)	Placebo + DMARD (N=181)	150mg q2w + DMARD (N=181)	200mg q2w + DMARD (N=184)
Responders	33 (18.2%)	67 (37.0%)	75 (40.8%)
Non-responders	148 (81.8%)	114 (63.0%)	109 (59.2%)
P-value vs placebo[a]	-	<0.0001	<0.0001
OR, CI vs placebo[b]	-	2.958 (1.764, 4.959)	3.374 (2.045, 5.566)

OR: Odds ratio.

ACR50 response = at least 50% improvement from baseline in both TJC and SJC, and in at least three of the HAQ score, CRP and three VAS assessments.

Patients are considered non-responders from the time they started rescue medication or discontinued study medication.

Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.

[a] CMH test stratified by number of previous anti-TNFs and region. [b] Mantel-Haenszel estimate.

Table 36: Incidence of ACR50 response at Week 12 - ITT population

ACR50 at Week 12 n(%)	Placebo + DMARD (N=181)	Sarilumab 150mg q2w + DMARD (N=181)	Sarilumab 200mg q2w + DMARD (N=184)
Responders	24 (13.3%)	55 (30.4%)	61 (33.2%)
Non-responders	157 (86.7%)	126 (69.6%)	123 (66.8%)
P-value vs placebo[a]	-	<0.0001	<0.0001
OR, CI vs placebo[b]	-	3.105 (1.777, 5.426)	3.590 (2.067, 6.236)

OR: Odds ratio.

ACR50 response = at least 50% improvement from baseline in both TJC and SJC, and in at least three of the HAQ score, CRP and three VAS assessments.

Patients are considered non-responders from the time they started rescue medication or discontinued study medication.

Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.

[a] CMH test stratified by number of previous anti-TNFs and region. [b] Mantel-Haenszel estimate.

Incidence of ARC70 at Weeks 12 and 24

Figure 9: Incidence of ACR70 response at each visit - ITT population

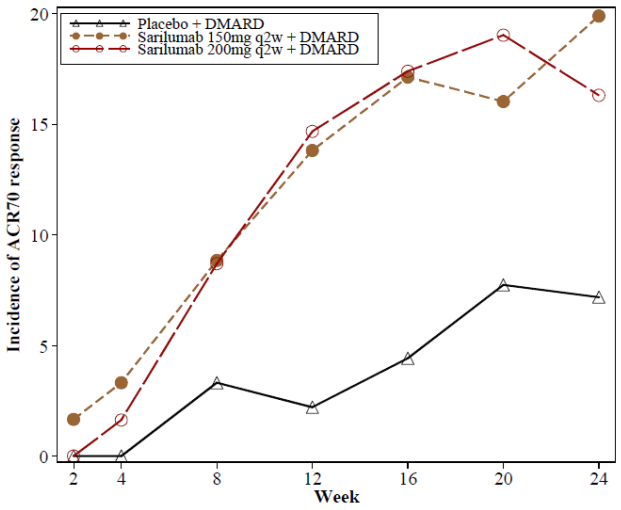


Table 37: Incidence of ACR70 response at Week 24 - ITT population

ACR70 at Week 24 n(%)	Placebo + DMARD (N=181)	Sarilumab 150mg q2w + DMARD (N=181)	Sarilumab 200mg q2w + DMARD (N=184)
Responders	13 (7.2%)	36 (19.9%)	30 (16.3%)
Non-responders	168 (92.8%)	145 (80.1%)	154 (83.7%)
P-value vs placebo[a]	-	0.0002	0.0056
OR, CI vs placebo[b]	-	3.607 (1.774, 7.332)	2.653 (1.308, 5.383)

OR: Odds ratio.

ACR70 response = at least 70% improvement from baseline in both TJC and SJC, and in at least three of the HAQ score, CRP and three VAS assessments.

Patients are considered non-responders from the time they started rescue medication or discontinued study medication.

Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.

[a] CMH test stratified by number of previous anti-TNFs and region. [b] Mantel-Haenszel estimate.

Table 38: Incidence of ACR70 response at Week 12 - ITT population

ACR70 at Week 12 n(%)	Placebo + DMARD (N=181)	Sarilumab 150mg q2w + DMARD (N=181)	Sarilumab 200mg q2w + DMARD (N=184)
Responders	4 (2.2%)	25 (13.8%)	27 (14.7%)
Non-responders	177 (97.8%)	156 (86.2%)	157 (85.3%)
P-value vs placebo[a]	-	<0.0001	<0.0001
OR, CI vs placebo[b]	-	7.556 (2.526, 22.602)	8.090 (2.730, 23.972)

OR: Odds ratio.

ACR70 response = at least 70% improvement from baseline in both TJC and SJC, and in at least three of the HAQ score, CRP and three VAS assessments.

Patients are considered non-responders from the time they started rescue medication or discontinued study medication.

Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.

[a] CMH test stratified by number of previous anti-TNFs and region. [b] Mantel-Haenszel estimate.

ACR-n at Week 12 and Week 24

All treatment groups showed an improvement in the ACR-n. At Week 24, the mean was 28.37% for the placebo group, 46.55% for the sarilumab 150 mg q2w group and 46.04% for the sarilumab 200 mg qw2 group (nominal p-values <0.0001). The results at Week 12 were consistent with the results at Week 24 (nominal p-values <0.0001).

ACR components

Table 39 and Table 40 show summaries of the ACR components at Weeks 24 and 12.

Table 39: Change from baseline in ACR components at Week 24 - ITT population

	Placebo (N=181)	Sarilumab 150mg q2w (N=181)	Sarilumab 200mg q2w (N=184)
Tender joint count (0-68)			
Number	101	127	137
LS mean change from baseline (SE)	-10.55(1.060)	-14.44(1.017)	-16.95(0.992)
P-value vs placebo[a]	-	0.0065	<0.0001
Swollen joint count (0-66)			
Number	101	127	137
LS mean change from baseline (SE)	-8.19(0.721)	-11.56(0.691)	-11.94(0.674)
P-value vs placebo[a]	-	0.0005	<0.0001
Pain VAS (0-100mm)			
Number	98	127	135
LS mean change from baseline (SE)	-21.27(2.250)	-31.90(2.086)	-33.65(2.037)
P-value vs placebo[a]	-	0.0004	<0.0001
Physician global VAS (0-100 mm)			
Number	101	127	137
LS mean change from baseline (SE)	-28.55(1.806)	-40.65(1.695)	-43.22(1.646)
P-value vs placebo[a]	-	<0.0001	<0.0001
Patient global VAS (0-100 mm)			
Number	100	127	136
LS mean change from baseline (SE)	-19.76(2.171)	-29.59(2.046)	-31.28(1.997)
P-value vs placebo[a]	-	0.0008	<0.0001
HAQ-DI (0-3)			
Number	101	127	136
LS mean change from baseline (SE)	-0.34 (0.051)	-0.52 (0.049)	-0.58 (0.048)
P-value vs placebo[a]	-	0.0078	0.0004
CRP (mg/L)			
Number	100	126	137
LS mean change from baseline (SE)	-3.60(1.556)	-15.24(1.457)	-23.27(1.421)
P-value vs placebo[a]	-	<0.0001	<0.0001

Table 40: Change from baseline in ACR components at Week 12 - ITT population

	Placebo (N=181)	150mg q2w (N=181)	200mg q2w (N=184)
Tender joint count (0-68)			
Number	172	165	172
LS mean change from baseline (SE)	-8.55(0.959)	-13.74(0.975)	-14.87(0.954)
P-value vs placebo[a]	-	<0.0001	<0.0001
Swollen joint count (0-66)			
Number	172	165	172
LS mean change from baseline (SE)	-6.75(0.687)	-10.54(0.698)	-10.59(0.684)
P-value vs placebo[a]	-	<0.0001	<0.0001
Pain VAS (0-100mm)			
Number	171	166	171
LS mean change from baseline (SE)	-15.13(1.908)	-26.93(1.933)	-30.56(1.901)
P-value vs placebo[a]	-	<0.0001	<0.0001
Physician global VAS (0-100 mm)			
Number	172	165	171
LS mean change from baseline (SE)	-22.74(1.744)	-33.64(1.775)	-35.44(1.740)
P-value vs placebo[a]	-	<0.0001	<0.0001
Patient global VAS (0-100 mm)			
Number	172	165	171
LS mean change from baseline (SE)	-13.75(1.807)	-25.28(1.836)	-27.38(1.803)
P-value vs placebo[a]	-	<0.0001	<0.0001
HAQ-DI (0-3)			
Number	170	165	171
LS mean change from baseline (SE)	-0.26 (0.043)	-0.46 (0.044)	-0.47 (0.043)
P-value vs placebo[a]	-	0.0007	0.0004
CRP (mg/L)			
Number	168	165	170
LS mean change from baseline (SE)	-3.63(1.436)	-15.08(1.452)	-22.98(1.432)
P-value vs placebo[a]	-	<0.0001	<0.0001

All assessments are set to missing from the time a patient receives rescue medication or discontinues study medication early. Missing measurements are not imputed.

DAS28-CRP and DAS28-CRP <2.6 at Week 12 and Week 24

Table 41: Incidence of DAS28-CRP <2.6 at Week 24 - ITT population

DAS28-CRP < 2.6 at Week 24 n(%)	Placebo + DMARD (N=181)	Sarilumab 150mg q2w + DMARD (N=181)	Sarilumab 200mg q2w + DMARD (N=184)
Number	181	181	184
Yes	13 (7.2%)	45 (24.9%)	53 (28.8%)
No	168 (92.8%)	136 (75.1%)	131 (71.2%)
P-value vs placebo[a]	-	<0.0001	<0.0001
OR, CI vs placebo[b]	-	4.622 (2.339, 9.132)	5.801 (2.948, 11.413)
Of responders, proportion with 0 active joints (n)	10 (76.9%)	12 (26.7%)	13 (24.5%)
Of responders, proportion with 1 active joints (n)	0	13 (28.9%)	7 (13.2%)
Of responders, proportion with 2 active joints (n)	0	6 (13.3%)	9 (17.0%)
Of responders, proportion with 3 or more active joints (n)	3 (23.1%)	14 (31.1%)	24 (45.3%)

OR: Odds ratio.

DAS28-CRP =0.56 x sqrt(28TJC) + 0.28 x sqrt(28SJC) + 0.36 x Log(CRP+1) + 0.014 x Patient global VAS + 0.96.

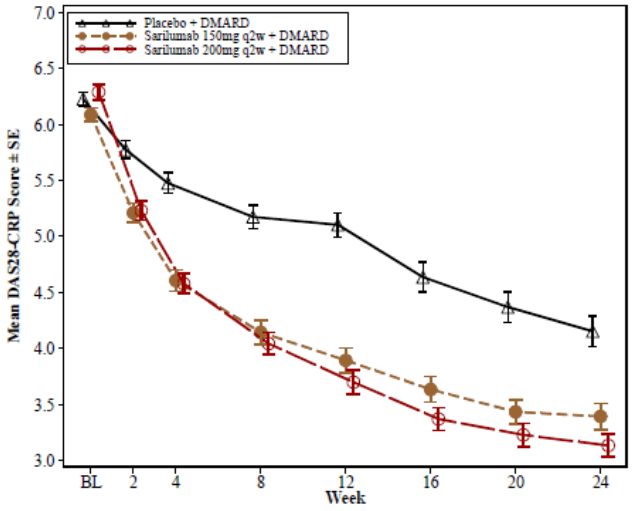
Patients are considered to be not < 2.6 from the time they started rescue medication or discontinued study medication.

Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.

[a] CMH test stratified by number of previous anti-TNFs and region. [b] Mantel-Haenszel estimate.

Note: Active joint is defined as a joint that is either tender or swollen or both

Figure 10: Figure of DAS28-CRP at each visit - ITT population



# subjects								
Placebo + DMARD	181	177	175	170	168	110	106	99
Sarilumab 150mg q2w + DMARD	181	176	172	164	163	141	133	126
Sarilumab 200mg q2w + DMARD	184	181	178	176	169	144	138	136

Clinical disease activity index

Baseline CDAI values were similar across the treatment groups, ranging from 41.59 to 44.10. At Week 24, the mean change from baseline was -27.14 for the sarilumab 150 mg q2w group and -30.43 for the sarilumab 200 mg q2w group compared to -23.90 for the placebo group ($p < 0.0001$ for both treatment groups compared to placebo). Results at Week 12 were consistent with Week 24 (nominal $p < 0.0001$ for both treatment groups compared to placebo). The proportion of patients achieving CDAI remission (ie, CDAI $\leq$ 2.8) was numerically higher in the sarilumab groups (9.4% for the sarilumab 150 mg q2w group [nominal p-value=0.0971] and 8.2% for the sarilumab 200 mg q2w group [nominal p-value=0.2134]) at Week 24 and (3.3% for the sarilumab 150 mg q2w group [nominal p-value=0.0551] and 4.9% for the sarilumab 200 mg q2w group[nominal p-value=0.0106]) at Week 12.

Simplified disease activity index

Baseline SDAI values were similar across the treatment groups, ranging from 44.89 to 47.20. All treatment groups showed a decrease from baseline in the SDAI.

At Week 24, the mean change from baseline was -28.45 for the sarilumab 150 mg q2w group and –33.36 for the sarilumab 200 mg q2w group compared to -24.48 for the placebo group (nominal p-values <0.0001 for both treatment groups compared to placebo).

The results at Week 12, were consistent with the results at Week 24 (nominal p-value <0.0001 for both treatment groups compared to placebo). The proportion of patients achieving SDAI remission (ie, SDAI $\leq$ 3.3) was higher in patients in the sarilumab groups (9.9% for the sarilumab 150 mg q2w group and 8.7% for the sarilumab 200 mg q2w group) at Week 24 when compared with placebo (2.8%). The nominal p-values at Week 24 for the sarilumab 150 mg q2w group and for the sarilumab 200 mg q2w group were 0.0044 and 0.0146, respectively. The results at Week 12 were consistent with the results at Week 24 (nominal p-value=0.0007 and 0.0014 for the sarilumab 150 mg q2w group and for the sarilumab 200 mg q2w group, respectively).

EULAR Response at Week 12 and Week 24

A larger proportion of patients in the sarilumab treatment groups achieved a good or moderate EULAR response compared to the placebo group at Week 24 (44.2% for placebo, 62.4% for the sarilumab 150 mg q2w group and 71.7% for the sarilumab 200 mg q2w group). The nominal p-value for testing the difference in the EULAR response between each of the sarilumab groups and the placebo group was p=0.0004 and p <0.0001 at Week 24 for the sarilumab 150 mg q2w group and the sarilumab 200 mg q2w group, respectively. The results at Week 12 were consistent with the results at Week 24.

Boolean-based (ACR/EULAR Remission) at Week 12 and Week 24

The proportion of patients achieving Boolean-based ACR/EULAR remission at Weeks 12 (3.3% for the sarilumab 150 mg q2w group and 2.7% for the sarilumab 200 mg q2w group) and at Week 24 (5.5% for the sarilumab 150 mg q2w group and 6.0% for the sarilumab 200 mg q2w group) was numerically higher in patients treated with sarilumab than in patients treated with placebo (0 at Week 12 and 2.8% at Week 24). At Week 24, nominal p-values for testing the difference in increase in Boolean-based ACR/EULAR response between each of the sarilumab groups and the placebo group were p >0.025. At Week 12, nominal p-values for testing the difference in increase in Boolean-based ACR/EULAR response between each of the sarilumab groups and the placebo group were 0.0129 for the sarilumab 150 mg q2w group and 0.0252 for the sarilumab 200 mg q2w group.

Quality of life and health economics observations

SF-36 at Weeks 12 and 24

The PCS and MCS scores evaluated at Weeks 24 were part of the hierarchical testing procedure. The 8 health domain scores were tested but were not part of the hierarchical testing procedure.

The SF-36 can be scored on a 0-100 scale or as a norm-based t-score.

Scores were considered clinically meaningful if the within group change from baseline met or exceeded values for the minimum clinically important difference (MCID). The MCID was a change of 2.5 points for PCS and MCS, and a change of 5 points for the 8 health domains (29).

Change from baseline in SF-36 at Weeks 12 and 24 – Physical component summary and Physical Health Domains

The differences in SF-36 PCS scores at Weeks 12 and 24 were statistically significant for both sarilumab treatment groups compared with placebo (Week 12: p<0.0001 for the sarilumab 150 mg q2w group and p<0.0001 for the sarilumab 200 mg q2w group; Week 24: p<0.0004 for the sarilumab 150 mg q2w group and p<0.0001 for the sarilumab 200 mg q2w group) (~xr124i and ~xr125i). The within-group mean changes from baseline for both active treatment groups exceeded MCID.

At Week 12 and 24, both sarilumab treatment groups had clinically meaningful changes from baseline in all 4 SF-36 physical health domains and these changes were significantly different from placebo (p<0.05) with the exception of the General Health domain for the sarilumab 150 mg q2w group.

Change from baseline in SF-36 at Weeks 12 and 24 – Mental component summary and Mental Health Domains

The differences in SF-36 MCS scores at Week 12 were statistically significant for the sarilumab 200 mg q2w group compared with placebo (p=0.0028). The difference in SF-36 MCS scores at Week 12 was not statistically significant for the sarilumab 150 mg q2w group compared with placebo (p=0.1005).

At Week 12, the sarilumab 200 mg group had clinically meaningful changes from baseline on all 4 SF-36 mental health domains (nominal p-values of p=0.0007 for Vitality, p=0.0018 for Social Functioning, p=0.0338 for Role Emotional, and p=0.0001 for Mental Health). The sarilumab 150 mg q2w group had clinically meaningful changes in all 4 domains; however, these changes were only different from placebo for Vitality (p=0.0163) and Social Functioning (p=0.0004).

The differences in SF-36 MCS scores at Week 24 for both sarilumab treatment groups compared with placebo did not reach statistical significance (p=0.2026 for the sarilumab 150 mg q2w group and p=0.0854 for the sarilumab 200 mg q2w group).

At Week 24, both sarilumab treatment groups had clinically meaningful changes from baseline on all 4 SF-36 mental health domains; however, these changes were only different from placebo for the Vitality domain (nominal p-values of p=0.0167 for the sarilumab 150 mg q2w group and p=0.0008 for the sarilumab 200 mg q2w group) and the Social Functioning domain (nominal p values of p=0.0203 for the sarilumab 150 mg q2w group and p=0.0138 for the sarilumab 200 mg q2w group). Changes were also different from placebo in the Mental Health domain for the sarilumab 200 mg q2w group.

FACIT-Fatigue at Week 24

The FACIT-Fatigue scores evaluated at Weeks 24 were part of the hierarchical testing procedure. Statistical significance of this endpoint is not claimed since the testing hierarchy was broken prior to this parameter. Scores were considered to be clinically meaningful if the within group mean change from baseline met or exceeded the minimum clinically important difference (MCID) of 4.0.

Clinically meaningful changes from baseline in FACIT-Fatigue scores were reported at Week 24 for both sarilumab treatment groups compared to placebo (nominal p-values of p=0.0078 for the sarilumab 150 mg q2w group and p=0.0040 for the sarilumab 200 mg q2w group).

Morning Stiffness VAS at Week 24

Statistical significance of this endpoint is not claimed since the testing hierarchy was broken prior to this parameter. Scores were considered to be clinically meaningful if the within-group mean change from baseline met or exceeded the minimum clinically important difference (MCID) of 10.0.

Clinically meaningful changes from baseline in morning stiffness VAS scores were reported at Week 24 for both sarilumab treatment groups compared to placebo (nominal p-values of p=0.0008 for the sarilumab 150 mg q2w group and p=0.0001 for the sarilumab 200 mg q2w group).

WPS-RA at Week 24.

Statistical significance of this endpoint is not claimed since the testing hierarchy was broken prior to this parameter.

The O'Brien global test (nominal p-values of p=0.0004 for the sarilumab 150 mg q2w group and p=0.0003 for the sarilumab 200 mg q2w group) demonstrated an overall effect at Week 24 for both sarilumab treatment groups.

At Week 24, the sarilumab 150 mg q2w group demonstrated changes from placebo in 4 of 8 components of the WPS-RA, including hours worked due to arthritis (nominal p-value of 0.0006), days with family, social or leisure activities missed due to arthritis (nominal p-value of 0.0138), days with outside help hired due to arthritis (nominal p-value of 0.0023), and rate of arthritis interference with household work productivity (nominal p-value of 0.0004).

At Week 24, the sarilumab 200mg group demonstrated changes from placebo in 6 of 8 components of the WPS-RA, including work days missed due to arthritis (nominal p-value of 0.0478), rate of arthritis interference with work productivity (nominal p-value of 0.0421), hours worked due to arthritis (nominal p-value of 0.0004), days with family, social or leisure activities missed due to arthritis (nominal p-value of 0.0005), days with outside help hired due to arthritis (nominal p-value of 0.0022), and rate of arthritis interference with household work productivity (nominal p-value of <0.0001).

EQ-5D-3L at Weeks 12 and 24

Statistical significance of this endpoint is not claimed since the testing hierarchy was broken prior to this parameter. The EQ-5D single utility index responder threshold [MID] has been identified as a 0.05 increase over a 6-month period.

Clinically meaningful changes from baseline in EQ-5D were reported at Week 24 for both sarilumab treatment groups compared with placebo (nominal p-value of 0.0034 for the sarilumab 150 mg q2w group and p<0.0001 for the sarilumab 200 mg q2w group).

RAID at Weeks 12 and 24

Statistical significance of this endpoint is not claimed since the testing hierarchy was broken prior to this parameter. Clinically meaningfulness was determined if the within group change from baseline met or exceeded the minimum clinically important improvement threshold value of 3.

Clinically meaningful changes from baseline in RAID scores were reported at Week 24 for the sarilumab 200 mg q2w group compared to placebo (nominal p-values of p=0.0002 for the sarilumab 200 mg q2w group).

Ancillary analyses

Subgroup analysis

Subgroup interactions for ACR20 at Week 24 are displayed in Table 42.

Table 42: Incidence of ACR20 response at week 24 by select subgroups – ITT population

		Sarilumab		
	Placebo + DMARD	150mg q2w + DMARD	200mg q2w + DMARD	p-value for interaction[a]
Gender				0.6818
Male				
Responders	10/27 (37.0%)	19/39 (48.7%)	18/33 (54/5%)	
OR, 95% CI vs placebo[b]		2.337 (0.746, 7.314)	2.921 (0.881, 9.689)	
Female				
Responders	51/154 (33.1%)	82/142 (57.7%)	94/151 (62.3%)	
OR, 95% CI vs placebo[b]		3.010 (1.825, 4.966)	3.469 (2.144, 5.614)	
Race				0.0337
Caucasian/White				
Responders	33/124 (26.6%)	72/134 (53.7%)	81/130 (62.3%)	
OR, 95% CI vs placebo[b]		3.231 (1.869, 5.587)	4.874 (2.775, 8.561)	
All Other races				
Responders	28/57 (49.1%)	29/47 (61.7%)	31/54 (57.4%)	
OR, 95% CI vs placebo[b]		2.395 (0.997, 5.753)	1.436 (0.670, 3.078)	
Region				0.7319
Region 1				
Responders	17/77 (22.1%)	29/77 (37.7%)	39/79 (49.4%)	
OR, 95% CI vs placebo[b]		2.141 (1.052, 4.357)	3.425 (1.710, 6.860)	
Region 2				
Responders	35/74 (47.3%)	52/74 (70.3%)	53/74 (71.6%)	
OR, 95% CI vs placebo[b]		2.707 (1.361, 5.382)	2.799 (1.417, 5.531)	
Region 3				
Responders	9/30 (30.0%)	20/30 (66.7%)	20/31 (64.5%)	
OR, 95% CI vs placebo[b]		4.788 (1.583, 4.486)	4.438 (1.495, 13.173)	
Rheumatoid factor				0.0012
Positive				
Responders	42/142 (29.6%)	84/135 (62.2%)	81/132 (61.4%)	
OR, 95% CI vs placebo[b]		4.330 (2.525, 7.424)	4.213 (2.476, 7.169)	
Negative				
Responders	19/38 (50.0%)	17/46 (37.0%)	31/49 (63.3%)	
OR, 95% CI vs placebo[b]		0.617 (0.242, 1.578)	2.098 (0.843, 5.218)	
Anti CCP antibody				0.0453
Positive				
Responders	48/150 (32.0%)	82/135 (60.7%)	81/137 (59.1%)	
OR, 95% CI vs placebo[b]		3.659 (2.161, 6.194)	3.445 (2.063, 5.752)	
Negative				
Responders	12/30 (40.0%)	19/45 (42.2%)	30/43 (69.8%)	
OR, 95% CI vs placebo[b]		1.173 (0.455, 3.024)	5.314 (1.762, 16.031)	

OR: Odds ratio.

ACR20 response = at least 20% improvement from baseline in both TJC and SJC, and in at least three of the HAQ score, CRP and three VAS assessments.

Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group within each subgroup as denominator.

Region 1 (Western countries): Australia, Canada, Czech Republic, Germany, Greece, Hungary, Israel, Italy, New Zealand, Portugal, Spain, USA

Region 2 (South American): Argentina, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Peru.

Region 3 (Rest of the world): South Korea, Lithuania, Poland, Russia,Taiwan, Turkey, Ukraine.

[a] Logistic regression model with terms of treatment, number of previous anti-TNFs, region, subgroup, treatment-by-subgroup.

[b] Mantel-Haenszel estimate: model stratified by number of previous anti-TNFs and region.

Table 43: Incidence of ACR20 response at week 12 – ITT population

		Sarilumab	
ACR20 at Week 12 n(%)	Placebo + DMARD (N=181)	150mg q2w + DMARD (N=181)	200mg q2w + DMARD (N=184)
Responders	68 (37.6%)	98 (54.1%)	115 (62.5%)
Non-responders	113 (62.4%)	83 (45.9%)	69 (37.5%)
P-value vs placebo[a]	-	0.0013	<0.0001
OR, CI vs placebo[b]	-	2.019 (1.314, 3.102)	2.964 (1.909, 4.602)

OR: Odds ratio.

ACR20 response = at least 20% improvement from baseline in both TJC and SJC, and in at least three of the HAQ score, CRP and three VAS assessments.

Patients are considered non-responders from the time they started rescue medication or discontinued study medication.

Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.

[a] CMH test stratified by number of previous anti-TNFs and region. [b] Mantel-Haenszel estimate.

HAQ-DI

Subgroup interactions for HAQ-DI at Week 12 are displayed in Table 44.

Table 44: Change from baseline in HAQ-DI at week 12 by select subgroups – ITT population

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD	p-value for interaction[a]
Gender				0.0425
Male				
Change mean (SD)	-0.43 (0.60)	-0.35 (0.56)	-0.48 (0.61)	
LS mean diff, 95% CI[b]		0.125 (-0.149,0.400)	-0.042 (-0.326,0.242)	
Female				
Change mean (SD)	-0.27 (0.52)	-0.54 (0.66)	-0.49 (0.55)	
LS mean diff, 95% CI[b]		-0.269 (-0.397,-0.141)	-0.237 (-0.362,-0.111)	
Race				0.6922
Caucasian/White				
Change mean (SD)	-0.21 (0.47)	-0.46 (0.62)	-0.45 (0.53)	
LS mean diff, 95% CI[b]		-0.224 (-0.355,-0.093)	-0.246 (-0.377,-0.114)	
All Other races				
Change mean (SD)	-0.47 (0.63)	-0.59 (0.70)	-0.60 (0.63)	
LS mean diff, 95% CI[b]		-0.177 (-0.421,0.067)	-0.133 (-0.367,0.101)	
Region				0.9407
Region 1				
Change mean (SD)	-0.13 (0.46)	-0.39 (0.55)	-0.36 (0.45)	
LS mean diff, 95% CI[b]		-0.223 (-0.388,-0.058)	-0.234 (-0.398,-0.070)	
Region 2				
Change mean (SD)	-0.52 (0.59)	-0.70 (0.74)	-0.67 (0.65)	
LS mean diff, 95% CI[b]		-0.233 (-0.442,-0.023)	-0.185 (-0.392,0.021)	
Region 3				
Change mean (SD)	-0.14 (0.39)	-0.25 (0.43)	-0.38 (0.47)	
LS mean diff, 95% CI[b]		-0.116 (-0.333,0.100)	-0.227 (-0.440,-0.013)	
Rheumatoid factor				0.0204
Positive				
Change mean (SD)	-0.28 (0.52)	-0.55 (0.65)	-0.58 (0.61)	
LS mean diff, 95% CI[b]		-0.278 (-0.413,-0.143)	-0.302 (-0.437,-0.167)	
Negative				
Change mean (SD)	-0.34 (0.61)	-0.31 (0.61)	-0.28 (0.33)	
LS mean diff, 95% CI[b]		0.056 (-0.170,0.281)	0.052 (-0.166,0.270)	
Anti CCP antibody				0.0934
Positive				
Change mean (SD)	-0.28 (0.52)	-0.53 (0.66)	-0.55 (0.61)	
LS mean diff, 95% CI[b]		-0.259 (-0.393,-0.126)	-0.285 (-0.416,-0.153)	
Negative				
Change mean (SD)	-0.37 (0.63)	-0.41 (0.59)	-0.35 (0.35)	
LS mean diff, 95% CI[b]		-0.000 (-0.246,0.246)	0.038 (-0.209,0.285)	

All assessments are set to missing from the time a patient receives rescue medication or discontinues study medication early. Missing HAQ-DI measurements are not imputed.

Note: Number = Number of patients with assessment at both baseline and Week 12 within each subgroup.

Region 1 (Western countries): Australia, Canada, Czech Republic, Germany, Greece, Hungary, Israel, Italy, New Zealand, Portugal, Spain, USA

Region 2 (South American): Argentina, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Peru.

Region 3 (Rest of the world): South Korea, Lithuania, Poland, Russia,Taiwan, Turkey, Ukraine.

[a] MMRM assuming an unstructured covariance structure with covariate baseline and terms of treatment, number of previous anti-TNFs, region, subgroup, treatment-by-subgroup, visit, treatment-by-visit, treatment-by-visit-by-subgroup.

[b] MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, number of previous anti-TNFs, region, visit, treatment-by-visit interaction.

Table 45: Proportion of HAQ-DI responder (HAQ-DI >= 0.22 units improvement) at Week 12 (Supportive analysis) by region - ITT population

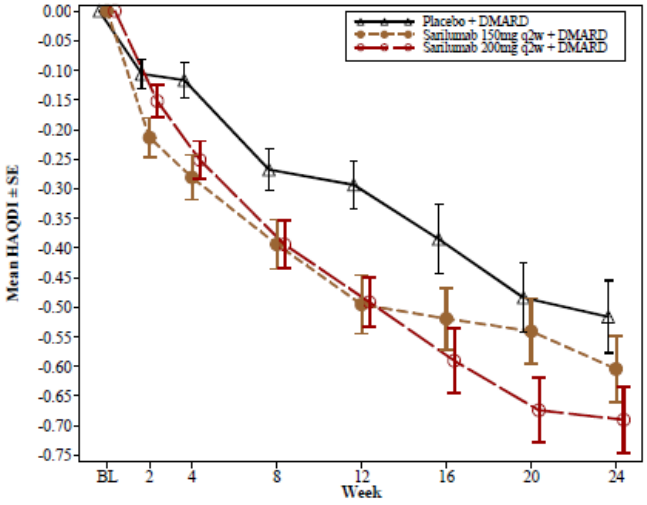
		Sarilumab	
HAQ-DI	Placebo + DMARD (N=181)	150mg q2w + DMARD (N=181)	200mg q2w + DMARD (N=184)
Region 1			
Number	77	77	79
Responders	29 (37.7%)	38 (49.4%)	40 (50.6%)
Non-responders	48 (62.3%)	39 (50.6%)	39 (49.4%)
OR, 95% CI vs placebo[a]	-	1.613 (0.849, 3.067)	1.706 (0.898, 3.241)
Region 2			
Number	74	74	74
Responders	47 (63.5%)	48 (64.9%)	50 (67.6%)
Non-responders	27 (36.5%)	26 (35.1%)	24 (32.4%)
OR, 95% CI vs placebo[a]	-	1.061 (0.540, 2.083)	1.189 (0.602, 2.349)
Region 3			
Number	30	30	31
Responders	10 (33.3%)	14 (46.7%)	18 (58.1%)
Non-responders	20 (66.7%)	16 (53.3%)	13 (41.9%)
OR, 95% CI vs placebo[a]	-	1.754 (0.616, 4.995)	2.750 (0.982, 7.696)

OR: Odds ratio.
HAQ-DI responder is defined as ≥0.22 units improvement in the change from baseline in HAQ-DI.
Patients are considered non-responders from the time they started rescue medication or discontinued study medication.
Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group within each region as denominator.
Region 1 (Western countries): Australia, Canada, Czech Republic, Germany, Greece, Hungary, Israel, Italy, New Zealand, Portugal, Spain, USA
Region 2 (South American): Argentina, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Peru.
Region 3 (Rest of the world): South Korea, Lithuania, Poland, Russia,Taiwan, Turkey, Ukraine.
[a] Mantel-Haenszel estimate: model stratified by number of previous anti-TNFs.

Over time

Figure 11 shows the change from baseline in HAQ-DI over time for each treatment group. Physical function improved in all treatment groups. Starting at Week 4, the improvement in physical function was greater for both sarilumab groups compared to the placebo group (nominal p-values <0.025 from Week 4 through Week 24 for both sarilumab groups).

Figure 11: Change from baseline in HAQ-DI at each visit - ITT population



# subjects								
Placebo + DMARD	181	180	177	174	170	114	108	101
Sarilumab 150mg q2w + DMARD	181	179	174	169	165	142	134	127
Sarilumab 200mg q2w + DMARD	184	181	179	178	171	145	140	136

Incidence of ACR50 at weeks 12 and 24

Table 46: Incidence of ACR50 response at Week 24 - ITT population

ACR50 at Week 24 n(%)	Placebo + DMARD (N=181)	Sarilumab 150mg q2w + DMARD (N=181)	Sarilumab 200mg q2w + DMARD (N=184)
Responders	33 (18.2%)	67 (37.0%)	75 (40.8%)
Non-responders	148 (81.8%)	114 (63.0%)	109 (59.2%)
P-value vs placebo[a]	-	<0.0001	<0.0001
OR, CI vs placebo[b]	-	2.958 (1.764, 4.959)	3.374 (2.045, 5.566)

OR: Odds ratio.

ACR50 response = at least 50% improvement from baseline in both TJC and SJC, and in at least three of the HAQ score, CRP and three VAS assessments.

Patients are considered non-responders from the time they started rescue medication or discontinued study medication.

Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.

[a] CMH test stratified by number of previous anti-TNFs and region. [b] Mantel-Haenszel estimate.

Table 47: Incidence of ACR50 response at Week 12 - ITT population

ACR50 at Week 12 n(%)	Placebo + DMARD (N=181)	Sarilumab 150mg q2w + DMARD (N=181)	Sarilumab 200mg q2w + DMARD (N=184)
Responders	24 (13.3%)	55 (30.4%)	61 (33.2%)
Non-responders	157 (86.7%)	126 (69.6%)	123 (66.8%)
P-value vs placebo[a]	-	<0.0001	<0.0001
OR, CI vs placebo[b]	-	3.105 (1.777, 5.426)	3.590 (2.067, 6.236)

OR: Odds ratio.

ACR50 response = at least 50% improvement from baseline in both TJC and SJC, and in at least three of the HAQ score, CRP and three VAS assessments.

Patients are considered non-responders from the time they started rescue medication or discontinued study medication.

Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.

Incidence of ARC70 at Weeks 12 and 24

Table 48: Incidence of ACR70 response at Week 24 - ITT population

ACR70 at Week 24 n(%)	Placebo + DMARD (N=181)	Sarilumab 150mg q2w + DMARD (N=181)	Sarilumab 200mg q2w + DMARD (N=184)
Responders	13 (7.2%)	36 (19.9%)	30 (16.3%)
Non-responders	168 (92.8%)	145 (80.1%)	154 (83.7%)
P-value vs placebo[a]	-	0.0002	0.0056
OR, CI vs placebo[b]	-	3.607 (1.774, 7.332)	2.653 (1.308, 5.383)

OR: Odds ratio.

ACR70 response = at least 70% improvement from baseline in both TJC and SJC, and in at least three of the HAQ score, CRP and three VAS assessments.

Patients are considered non-responders from the time they started rescue medication or discontinued study medication.

Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.

[a] CMH test stratified by number of previous anti-TNFs and region. [b] Mantel-Haenszel estimate.

Table 49: Incidence of ACR70 response at Week 12 - ITT population

ACR70 at Week 12 n(%)	Placebo + DMARD (N=181)	Sarilumab 150mg q2w + DMARD (N=181)	Sarilumab 200mg q2w + DMARD (N=184)
Responders	4 (2.2%)	25 (13.8%)	27 (14.7%)
Non-responders	177 (97.8%)	156 (86.2%)	157 (85.3%)
P-value vs placebo[a]	-	<0.0001	<0.0001
OR, CI vs placebo[b]	-	7.556 (2.526, 22.602)	8.090 (2.730, 23.972)

OR: Odds ratio.

ACR70 response = at least 70% improvement from baseline in both TJC and SJC, and in at least three of the HAQ score, CRP and three VAS assessments.

Patients are considered non-responders from the time they started rescue medication or discontinued study medication.

Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.

DAS28-CRP and DAS28-CRP <2.6 at Week 12 and Week 24

Table 50: Incidence of DAS28-CRP <2.6 at Week 24 - ITT population

DAS28-CRP < 2.6 at Week 24 n(%)	Placebo + DMARD (N=181)	Sarilumab 150mg q2w + DMARD (N=181)	Sarilumab 200mg q2w + DMARD (N=184)
Number	181	181	184
Yes	13 (7.2%)	45 (24.9%)	53 (28.8%)
No	168 (92.8%)	136 (75.1%)	131 (71.2%)
P-value vs placebo[a]	-	<0.0001	<0.0001
OR, CI vs placebo[b]	-	4.622 (2.339, 9.132)	5.801 (2.948, 11.413)
Of responders, proportion with 0 active joints (n)	10 (76.9%)	12 (26.7%)	13 (24.5%)
Of responders, proportion with 1 active joints (n)	0	13 (28.9%)	7 (13.2%)
Of responders, proportion with 2 active joints (n)	0	6 (13.3%)	9 (17.0%)
Of responders, proportion with 3 or more active joints (n)	3 (23.1%)	14 (31.1%)	24 (45.3%)

OR: Odds ratio.

DAS28-CRP =0.56 x sqrt(28TJC) + 0.28 x sqrt(28SJC) + 0.36 x Log(CRP+1) + 0.014 x Patient global VAS + 0.96.

Patients are considered to be not < 2.6 from the time they started rescue medication or discontinued study medication.

Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.

[a] CMH test stratified by number of previous anti-TNFs and region. [b] Mantel-Haenszel estimate.

Note: Active joint is defined as a joint that is either tender or swollen or both.

Immunogenicity

Table 51: Summary of ADA assay response - Immunogenicity population

	Placebo + DMARD (N=180)	Sarilumab 150mg q2w + DMARD (N=180)	Sarilumab 200mg q2w + DMARD (N=182)
Number of patients with ADA assay results available	180/180 (100%)	180/180 (100%)	182/182 (100%)
Patients with an ADA negative sample at baseline	178/180 (98.9%)	176/179 (98.3%)	175/178 (98.3%)
Patients with an ADA positive sample at baseline	2/180 (1.1%)	3/179 (1.7%)	3/178 (1.7%)
Neutralizing	0/180	0/179	0/178
Non-Neutralizing	2/180 (1.1%)	3/179 (1.7%)	3/178 (1.7%)
Titer			
Median	45.00	30.00	120.00
Q1 : Q3	30.00 : 60.00	30.00 : 480.00	30.00 : 120.00
Min : Max	30.0 : 60.0	30.0 : 480.0	30.0 : 120.0
ADA negative patients during the TEAE period	177/180 (98.3%)	147/180 (81.7%)	160/182 (87.9%)
ADA positive patients[a] during the TEAE period	3/180 (1.7%)	33/180 (18.3%)	22/182 (12.1%)
Neutralizing[b]	0/180	5/180 (2.8%)	2/182 (1.1%)
Non-Neutralizing	3/180 (1.7%)	28/180 (15.6%)	20/182 (11.0%)
Treatement-boosted ADA positive patients	0/180	0/180	0/182
Treatment-emergent ADA positive patients	3/180 (1.7%)	33/180 (18.3%)	22/182 (12.1%)
Peak titer			
Median	30.00	30.00	30.00
Q1 : Q3	30.00 : 30.00	30.00 : 60.00	30.00 : 60.00
Min : Max	30.0 : 30.0	30.0 : 120.0	30.0 : 7680.0
Patients with a persistent positive response[c]	2/180 (1.1%)	11/180 (6.1%)	9/182 (4.9%)
Neutralizing[b]	0/180	4/180 (2.2%)	2/182 (1.1%)
Non-Neutralizing	2/180 (1.1%)	7/180 (3.9%)	7/182 (3.8%)
Patients with a transient positive response[d]	1/180 (0.6%)	22/180 (12.2%)	13/182 (7.1%)
Neutralizing[b]	0/180	1/180 (0.6%)	0/182
Non-Neutralizing	1/180 (0.6%)	21/180 (11.7%)	13/182 (7.1%)

Percentages based on number of patients with ADA assay results available.

TEAE: Treatment-emergent adverse event, ADA: Anti-sarilumab antibody, Negative = below the assay cut point or not drug specific, Positive = drug specific signal above the assay cut point.

No imputation is used for missing ADA results.

[a] Patients with no positive assay response at baseline but with a positive assay response during the TEAE period (ie, treatment-emergent positive) or patients with a positive ADA assay response at baseline and also have at least a 4-fold increase in titer during the TEAE period (ie, treatment-boosted).

[b] At least one post-baseline measurement classified as neutralizing positive.

[c] Persistent positive response: treatment-emergent positive ADA detected at 2 or more consecutive sampling time points during the TEAE period, where the first and last ADA positive samples are separated by a period of at least 16 weeks. Also persistent in case last sample analyzed is positive.

[d] Transient positive response is defined as any positive ADA assay response that is not considered persistent.

There were 7 patients (5 in the sarilumab 150 mg q2w group and 2 in the sarilumab 200 mg q2w group) who had neutralizing antibodies. One patient (010832-840-106-407) had discontinued due to lack of efficacy with the last dose on Day 72. He had neutralizing antibodies on Day 30 and Day 86 with ADA titer on Day 30 of 120 and on Day 86 of 240. No subsequent ADA sampling was done. This patient's sarilumab concentrations were all below the LLOQ (312.5 ng/mL) from pre-dose to Day 86, ie, the sarilumab concentration were not detectable before and after he had neutralizing antibodies. None of the patients with neutralizing antibodies experienced a hypersensitivity reaction.

Two patients who were ADA positive had an AE identified by the hypersensitivity SMQ. Both patients had systemic hypersensitivity reactions. Neither patient had neutralizing antibodies. Patient 010832-724-001-401 had a generalized rash. The other patient (010832-840-055-412) had a rash on the inner thighs that began on Day 121; it was treated with topical antifungal and resolved on Day 149. The patient had an isolated ADA sample that was positive with a titer of 30 on Day 31. The patient completed study and enrolled into LTS11210.

No ADA positive patient had evidence of loss of efficacy (ie, defined as permanent treatment discontinuation due to lack of efficacy after achieving an ACR50 or EULAR Good response).

Table 52: Number (%) of patients with lack of efficacy or loss of efficacy during the TEAE period by ADA status - ITT population

n(%)	Placebo (N=181)	ADA negative (N=307)	ADA positive (N=55)
Lack of efficacy	68 (37.6%)	50 (16.3%)	7 (12.7%)
Permanent treatment discontinuation due to lack of efficacy	68 (37.6%)	50 (16.3%)	7 (12.7%)
Loss of efficacy	0	8 (2.6%)	0
Permanent treatment discontinuation due to lack of efficacy after achieving an ACR 50 or EULAR Good response	0	8 (2.6%)	0
After achieving ACR50 responder status	0	5 (1.6%)	0
After achieving EULAR good response	0	7 (2.3%)	0

TEAE: Treatment-emergent adverse event, ADA: Anti-sarilumab antibody.
No imputation used for missing ADA results.
Lack of efficacy is defined as permanent treatment discontinuation due to lack of efficacy.
Loss of efficacy is defined as permanent treatment discontinuation due to lack of efficacy after achieving an ACR50 or EULAR Good response.
Patients with a positive ADA assay response during the TEAE period is defined as the total of patients with no positive assay response at baseline but with a positive assay response during the TEAE period and Patients with a positive ADA assay response at baseline
Note: Percentages are calculated using the number of ITT patients in the corresponding group as denominator.
Note: Excludes 3 sarilumab treated patients with missing ADA assay results.

A randomized, double-blind, parallel-group study assessing the efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy in patients with rheumatoid arthritis (EFC14092)

Methods

Study Participants

Table 53: Main inclusion and exclusion criteria in key active-controlled study

	EFC14092
Main inclusion criteria	
Diagnostic criteria	2010 ACR/EULAR criteria
Duration of RA	≥3 months
Tender joint count	≥8/68
Swollen joint count	≥6/66
CRP (mg/L)	≥8 (or ESR ≥28 mm/H)
Target population	Inadequate response to or intolerant of or inappropriate to continue MTX (=MTX-IR)
Baseline disease activity	DAS28-ESR >5.1
Main exclusion criteria	
DMARDs	Current treatment with DMARDS/immunosuppressive agents within 2 to 12 weeks prior to the baseline depending on DMARD/immunosuppressive agent Any prior treatment with tofacitinib or other JAK inhibitor
Biologic DMARDs	Any prior biologic agent, including IL-6, IL-6R antagonists
Corticosteroids	Parenteral or intra articular use within 4 weeks prior to screening Systemic dose >10 mg/day of prednisone or change in dose within 4 weeks prior to baseline

ACR/EULAR = American College of Rheumatology/European League Against Rheumatism; BL = baseline; CRP = C-reactive protein; DMARD = disease-modifying antirheumatic drug; JAK = Janus kinase inhibitor; IL-6R = interleukin 6 receptor; MTX = methotrexate; RA = rheumatoid arthritis; RF = rheumatoid factor

Treatments

Sarilumab

One injection of sarilumab 200 mg or matching placebo (for patients in the adalimumab group) was administered q2w during the 24-week randomized period (an IMP administration window of ± 3 days). In the open label period, the sarilumab dose may have been reduced to 150 mg q2w in case of pre-defined levels of neutropenia, thrombocytopenia, or an increase in liver enzymes (ALT) or alternately resumed at the prior dose of 200 mg q2w based on investigator judgment, provided other conditions for resumption of the IMP were met.

Adalimumab

One injection of adalimumab 40 mg or matching placebo (for patients in the sarilumab group) was administered q2w (an IMP administration window of ± 3 days was permitted).

For patients who required dose escalation to weekly adalimumab 40 mg (or matching placebo) dosing in the randomized treatment period, the IMP was to be administered every 7 days; in this case, an IMP administration window of ±1 day was permitted per protocol to accommodate exceptional circumstances.

Prior and concomitant therapy

Prior medications were those the patient used prior to first IMP intake (Day-28 to Day-1). Prior medications could be discontinued before first dosing or could be ongoing during the treatment phase. All medications taken within a certain period of time before randomization and until the end of the study, including vaccines taken within 10 years before screening, DMARDs and immunosuppressive agents taken since diagnosis of RA (especially MTX, sulfasalazine, leflunomide, hydroxychloroquine, etc.) were reported.

A concomitant medication was any treatment received by the patient concomitantly to any IMP(s).

Objectives

Primary Objectives

To demonstrate that sarilumab monotherapy is superior to adalimumab monotherapy with respect to signs and symptoms as assessed by disease activity score 28 based on erythrocyte sedimentation rate (DAS28-ESR) at Week 24 in patients with active RA who are either intolerant of, or considered inappropriate candidates for continued treatment with MTX, or after at least 12 weeks of continuous treatment with MTX, are determined to be inadequate responders.

Secondary Objectives

To demonstrate that sarilumab monotherapy is superior to adalimumab monotherapy in patients with active RA who are either intolerant of or considered inappropriate candidates for continued treatment with MTX, or after at least 12 weeks of continuous treatment with MTX, are determined to be inadequate responders, with respect to:

• Reduction of signs and symptoms of RA at Week 24 (DAS28-ESR remission, American College of Rheumatology [ACR] 20/50/70 response, etc)

• Improvement in quality of life assessed by patient reported outcome questionnaires at Week 24 Assessment of the safety and tolerability of sarilumab monotherapy (including immunogenicity) throughout the study.

Exploratory Objectives

In patients with active RA who are either intolerant of, or considered inappropriate candidates for continued treatment with MTX, or after at least 12 weeks of continuous treatment with MTX, are determined to be inadequate responders:

• To describe maintenance of response over time of sarilumab monotherapy

• To describe pharmacokinetics of sarilumab monotherapy

To collect DNA, RNA, and other biomarkers for future use for the purpose of discovery of predictive biomarkers.

Outcomes/endpoints

Primary efficacy variable:

DAS28-ESR score change from baseline at Week 24

The DAS28-ESR score was assessed with a composite score that included 4 variables:

• Tender Joints Count (TJC) (based on 28 joints)

• Swollen Joints Count (SJC) (based on 28 joints)

• General health assessment by the patient assessed from the ACR RA core set questionnaire (patient global assessment) in 100 mm visual analogue scale (VAS)

• Marker of inflammation assessed by the ESR in mm/hr.

It was a continuous measure allowing for measurement of absolute change in disease activity and percentage improvement.

Secondary efficacy variables:

DAS28-ESR remission (<2.6) at Week 24, low disease activity (DAS28-ESR <3.2) at Week 24, change from baseline in disease activity score for 28 Joints based on C-reactive protein (DAS28-CRP) at Week 24, DAS28-CRP remission (<2.6) at Week 24, ACR20/50/70 response (including Health Assessment Question-Disability Index [HAQ-DI]) at Week 24, change from baseline in each individual ACR component at Week 24, remission based on clinical disease activity index (CDAI) (≤2.8) at Week 24 and change from baseline in CDAI at Week 24.

Patient-reported outcomes: Short-Form 36 (SF-36), EuroQol (EQ-5D-3L), Rheumatoid Arthritis Impact of Disease (RAID), RAspecific Work Productivity Survey (WPS-RA), Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACITFatigue), and morning stiffness VAS at Week 24.

Sample size

A difference of 0.6 in DAS28-ESR between 2 active treatments was considered to be clinically relevant. From prior trial data (ADACTA) the SD of the change from baseline in DAS28-ESR at week 24 was expected to be 1.7. In order for a 2-sample t-test to have 90% power to detect a 0.6 difference at the 5% significance level (2-sided test), 170 patients per group were required.

Randomisation

Patients were randomized at a ratio of 1:1 (sarilumab 200 mg q2w: adalimumab 40 mg q2w). Randomization was stratified by region. Permuted block randomisation (block length: 4) was applied.

Blinding (masking)

Double-dummy blinding.

Statistical methods

In general data were summarized by statistical characteristics (continuous data: n, mean, SD, median, minimum, and maximum; qualitative data: absolute and relative frequencies) stratified by treatment and visit (if applicable).

The primary efficacy analysis population was the ITT population of all randomized patients.

The primary efficacy endpoint, change from baseline in DAS28-ESR was analysed with a MMRM approach assuming an unstructured covariance structure to model the within-subject errors. The model, including terms for treatment, visit, treatment-by-visit interaction and region as fixed effects and baseline DAS28-ESR as a continuous covariate, was used to assess the difference between treatment groups in the change from baseline in DAS28-ESR at week 24. Data collected after permanent treatment discontinuation was excluded from the primary analysis.

Two sensitivity analyses of DAS28-ESR at Week 24 were performed:

- including assessments made after permanent treatment discontinuation,
- using multiple imputation for all data after treatment discontinuation or adalimumab (or matching placebo) dose increase.

Subgroup analyses were pre-specified for the primary endpoint with respect to subgroups defined by gender, race, region, age, baseline weight, BMI, RF, anti-CCP antibody, baseline CRP, baseline ESR, duration of RA, number of prior DMARDs, MTX history, and smoking history.

The same approach as for the primary endpoint was used to analyse continuous secondary efficacy endpoints. Binary secondary efficacy variables were analysed using a 2-sided CMH test stratified by region. In these analyses, patients who discontinued treatment prior to week 24 were considered as non-responders.

Treatment effects were described by point estimates and the corresponding 95%-CI derived from the analyses models mentioned above.

To control the type I error, if the primary endpoint was declared significant, a hierarchical testing procedure was pre-specified for the analysis of the secondary endpoints.

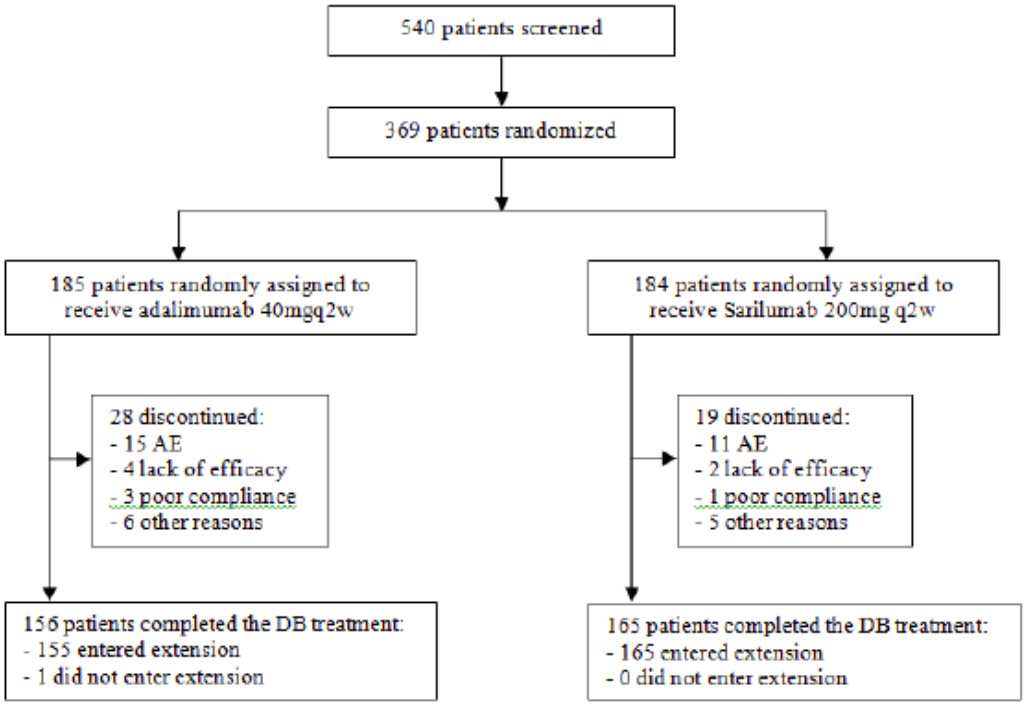
Results

Participant flow

Of the 540 patients that were screened, 171 patients were screen failures (31.7%) and 369 were randomized. Screen failures were mainly due to meeting the exclusion criteria related to tuberculosis (12.0%), and due to failure to meet the inclusion criterion for the severity of the disease (8.1%).

The ITT population consisted of the 369 randomized patients. For the primary safety analysis the safety population consisted of 368 patients. One patient was randomized but not treated in the adalimumab group because she did not meet inclusion/exclusion criteria and the randomization was done in error.

Figure 12: Disposition of patients



Recruitment

Date first patient enrolled: 11-February-2015.

Date last patient completed: 20-January-2016.

Conduct of the study

There were five amendments of the protocol with amendment 1 introduced on 17 December 2014 before inclusion of any patients. Amendments 1 and 2 were applicable to UK only. Amendment 3 was applicable to Germany. Amendments 4 and 5 were applicable to all countries.

Amendment 1, 17-Dec-2014:

• To comply with the MHRA guidelines on contraceptive wording in Clinical Trials.

Amendment 2, 19-Feb-2015:

• To comply with the MHRA guidelines on contraceptive wording in Clinical Trials.

Amendment 3, 29-Apr-2015:

- To comply with the German national EC guidance.

Amendment 4, 17-Jun-2015:

This protocol amendment was applicable in all countries participating in the SARIL-RAMONARCH (EFC14092) study. The protocol was updated to address the following items:

• Added assessment of potential opportunistic infections and study treatment continuation

• To correct errors or inconsistencies in protocol schedule of events and footnotes.

• To correct inconsistencies in criteria for dose escalation.

• To detail the requirement for an independent joint assessor.

Amendment 5, 20-Nov-2015:

This protocol amendment was applicable in all countries participating in the SARIL-RAMONARCH (EFC14092) study, with some elements that were country specific detailed as such. The aim of this protocol amendment 5 was to modify the study duration to provide long term open label treatment with sarilumab 200mg q2w beyond week 48, until anticipated commercial availability of sarilumab or until 2020 at the latest when the study will be closed.

Dose reduction: Incorporate dose reduction to 150mg sarilumab q2w in open label extension, as option in cases of pre-defined neutropenia, thrombocytopenia, and liver function abnormality (ALT elevation) requiring temporary holding of IMP.

Baseline data

Table 54: Demographics and patient characteristics at baseline - Randomized population

	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)	All (N=369)
Age (years)			
Number	185	184	369
Mean (SD)	53.6 (11.9)	50.9 (12.6)	52.2 (12.3)
Median	54.0	52.0	53.0
Min : Max	25 : 80	20 : 77	20 : 80
Age Group (years) [n (%)]			
Number	185	184	369
<65	145 (78.4%)	158 (85.9%)	303 (82.1%)
≥65 and <75	35 (18.9%)	25 (13.6%)	60 (16.3%)
≥75	5 (2.7%)	1 (0.5%)	6 (1.6%)
Sex [n (%)]			
Number	185	184	369
Male	35 (18.9%)	27 (14.7%)	62 (16.8%)
Female	150 (81.1%)	157 (85.3%)	307 (83.2%)
Race [n (%)]			
Number	185	184	369
Caucasian/White	164 (88.6%)	171 (92.9%)	335 (90.8%)
Black	3 (1.6%)	1 (0.5%)	4 (1.1%)
Asian/Oriental	9 (4.9%)	2 (1.1%)	11 (3.0%)
Other	9 (4.9%)	10 (5.4%)	19 (5.1%)
Ethnicity [n (%)]			
Number	185	184	369
Hispanic	40 (21.6%)	46 (25.0%)	86 (23.3%)
Not Hispanic	145 (78.4%)	138 (75.0%)	283 (76.7%)
Weight (kg)			
Number	184	184	368
Mean (SD)	71.79 (17.79)	72.30 (16.54)	72.05 (17.15)
Median	68.25	71.25	69.90
Min : Max	33.0 : 172.0	43.0 : 138.4	33.0 : 172.0
Weight group(kg) [n (%)]			
Number	184	184	368
<60	50 (27.2%)	42 (22.8%)	92 (25.0%)
≥60 and <100	121 (65.8%)	130 (70.7%)	251 (68.2%)
≥100	13 (7.1%)	12 (6.5%)	25 (6.8%)
BMI (kg/m^2)			
Number	184	184	368
Mean (SD)	27.26 (6.45)	27.09 (5.64)	27.18 (6.05)
Median	26.79	26.39	26.68
Min : Max	14.1 : 67.2	16.9 : 47.9	14.1 : 67.2

	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)	All (N=369)
BMI group(kg/m^2) [n (%)]			
Number	184	184	368
<25	73 (39.7%)	71 (38.6%)	144 (39.1%)
≥25 and <30	61 (33.2%)	70 (38.0%)	131 (35.6%)
≥30	50 (27.2%)	43 (23.4%)	93 (25.3%)
Region [n(%)]			
Number	185	184	369
Region1	62 (33.5%)	61 (33.2%)	123 (33.3%)
Region2	35 (18.9%)	36 (19.6%)	71 (19.2%)
Region3	88 (47.6%)	87 (47.3%)	175 (47.4%)
Smoking Status [n(%)]			
Number	185	184	369
Never	131 (70.8%)	134 (72.8%)	265 (71.8%)
Former	30 (16.2%)	27 (14.7%)	57 (15.4%)
Current	24 (13.0%)	23 (12.5%)	47 (12.7%)
Alcohol Habits[a] [n(%)]			
Number	185	184	369
Never	139 (75.1%)	133 (72.3%)	272 (73.7%)
Monthly	30 (16.2%)	35 (19.0%)	65 (17.6%)
Weekly	15 (8.1%)	16 (8.7%)	31 (8.4%)
Daily	1 (0.5%)	0	1 (0.3%)

BMI = Body mass index
Region 1 (Western countries): Czech Republic, Germany, Hungary, Israel, Spain, and United States
Region 2 (South America): Chile and Peru
Region 3 (Rest of the world): South Korea, Poland, South Africa, Romania, Russia, and Ukraine
Percentages are calculated using number of patients assessed as denominator.
a Alcohol habits: how often subject has a drink containing alcohol in the last 5 years.

Table 55: Disease characteristics at baseline - Randomized population

	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)	All (N=369)
Duration of RA since diagnosis (Years)			
Number	185	184	369
Mean (SD)	6.56 (7.80)	8.11 (8.12)	7.33 (7.99)
Median	3.38	5.36	4.65
Min : Max	0.3 : 47.3	0.3 : 42.3	0.3 : 47.3
RA functional class [n(%)]			
Number	185	184	369
I	37 (20.0%)	29 (15.8%)	66 (17.9%)
II	115 (62.2%)	125 (67.9%)	240 (65.0%)
III	33 (17.8%)	30 (16.3%)	63 (17.1%)
Rheumatoid factor [n(%)]			
Number	179	178	357
Positive	116 (64.8%)	119 (66.9%)	235 (65.8%)
Negative	63 (35.2%)	59 (33.1%)	122 (34.2%)
Anti CCP antibody [n(%)]			
Number	180	178	358
Positive	138 (76.7%)	134 (75.3%)	272 (76.0%)
Negative	42 (23.3%)	44 (24.7%)	86 (24.0%)
Number of prior non-biologic DMARDs/Immunosuppressive agents [n(%)]			
Number	185	184	369
None	0	0	0
1	88 (47.6%)	83 (45.1%)	171 (46.3%)
2	58 (31.4%)	57 (31.0%)	115 (31.2%)
≥3	39 (21.1%)	44 (23.9%)	83 (22.5%)

	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)	All (N=369)
Tender joint count (0-68)			
Number	185	184	369
Mean (SD)	26.68 (13.63)	27.96 (13.19)	27.32 (13.41)
Median	24.00	25.00	24.00
Min : Max	7.0 : 68.0	6.0 : 64.0	6.0 : 68.0
Swollen joint count (0-66)			
Number	185	184	369
Mean (SD)	17.51 (10.25)	18.57 (10.74)	18.04 (10.50)
Median	15.00	16.00	15.00
Min : Max	1.0 : 66.0	6.0 : 61.0	1.0 : 66.0
HAQ-DI (0-3)			
Number	185	184	369
Mean (SD)	1.63 (0.64)	1.64 (0.55)	1.64 (0.60)
Median	1.63	1.63	1.63
Min : Max	0.0 : 3.0	0.3 : 2.9	0.0 : 3.0
CRP (mg/L)			
Number	185	184	369
Mean (SD)	24.05 (30.98)	17.36 (21.31)	20.71 (26.78)
Median	9.55	7.96	8.92
Min : Max	0.2 : 202.0	0.4 : 120.0	0.2 : 202.0
CRP group (mg/L) [n(%)]			
Number	185	184	369
≤15 mg/L	102 (55.1%)	117 (63.6%)	219 (59.3%)
> 15 mg/L	83 (44.9%)	67 (36.4%)	150 (40.7%)
DAS28-CRP			
Number	185	184	369
Mean (SD)	6.02 (0.89)	6.00 (0.88)	6.01 (0.89)
Median	5.99	5.93	5.97
Min : Max	3.9 : 8.3	3.5 : 8.0	3.5 : 8.3
DAS28-ESR			
Number	185	184	369
Mean (SD)	6.76 (0.83)	6.83 (0.76)	6.80 (0.80)
Median	6.69	6.80	6.77
Min : Max	4.0 : 9.1	4.5 : 8.6	4.0 : 9.1

	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)	All (N=369)
ESR (mm/hr)			
Number	185	184	369
Mean (SD)	47.51 (23.23)	46.48 (21.75)	47.00 (22.48)
Median	40.00	39.00	39.00
Min : Max	7.0 : 130.0	4.0 : 120.0	4.0 : 130.0
ESR group (mm/hr) [n (%)]			
Number	185	184	369
≤ Median	90 (48.6%)	96 (52.2%)	186 (50.4%)
> Median	95 (51.4%)	88 (47.8%)	183 (49.6%)
Baseline CDAI			
Number	185	184	369
Mean (SD)	42.40 (11.97)	43.62 (12.10)	43.01 (12.03)
Median	41.00	41.50	41.10
Min : Max	15.1 : 73.5	11.9 : 71.4	11.9 : 73.5

HAQ-D1: Health Assessment Questionnaire-Disability Index, DAS28-CRP: Disease Activity Score 28, CRP: C-reactive protein, DAS28-ESR: Disease Activity Score 28, erythrocyte sedimentation rate, ESR: erythrocyte sedimentation rate, CDAI: Clinical Disease Activity Index

Numbers analysed

Table 56: Patients disposition at Week 24 - Randomized population

	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)	All (N=369)
Randomized and not treated	1 (0.5%)	0	1 (0.3%)
Randomized and treated	184 (99.5%)	184 (100%)	368 (99.7%)
Completed DB treatment period	156 (84.3%)	165 (89.7%)	321 (87.0%)
Enrolled in open label extension period	155 (83.8%)	165 (89.7%)	320 (86.7%)
Did not enroll in open label extension period	1 (0.5%)	0	1 (0.3%)
Discontinued DB treatment period (Not enrolled in open label extension period)	28 (15.1%)	19 (10.3%)	47 (12.7%)
Subject's decision for treatment discontinuation	15 (8.1%)	8 (4.3%)	23 (6.2%)
Reason for treatment discontinuation			
Adverse event	15 (8.1%)	11 (6.0%)	26 (7.0%)
Lack of efficacy	4 (2.2%)	2 (1.1%)	6 (1.6%)
Poor compliance to protocol	3 (1.6%)	1 (0.5%)	4 (1.1%)
Other reasons	6 (3.2%)	5 (2.7%)	11 (3.0%)
Continue follow-up to Week 24	12 (6.5%)	9 (4.9%)	21 (5.7%)
Did not complete follow-up to Week 24	16 (8.6%)	10 (5.4%)	26 (7.0%)

	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)	All (N=369)
Reason for follow-up discontinuation			
Subject refused	11 (5.9%)	5 (2.7%)	16 (4.3%)
Subject unable	4 (2.2%)	3 (1.6%)	7 (1.9%)
Lost to follow-up	1 (0.5%)	2 (1.1%)	3 (0.8%)

DB=Double-blind, DB follow-up period=Visits up to Week 24.
Note: Percentages are calculated using the number of patients randomized as denominator.
Note: Subject's request for treatment discontinuation is a separate category and is not included in the reasons for discontinuation summaries.

Outcomes and estimation

Primary analysis

The change from baseline in the DAS28-ESR score at Week 24 showed a significantly greater improvement in the sarilumab group compared to adalimumab group. A greater difference was also observed at Week 12 when the first post-baseline assessment was done (nominal p<0.0001). The primary analysis included data regardless of dose escalation.

Table 57: Change from baseline in DAS28-ESR at Week 24 - ITT population

	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)
DAS28-ESR		
Number	163	165
Baseline Mean (SD)	6.73 (0.83)	6.81 (0.76)
Week 24 Mean (SD)	4.51 (1.35)	3.46 (1.44)
Change Mean (SD)	-2.22 (1.36)	-3.35 (1.37)
LS mean (SE)	-2.20 (0.106)	-3.28 (0.105)
LS mean diff, 95% CI		-1.077 (-1.361,-0.793)
P-value vs Adalimumab[a]		<0.0001

DAS28-ESR =0.56 x sqrt(28TJC) + 0.28 x sqrt(28SJC) + 0.70 x Ln(ESR) + 0.014 x Patient global VAS.
All assessments are set to missing after the end of treatment visit, which was re-mapped to the next scheduled visit, for a patient who discontinues study medication.
Note: Number = Number of patients with assessment at both baseline and Week 24.
a Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, region, visit, and treatment-by-visit interaction.

Sensitivity analyses

Two sensitivity analyses of the change from baseline in the DAS28-ESR score at Week 24 were performed.

In the first sensitivity analysis, all data including assessments made after permanent treatment discontinuation were included. Consistent with the primary analysis, a statistically significant difference in favor of sarilumab compared to adalimumab was observed.

In the second sensitivity analysis, all data after treatment discontinuation or adalimumab (or matching placebo) dose increase were set to missing and a multiple imputation approach was used. A statistically significant difference in favor of sarilumab compared to adalimumab was also observed, which was similar with that in the primary analysis.

Table 58: Change from baseline in DAS28-ESR at Week 24 (Sensitivity analysis #1) - ITT population

	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)
DAS28-ESR		
Number	172	171
Baseline Mean (SD)	6.75 (0.84)	6.81 (0.75)
Week 24 Mean (SD)	4.51 (1.36)	3.53 (1.47)
Change Mean (SD)	-2.24 (1.39)	-3.28 (1.39)
LS mean (SE)	-2.22 (0.105)	-3.24 (0.105)
LS mean diff, 95% CI		-1.020 (-1.303,-0.738)
P-value vs Adalimumab[a]		<0.0001

DAS28-ESR =0.56 x sqrt(28TJC) + 0.28 x sqrt(28SJC) + 0.70 x Ln(ESR) + 0.014 x Patient global VAS.
All assessments collected from the time a patient prematurely discontinues study medication are included in the analysis.
Note: Number = Number of patients with assessment at both baseline and Week 24.
a Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, region, visit, and treatment-by-visit interaction.

Table 59: Change from baseline in DAS28-ESR at Week 24 (Sensitivity analysis #2) - ITT population

	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)
DAS28-ESR		
Number	147	157
Baseline Mean (SD)	6.75 (0.79)	6.77 (0.74)
Week 24 Mean (SD)	4.37 (1.27)	3.33 (1.31)
Change Mean (SD)	-2.38 (1.26)	-3.44 (1.28)
LS mean (SE)	-2.27 (0.103)	-3.34 (0.108)
LS mean diff, 95% CI		-1.071 (-1.344,-0.798)
P-value vs Adalimumab		<0.0001

DAS28-ESR =0.56 x sqrt(28TJC) + 0.28 x sqrt(28SJC) + 0.70 x Ln(ESR) + 0.014 x Patient global VAS.
All assessments are set to missing from the time a patient discontinued study medication or has an adalimumab (or matching placebo) dose increase. Multiple imputation was used to handle the missing measurements.
Note: Number = Number of patients with assessment at both baseline and Week 24.

Supportive Analyses: the change from baseline in DAS28-ESR at Week 12

Table 60: Change from baseline in DAS28-ESR at Week 12 - ITT population

	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)
DAS28-ESR		
Number	174	177
Baseline Mean (SD)	6.76 (0.83)	6.82 (0.76)
Week12 Mean (SD)	4.90 (1.53)	4.05 (1.52)
Change Mean (SD)	-1.86 (1.44)	-2.77 (1.41)
LS mean (SE)	-1.88 (0.111)	-2.77 (0.110)
LS mean diff, 95% CI		-0.888 (-1.183,-0.592)
P-value vs Adalimumab[a]		<0.0001

DAS28-ESR =0.56 x sqrt(28TJC) + 0.28 x sqrt(28SJC) + 0.70 x Ln(ESR) + 0.014 x Patient global VAS.
All assessments are set to missing from the time a patient prematurely discontinues study medication.
Note: Number = Number of patients with assessment at both baseline and Week 12.
a Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, region, visit, and treatment-by-visit interaction.

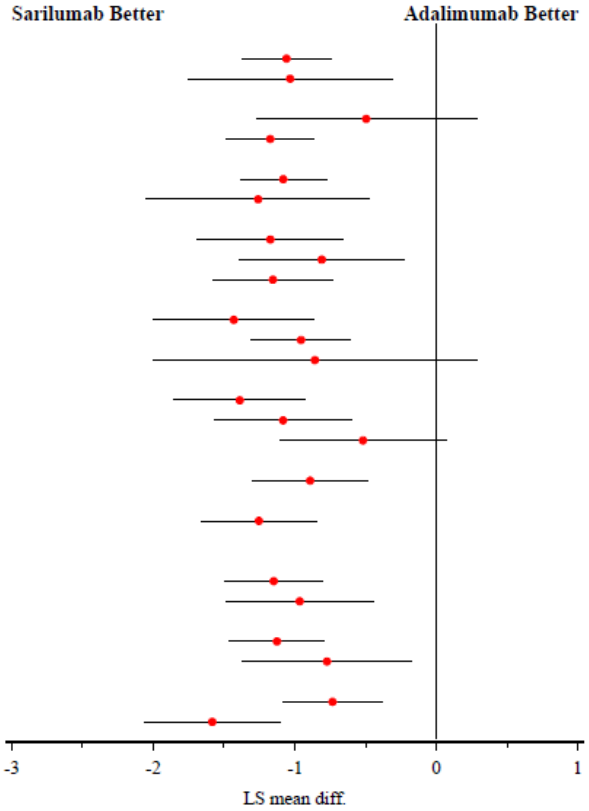
Subgroup analyses

As illustrated in Figure 13 and Table 61, the superior efficacy (change from baseline in DAS28-ESR at Week 24) of sarilumab relative to adalimumab was consistent among subgroups for age, gender, race, region, or body weight. There was no evidence that duration of RA, number of prior DMARDS, MTX intolerance/inadequate response, or smoking history had an impact on comparative efficacy between the treatment groups. Baseline ESR, RF, anti-CCP did not emerge as relevant factors in the subgroup analyses for change in DAS28-ESR.

There was a statistically significant interaction between treatment group and baseline CRP (p=0.0055, Table 65); a larger treatment effect was seen in patients with baseline CRP > 15 mg/L compared with patients with an average baseline CRP ≤ 15 mg/mL (Figure 13). Nevertheless, the change from baseline in DAS28-ESR at Week 24 was greater in the sarilumab group than in the adalimumab group across all categories of CRP.

Figure 13: DAS28-ESR change from baseline forest plot at Week 24 - ITT population

Subgroup	Adalimumab*	Sarilumab*
Age group (year)		
<65 (N=275)	-2.25	-3.30
>=65 (N=53)	-2.05	-3.08
Gender		
Male (N=52)	-3.11	-3.61
Female (N=276)	-2.10	-3.27
Race		
Caucasian/White (N=296)	-2.11	-3.20
All other races (N=32)	-2.60	-3.86
Region		
Region 1 (N=104)	-2.32	-3.49
Region 2 (N=64)	-2.25	-3.05
Region 3 (N=160)	-2.10	-3.26
Baseline weight (kg)		
<60 (N=83)	-2.13	-3.56
>=60 and <100 (N=222)	-2.23	-3.19
>=100 (N=23)	-1.57	-2.43
BMI(kg/m2)		
<25 (N=130)	-2.25	-3.63
>=25 and <30 (N=117)	-1.98	-3.07
>=30 (N=81)	-2.57	-3.08
MTX history		
Inadequate responders (N=181)	-2.30	-3.19
Intolerant/inappropriate to continue (N=147)	-2.10	-3.35
Rheumatoid factor		
Positive (N=210)	-2.20	-3.35
Negative (N=108)	-2.18	-3.14
Anti CCP antibody		
Positive (N=243)	-2.22	-3.34
Negative (N=75)	-2.31	-3.08
Baseline CRP		
<=15 mg/L (N=198)	-2.33	-3.07
>15 mg/L (N=130)	-2.05	-3.63
Baseline ESR		
<=median (N=172)	-2.27	-3.11
>median (N=156)	-2.15	-3.45
Duration of RA		
<=Median (N=163)	-2.25	-3.34
>Median (N=165)	-2.27	-3.28
Duration of RA (year)		
<=3 years (N=126)	-2.26	-3.34
>3 years (N=202)	-2.25	-3.28
Number of prior DMARDs		
<=1 (N=151)	-2.21	-3.08
2 (N=104)	-2.45	-3.64
>=3 (N=73)	-1.99	-3.28
Smoking history		
Never (N=238)	-2.18	-3.30
Former (N=52)	-1.97	-3.29
Current (N=38)	-2.51	-3.15



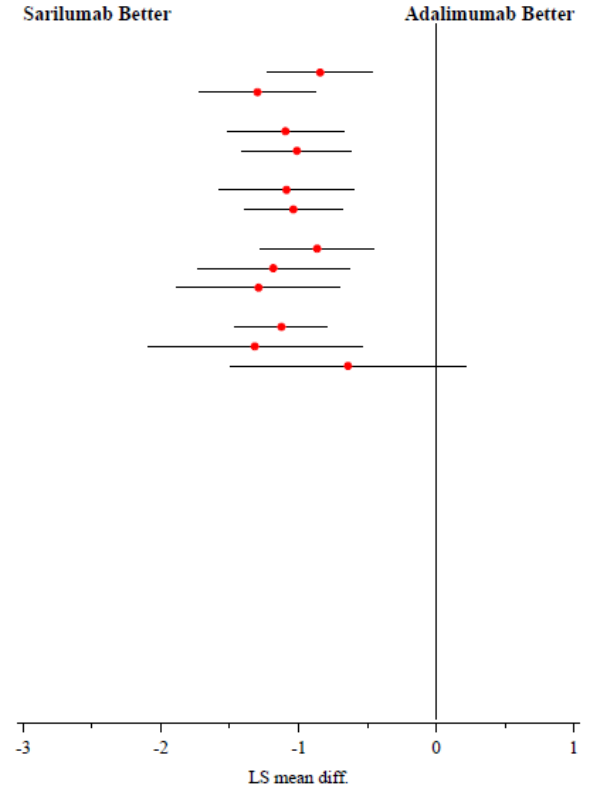


Table 61: Change from baseline in DAS28-ESR at Week 24 by subgroups - ITT population

	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)	p-value for interaction[a]
Age			0.8819
< 65			
Change Mean (SD)	-2.24 (1.34)	-3.33 (1.38)	
LS mean diff, 95% CI [b]		-1.058 (-1.372,-0.743)	
≥ 65			
Change Mean (SD)	-2.12 (1.45)	-3.46 (1.30)	
LS mean diff, 95% CI [b]		-1.033 (-1.754,-0.311)	
Gender			0.1953
Male			
Change Mean (SD)	-2.59 (1.54)	-3.43 (1.30)	
LS mean diff, 95% CI [b]		-0.495 (-1.273,0.283)	
Female			
Change Mean (SD)	-2.14 (1.31)	-3.34 (1.38)	
LS mean diff, 95% CI [b]		-1.173 (-1.480,-0.865)	
Race			0.6242
Caucasian/White			
Change Mean (SD)	-2.16 (1.39)	-3.30 (1.38)	
LS mean diff, 95% CI [b]		-1.081 (-1.384,-0.778)	
All Other races			
Change Mean (SD)	-2.62 (1.05)	-3.97 (0.94)	
LS mean diff, 95% CI [b]		-1.258 (-2.047,-0.469)	
Region			0.6213
Region 1			
Change Mean (SD)	-2.36 (1.49)	-3.59 (1.35)	
LS mean diff, 95% CI [b]		-1.172 (-1.689,-0.656)	
Region 2			
Change Mean (SD)	-2.23 (1.23)	-3.10 (1.23)	
LS mean diff, 95% CI [b]		-0.809 (-1.394,-0.224)	
Region 3			
Change Mean (SD)	-2.12 (1.32)	-3.29 (1.42)	
LS mean diff, 95% CI [b]		-1.154 (-1.576,-0.731)	
Baseline weight			0.2533
< 60 kg			
Change Mean (SD)	-2.10 (1.32)	-3.58 (1.30)	

	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)	p-value for interaction[a]
LS mean diff, 95% CI [b]		-1.431 (-1.995,-0.866)	
≥ 60 - < 100 kg			
Change Mean (SD)	-2.28 (1.43)	-3.31 (1.34)	
LS mean diff, 95% CI [b]		-0.955 (-1.303,-0.607)	
≥ 100 kg			
Change Mean (SD)	-2.10 (0.89)	-2.93 (1.86)	
LS mean diff, 95% CI [b]		-0.858 (-2.002,0.287)	
BMI			0.0466
< 25 kg/m^2			
Change Mean (SD)	-2.08 (1.51)	-3.54 (1.35)	
LS mean diff, 95% CI [b]		-1.388 (-1.851,-0.925)	
≥ 25 - < 30 kg/m^2			
Change Mean (SD)	-2.08 (1.17)	-3.24 (1.41)	
LS mean diff, 95% CI [b]		-1.082 (-1.566,-0.599)	
≥ 30 kg/m^2			
Change Mean (SD)	-2.56 (1.30)	-3.20 (1.30)	
LS mean diff, 95% CI [b]		-0.517 (-1.102,0.067)	
MTX history			0.2163
Inadequate responders			
Change Mean (SD)	-2.30 (1.37)	-3.18 (1.43)	
LS mean diff, 95% CI [b]		-0.891 (-1.293,-0.489)	
Intolerant/inappropriate to continue			
Change Mean (SD)	-2.11 (1.35)	-3.55 (1.27)	
LS mean diff, 95% CI [b]		-1.253 (-1.660,-0.846)	
Rheumatoid factor			0.6410
Positive			
Change Mean (SD)	-2.17 (1.28)	-3.44 (1.32)	
LS mean diff, 95% CI [b]		-1.148 (-1.489,-0.808)	
Negative			
Change Mean (SD)	-2.29 (1.40)	-3.25 (1.36)	
LS mean diff, 95% CI [b]		-0.965 (-1.484,-0.446)	
Anti CCP antibody			0.4771
Positive			
Change Mean (SD)	-2.21 (1.41)	-3.44 (1.34)	
LS mean diff, 95% CI [b]		-1.126 (-1.459,-0.793)	
Negative			
Change Mean (SD)	-2.36 (1.21)	-3.17 (1.31)	
LS mean diff, 95% CI [b]		-0.772 (-1.370,-0.174)	

	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)	p-value for interaction[a]
Baseline CRP			0.0055
≤ 15 mg/L			
Change Mean (SD)	-2.36 (1.31)	-3.16 (1.30)	
LS mean diff, 95% CI [b]		-0.733 (-1.083,-0.383)	
> 15 mg/L			
Change Mean (SD)	-2.02 (1.41)	-3.67 (1.43)	
LS mean diff, 95% CI [b]		-1.582 (-2.065,-1.100)	
Baseline ESR			0.1295
≤ median			
Change Mean (SD)	-2.30 (1.31)	-3.20 (1.36)	
LS mean diff, 95% CI [b]		-0.842 (-1.227,-0.458)	
> median			
Change Mean (SD)	-2.13 (1.41)	-3.53 (1.36)	
LS mean diff, 95% CI [b]		-1.298 (-1.724,-0.871)	
Duration of RA			0.8227
≤ median			
Change Mean (SD)	-2.18 (1.39)	-3.32 (1.41)	
LS mean diff, 95% CI [b]		-1.095 (-1.520,-0.670)	
> median			
Change Mean (SD)	-2.27 (1.32)	-3.37 (1.34)	
LS mean diff, 95% CI [b]		-1.012 (-1.408,-0.615)	
Duration of RA			0.8465
≤ 3 years			
Change Mean (SD)	-2.18 (1.46)	-3.30 (1.43)	
LS mean diff, 95% CI [b]		-1.087 (-1.580,-0.594)	
> 3 years			
Change Mean (SD)	-2.25 (1.28)	-3.37 (1.34)	
LS mean diff, 95% CI [b]		-1.037 (-1.392,-0.681)	
Number of prior DMARDs			0.3740
≤ 1			
Change Mean (SD)	-2.21 (1.23)	-3.08 (1.39)	
LS mean diff, 95% CI [b]		-0.865 (-1.277,-0.453)	
2			
Change Mean (SD)	-2.44 (1.47)	-3.58 (1.40)	
LS mean diff, 95% CI [b]		-1.183 (-1.733,-0.633)	
≥ 3			
Change Mean (SD)	-1.91 (1.45)	-3.55 (1.19)	
LS mean diff, 95% CI [b]		-1.290 (-1.881,-0.698)	

	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)	p-value for interaction[a]
Smoking history			0.3829
Never			
Change Mean (SD)	-2.19 (1.32)	-3.30 (1.42)	
LS mean diff, 95% CI [b]		-1.123 (-1.458,-0.788)	
Former			
Change Mean (SD)	-2.16 (1.57)	-3.63 (1.30)	
LS mean diff, 95% CI [b]		-1.318 (-2.096,-0.539)	
Current			
Change Mean (SD)	-2.46 (1.34)	-3.26 (1.08)	
LS mean diff, 95% CI [b]		-0.640 (-1.497,0.217)	

All assessments are set to missing from the time a patient prematurely discontinues study medication.
Region 1 (Western countries): Czech Republic, Germany, Hungary, Israel, Spain, and United States
Region 2 (South America): Chile and Peru
Region 3 (Rest of the world): South Korea, Poland, South Africa, Romania, Russia, and Ukraine

a MMRM assuming an unstructured covariance structure with covariate baseline and terms of treatment, region, subgroup, treatment-by-subgroup, visit, treatment-by-visit, treatment-by-visit-by-subgroup.

b MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, region, visit, treatment-by-visit interaction.

Secondary efficacy endpoints

Table 62 shows the results for the pre-specified hierarchy of primary and secondary efficacy endpoints including assessments of quality of life. The results that are bolded are statistically significant according to the order in the testing hierarchy. The last statistically significant endpoint in the testing hierarchy was the SF-36 physical score.

Table 62: Hierarchical order for the primary and secondary efficacy endpoints

Parameter[a]	Adalimumab 40 mg q2w (N=XXX)	Sarilumab 200 mg q2w (N=XXX)	
		Estimate[b]	P-value[c]
Primary endpoint			
DAS28-ESR	-2.20(0.106)	-3.28(0.105)	**<0.0001**
Secondary endpoints			
DAS28-ESR (remission) – Week 24	13(7.0)	49(26.6)	**<0.0001**
ACR50 response – Week 24	55 (29.7%)	84 (45.7%)	**0.0017**
ACR70 response – Week 24	22 (11.9%)	43 (23.4%)	**0.0036**
ACR20 response – Week 24	108 (58.4%)	132 (71.7%)	**0.0074**
HAQ-DI – Week 24	-0.43(0.045)	-0.61(0.045)	**0.0037**
SF-36 Physical – Week 24	6.09(0.555)	8.74(0.555)	**0.0006**
FACIT Fatigue – Week 24	8.41(0.709)	10.18(0.701)	0.0689
SF-36 Mental – Week 24	6.83(0.774)	7.86(0.773)	0.3319

a For further details on the endpoint definitions and analysis methods see 16-1-9-sap.
b Values presented are number and percent of responders for binary variables and LS mean change from baseline with standard error for continuous variables
c All values in bold font are significant according to the hierarchical testing procedure.

DAS28-ESR remission at Week 24

Table 63: Incidence of DAS28-ESR remission (DAS28-ESR < 2.6) at Week 24 - ITT population

DAS28-ESR < 2.6 at Week 24	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)
Number	185	184
Yes	13 (7.0%)	49 (26.6%)
No	172 (93.0%)	135 (73.4%)
P-value vs Adalimumab [a]		<0.0001
OR, CI vs Adalimumab [b]		4.879 (2.536, 9.389)
Of responders, proportion with 0 active joints (n)	7/13 (53.8%)	14/49 (28.6%)
Of responders, proportion with 1 active joints (n)	2/13 (15.4%)	11/49 (22.4%)
Of responders, proportion with 2 active joints (n)	2/13 (15.4%)	9/49 (18.4%)
Of responders, proportion with 3 or more active joints (n)	2/13 (15.4%)	15/49 (30.6%)

OR: Odds ratio. CI: Confidence interval
DAS28-ESR =0.56 x sqrt(28TJC) + 0.28 x sqrt(28SJC) + 0.70 x Ln(ESR) + 0.014 x Patient global VAS.
Patients are considered to be not < 2.6 from the time they discontinued study medication.
Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.
a CMH test stratified by region
b Mantel-Haenszel estimate.
Note: Active joint is defined as a joint that is either tender or swollen or both.

Table 64: Incidence of DAS28-ESR remission (DAS28-ESR < 2.6) at Week 12 - ITT population
Source: efc14092-1-15-body p.87

DAS28-ESR < 2.6 at Week 12	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)
Number	185	184
Yes	13 (7.0%)	30 (16.3%)
No	172 (93.0%)	154 (83.7%)
P-value vs Adalimumab [a]		0.0051
OR, CI vs Adalimumab [b]		2.613 (1.312, 5.204)
Of responders, proportion with 0 active joints (n)	8/13 (61.5%)	12/30 (40.0%)
Of responders, proportion with 1 active joints (n)	1/13 (7.7%)	5/30 (16.7%)
Of responders, proportion with 2 active joints (n)	0/13	4/30 (13.3%)
Of responders, proportion with 3 or more active joints (n)	4/13 (30.8%)	9/30 (30.0%)

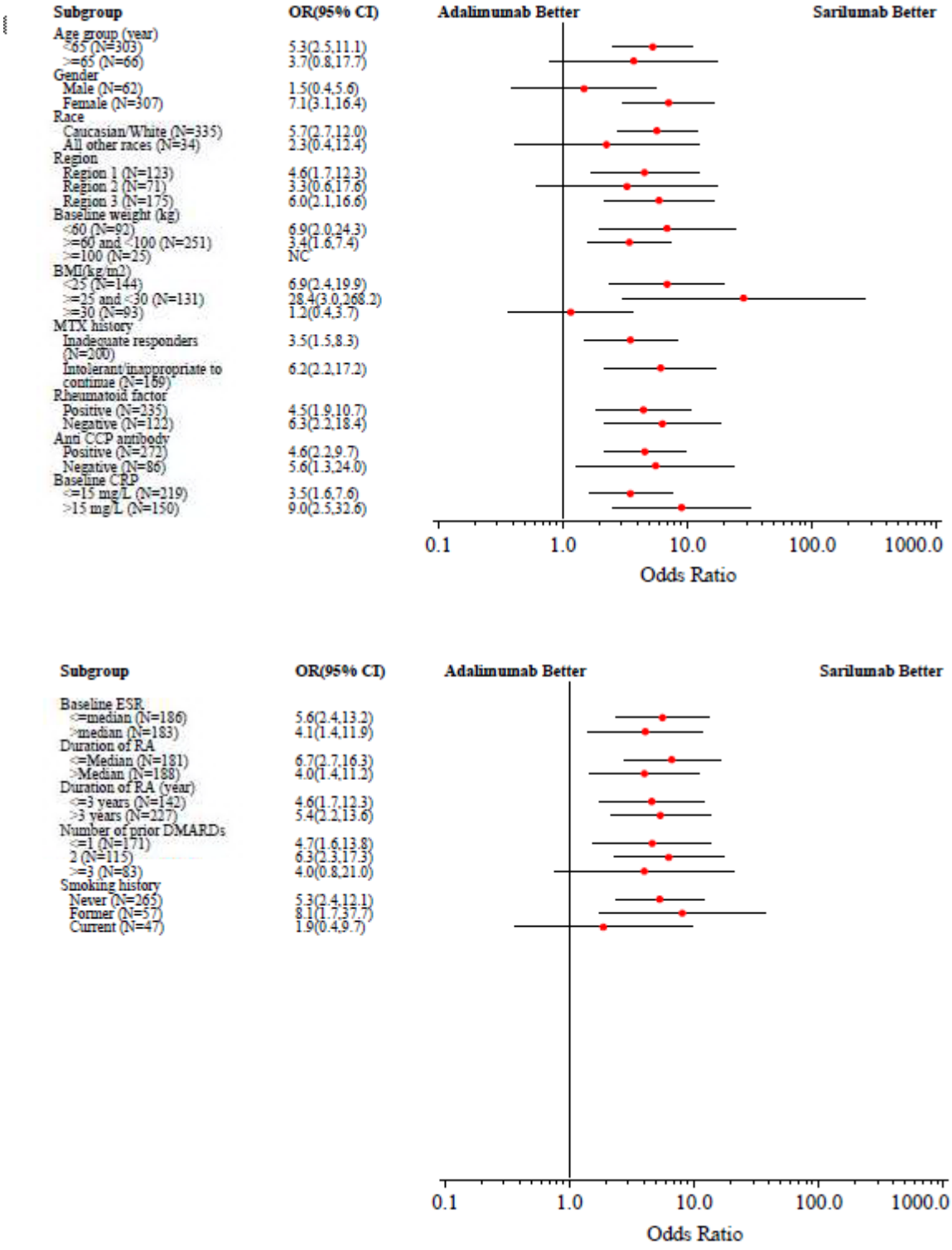
OR: Odds ratio. CI: Confidence interval
DAS28-ESR =0.56 x sqrt(28TJC) + 0.28 x sqrt(28SJC) + 0.70 x Ln(ESR) + 0.014 x Patient global VAS.
Patients are considered to be not < 2.6 from the time they discontinued study medication.
Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.
a CMH test stratified by region
b Mantel-Haenszel estimate.
Note: Active joint is defined as a joint that is either tender or swollen or both.

Subgroup Analyses: DAS28-ESR remission at Week 24

While there was a statistically significant interaction between baseline BMI and treatment group in DAS28-ESR remission (DAS28-ESR <2.6) at Week 24 (p=0.0094), where the smallest treatment effect was seen in patients with BMI ≥ 30 kg/m2, the overall number of patients achieving DAS28-ESR remission in each of the BMI categories was numerically greater in the sarilumab group than the adalimumab group (<25 kg/m2: 33.8% vs 6.8%; ≥ 25 - <30 kg/m2: 25.7% vs 1.6%; ≥ 30 kg/m2: 16.3% vs 14.0%). A similar significant interaction between baseline BMI and treatment group for change from baseline in DAS28-ESR at Week 24 was also identified.

In contrast to the change from baseline in DAS-ESR at Week 24, where a statistically significant interaction between treatment group and baseline CRP was identified, there was no significant interaction between baseline CRP and treatment group in DAS28-ESR remission. No other significant interaction was identified for the other factors, including baseline weight, and treatment group in the subgroup analyses for DAS28-ESR remission.

Figure 14: DAS28-ESR remission forest plot at Week 24 - ITT population



Low Disease Activity at Week 24

More patients treated with sarilumab than adalimumab achieved DAS28 low disease activity (<3.2) at Week 24.

Low Disease Activity at Week 12

More patients treated with sarilumab than adalimumab achieved DAS28 low disease activity (<3.2) at Week 12.

Change from baseline in DAS28-CRP score at Week 24

Baseline DAS28-CRP values were similar across treatment groups. Sarilumab was superior to adalimumab in the change from baseline in DAS28-CRP at Week 24. This superiority was observed as early as Week 4 (nominal p=0.0005) and increased over time.

Table 65: Change from baseline in DAS28-CRP at Week 24 - ITT population

	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)
DAS28-CRP		
Number	156	163
Baseline Mean (SD)	5.98 (0.88)	6.00 (0.87)
Week 24 Mean (SD)	3.92 (1.24)	3.07 (1.21)
Change Mean (SD)	-2.06 (1.22)	-2.93 (1.25)
LS mean (SE)	-1.97 (0.094)	-2.86 (0.093)
LS mean diff, 95% CI		-0.884 (-1.138,-0.629)
P-value vs Adalimumab[a]		<0.0001

DAS28-CRP =0.56 x sqrt(28TJC) + 0.28 x sqrt(28SJC) + 0.36 x Log(CRP+1) + 0.014 x Patient global VAS + 0.96.
All assessments are set to missing from the time a patient prematurely discontinues study medication.
Note: Number = Number of patients with assessment at both baseline and Week 24.
a Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, region, visit, and treatment-by-visit interaction.

DAS28-CRP remission and low disease activity (< 2.6 and < 3.2) at Week 24

As shown in Table 66, sarilumab was superior to adalimumab in the proportion of patients achieving DAS28-CRP remission (<2.6) at Week 24. Incidence of low disease activity (DAS28-CRP < 3.2) at Week 24 was also greater in patients treated with sarilumab than in patients treated with adalimumab (51.6% versus 24.3%; nominal p <0.0001)

Table 66: Incidence of DAS28-CRP Remission (<2.6) at Week 24 - ITT population

DAS28-CRP < 2.6 at Week 24	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)
Number	185	184
Yes	25 (13.5%)	63 (34.2%)
No	160 (86.5%)	121 (65.8%)
P-value vs Adalimumab [a]		<0.0001
OR, CI vs Adalimumab [b]		3.314 (1.973, 5.566)
Of responders, proportion with 0 active joints (n)	7/25 (28.0%)	15/63 (23.8%)
Of responders, proportion with 1 active joints (n)	4/25 (16.0%)	12/63 (19.0%)
Of responders, proportion with 2 active joints (n)	6/25 (24.0%)	13/63 (20.6%)
Of responders, proportion with 3 or more active joints (n)	8/25 (32.0%)	23/63 (36.5%)

OR: Odds ratio. CI: Confidence interval
DAS28-CRP =0.56 x sqrt(28TJC) + 0.28 x sqrt(28SJC) + 0.36 x Log(CRP+1) + 0.014 x Patient global VAS + 0.96.
Patients are considered to be not < 2.6 from the time they discontinued study medication.
Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.
a CMH test stratified by region.
b Mantel-Haenszel estimate.
Note: Active joint is defined as a joint that is either tender or swollen or both.

ACR20 Response at Week 24

The incidence of ACR20 response at Week 24 was statistically significantly greater in patients treated with sarilumab compared with patients treated with adalimumab. The results at Week 12, which were not part of the testing hierarchy, were consistent with the results at Week 24 (65.2% in the sarilumab group versus 54.6% in the adalimumab group, nominal p=0.0380.

The ACR20 response generally increased over time for the sarilumab group, and was greater than the increases over time in the adalimumab group.

Table 67: Incidence of ACR20 response at Week 24 - ITT population
Source: efc14092-1-15-body p.94

ACR20 at Week 24 n(%)	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)
Responders	108 (58.4%)	132 (71.7%)
Non-responders	77 (41.6%)	52 (28.3%)
P-value vs Adalimumab [a]		0.0074
OR, CI vs Adalimumab [b]		1.800 (1.168, 2.773)

OR: Odds ratio. CI: Confidence interval
ACR20 response = at least 20% improvement from baseline in both TJC and SJC, and in at least three of the HAQ score, CRP and three VAS assessments. If CRP was missing, ESR was substituted.
Patients are considered non-responders from the time they discontinued study medication.
Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.

ACR50 response at Week 24

The incidence of ACR50 response at Week 24 was statistically significantly greater in patients treated with sarilumab compared with patients treated with adalimumab. The results at Week 12, which were not part of the testing hierarchy, were consistent with the results at Week 24 (35.3% in the sarilumab group versus 20.5% in the adalimumab group, nominal p=0.0015.

The ACR50 response generally increased over time for the sarilumab group and was greater than the increases over time in the adalimumab group.

Table 68: Incidence of ACR50 response at Week 24 - ITT population

ACR50 at Week 24 n(%)	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)
Responders	55 (29.7%)	84 (45.7%)
Non-responders	130 (70.3%)	100 (54.3%)
P-value vs Adalimumab [a]		0.0017
OR, CI vs Adalimumab [b]		1.976 (1.289, 3.028)

OR: Odds ratio. CI: Confidence interval
ACR50 response = at least 50% improvement from baseline in both TJC and SJC, and in at least three of the HAQ score, CRP and three VAS assessments. If CRP was missing, ESR was substituted.
Patients are considered non-responders from the time they discontinued study medication.
Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.
a CMH test stratified by region.
b Mantel-Haenszel estimate.

ACR70 Response at Week 24

The incidence of ACR70 response at Week 24 was statistically significant in patients treated with sarilumab compared with patients treated with adalimumab. The results at Week 12, which were not part of the testing hierarchy, were consistent with the results at Week 24 (14.1% in the sarilumab group versus 6.5% in the

adalimumab group, nominal p=0.0154. The ACR70 response generally increased over time for the sarilumab group and was greater than the increases over time in the adalimumab group.

Table 69: Incidence of ACR70 response at Week 24 - ITT population

ACR70 at Week 24 n(%)	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)
Responders	22 (11.9%)	43 (23.4%)
Non-responders	163 (88.1%)	141 (76.6%)
P-value vs Adalimumab [a]		0.0036
OR, CI vs Adalimumab [b]		2.286 (1.300, 4.020)

OR: Odds ratio. CI: Confidence interval
ACR70 response = at least 70% improvement from baseline in both TJC and SJC, and in at least three of the HAQ score, CRP and three VAS assessments. If CRP was missing, ESR was substituted.
Patients are considered non-responders from the time they discontinued study medication.
Note: Percentages are calculated using the number of ITT patients in the corresponding treatment group as denominator.
a CMH test stratified by region.
b Mantel-Haenszel estimate.

HAQ-DI at Week 24

Table 70 shows that the improvement in HAQ-DI from baseline in the sarilumab group versus adalimumab group was statistically significant at Week 24. This improvement in HAQ-DI score was observed as early as Week 8 (nominal p=0.0453), and generally increased over time.

Superiority of sarilumab relative to adalimumab was demonstrated as measured by the proportion of patients with a clinically meaningful improvement in HAQ-DI (cutpoint 0.22) at Week 24 (67.4% versus 54.1% respectively; nominal p=0.0090).

Superiority of sarilumab relative to adalimumab was also demonstrated in HAQ-DI using a higher cutpoint of 0.3 at Week 24 (62.0% versus 47.6% respectively; nominal p=0.0057).

Table 70: Change from baseline in HAQ-DI at Week 24 - ITT population

	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)
HAQ-DI		
Number	158	165
Baseline Mean (SD)	1.62 (0.64)	1.64 (0.54)
Week24 Mean (SD)	1.21 (0.66)	1.01 (0.65)
Change Mean (SD)	-0.42 (0.58)	-0.63 (0.66)
LS mean (SE)	-0.43 (0.045)	-0.61 (0.045)
LS mean diff, 95% CI		-0.182 (-0.305,-0.059)
P-value vs Adalimumab[a]		0.0037

All assessments are set to missing from the time a patient prematurely discontinues study medication. Missing HAQ-DI measurements are not imputed.
Note: Number = Number of patients with assessment at both baseline and Week 24.
a Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, region, visit, and treatment-by-visit interaction.

Change from baseline in CDAI at Week 24

Table 71: Change from baseline in CDAI at Week 24 - ITT population

	Adalimumab 40mg q2w (N=185)	Sarilumab 200mg q2w (N=184)
CDAI		
Number	158	165
Baseline Mean (SD)	42.00 (11.76)	43.52 (11.94)
Week 24 Mean (SD)	16.55 (10.38)	13.84 (11.43)
Change Mean (SD)	-25.45 (12.89)	-29.68 (12.74)
LS mean (SE)	-25.20 (0.842)	-28.94 (0.834)
LS mean diff, 95% CI		-3.741 (-6.016,-1.466)
P-value vs Adalimumab[a]		0.0013

CDAI = 28TJC + 28SJC + Patient global VAS + Physician global VAS.
All assessments are set to missing from the time a patient discontinues study medication early. No imputation is performed.
Note: Number = Number of patients with assessment at both baseline and Week 24.
a Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, region, visit, and treatment-by-visit interaction.

CDAI remission (CDAI <= 2.8) at Week 24

The proportion of patients achieving CDAI remission (≤ 2.8) at Week 24 was more than twice that in the sarilumab group compared to the adalimumab group. The proportion of patients achieving CDAI remission at Week 12 was also higher in the sarilumab group compared to the adalimumab group (6.0% versus 3.2%; nominal p=0.2007).

Ancillary analyses

Quality of life / health related outcomes

Change from baseline in SF-36 at Week 24 (physical and mental health components summary scores)

At Week 24, the mean change from baseline in the PCS score in the sarilumab group was significantly greater than that in the adalimumab group. At Week 24, the mean change from baseline in the MCS score in the sarilumab group was numerically, but not significantly greater than that in the adalimumab group.

Change from baseline in FACIT-Fatigue at Week 24

The FACIT-Fatigue is a 13-item questionnaire assessing fatigue and ranging from 0 to 52. A higher score corresponds to a lower level of fatigue. The FACIT-Fatigue scores evaluated at Week 24 were part of the hierarchical testing procedure, although it fell below the break for statistical significance.

The change from baseline in the sarilumab group at Week 24 was numerically, but not significantly, superior to the adalimumab group.

Change from baseline in EQ-5D at Week 24

At Week 24, the mean change from baseline in the EQ-5D-3L index score in the sarilumab group was greater than that in the adalimumab group (nominal p=0.0382, Table 67). At Week 24, the mean change from baseline in the EQ-5D-3L VAS score in the sarilumab group was greater than that in the adalimumab group (nominal p=0.0699).

Change from baseline in morning stiffness VAS

Statistical significance of this endpoint is not claimed since it was not in the testing hierarchy.

At Week 24, the mean change from baseline in morning stiffness VAS score in the sarilumab group was greater than that in the adalimumab group (nominal p=0.0322).

Change from baseline in RAID at Week 24

Statistical significance of this endpoint is not claimed since it was not in the testing hierarchy.

At Week 24, the mean change from baseline in the RAID score in the sarilumab group was greater than that in the adalimumab group (LS mean difference: 0.779; nominal p=0.0008).

Change from baseline in WPS-RA at Week 24

Statistical significance of this endpoint is not claimed since it was not in the testing hierarchy. One hundred and forty-seven (147) patients (40.1% of the sample) were employed at baseline. Since the WPS-RA consists of independent items, the O'Brien global test was first used to determine overall significance prior to further evaluation. The results of the test demonstrated an overall effect at Week 24 for the sarilumab group compared to adalimumab (nominal p=0.0039). At Week 24, the mean change from baseline in the sarilumab group was greater in all 8 components (absenteeism, presenteeism [productivity interference, productivity reduction], rate of RA interference in household work [days missed, productivity interference, productivity reduction], days missed in family, leisure and social activities, and hiring of outside help). Three components had a difference in favor of sarilumab with a nominal p value <0.05: household work days missed due to arthritis (nominal p=0.0211), days with household work productivity reduced by ≥ 50% due to arthritis (nominal p=0.0032), and rate of arthritis interference with household work productivity (nominal p=0.0212).

Immunogenicity

A total of 184 patients had ADA results available; 98.9% of patients were ADA negative at baseline.

The incidence of persistent positive ADA was 2.7%, as defined by a positive ADA response at the last sample in all 5 patients. The overall incidence of treatment emergent ADA positive patients was 7.1%. The majority of these patients had a transient positive response (8 of 13 patients). There was no neutralizing ADA among all patients who had positive ADA response.

No patients who were positive in the ADA assay discontinued due to lack of efficacy or loss of efficacy. Although a higher incidence of ADA positive patients experienced hypersensitivity reactions compared with ADA negative patients, the overall number of patients was small (7/171 [4.1%] ADA negative patients versus 3/13 [23.1%] ADA positive patients with hypersensitivity reactions). The hypersensitivity reactions in the 3 ADA positive patients were mild, localized rashes. The ADA response was transient and the patients recovered for the hypersensitivity reactions without treatment interruption or discontinuation. There was no evidence of a direct relationship of the ADA formation and occurrence of these hypersensitivity reactions. There were no reported cases of anaphylaxis.

Summary of main studies

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

Table 72: Summary of efficacy for trial EFC11072 part B

Title: A randomized, double-blind, parallel, placebo-controlled study assessing the efficacy and safety of sarilumab added to non-biologic DMARD therapy in patients with rheumatoid arthritis who are inadequate responders to or intolerant to MTX				
Study identifier	EFC11072 part B			
Design	Multicenter, double-blind, parallel-group, placebo-controlled, 2-part, dose ranging (Part A) and confirmatory study (Part B)			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks not applicable not applicable	
Hypothesis	Superiority			
Treatments groups	Sarilumab 150		Sarilumab 150 mg q2w, 52 weeks, n = 400	
	Sarilumab 200		Sarilumab 200 mg q2w, 52 weeks, n = 399	
	Placebo		Placebo q2w, 52 weeks, n = 398	
Endpoints and definitions	Co-Primary	ACR20	ACR20 response at week 24	
	Co-primary	HAQ-DI	Change from baseline in HAQ-DI score at week 16	
	Co-Primary	mTSS	Change from baseline in mTSS at week 52	
	Key secondary	Major clinical response	Achieving and maintaining ACR70 for at least 24 consecutive weeks during the 52-week period.	
Database lock	6 November 2013			

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	All patients randomized following dose decision from part A (modified ITT)			
Descriptive statistics and estimate variability	Treatment group	Placebo	Sarilumab 150	Sariluamb 200
	Number of subjects	398	400	399
	ACR20 (n %)	133 (33.4%)	232 (58.0%)	265 (66.4%)
	HAQ-DI (Lsmean)	-0.29	-0.53	-0.55
	SE	0.028	0.029	0.029
	mTSS (Median) Q1 : Q3	1.00 0.00 : 2.00	0.00 -1.00 : 2.00	0.00 -0.50 : 1.00

Effect estimate per comparison	ACR20	Comparison groups	Sarilumab 150 vs. placebo
		OR	2.77
		95%-CI	(2.08 – 3.70)

		P-value	< 0.0001	
	ACR20	Comparison groups	Sarilumab 200 vs. placebo	
		OR	3.98	
		95%-CI	(2.96, 5.34)	
		P-value	< 0.0001	
	HAQ-DI	Comparison groups	Sarilumab 150 vs. placebo	
		LSmean diff	-0.235	
		95%-CI	(-0.213, -0.157)	
		P-value	< 0.0001	
	HAQ-DI	Comparison groups	Sarilumab 150 vs. placebo	
		LSmean diff	-0.258	
		95%-CI	(-0.336, -0.181)	
		P-value	< 0.0001	
	mTSS	Comparison groups	Sarilumab 150 vs. placebo	
		P-value	< 0.0001	
	mTSS	Comparison groups	Sarilumab 200 vs. placebo	
		P-value	< 0.0001	
Notes	Both sarilumab groups were statistically significant superior with regard to the 3 co-primary endpoints			
Analysis description	**Key secondary analysis**			
Analysis population and time point description	All patients randomized following dose decision from part A (modified ITT)			
Descriptive statistics and estimate variability	Treatment group	Placebo	Sarilumab 150	Sariluamb 200
	Number of subjects	398	400	399
	Major clinical response (n %)	12 (3.0%)	51 (12.8%)	59 (14.8%)
Effect estimate per comparison	Major clinical response	Comparison groups	Sarilumab 150 vs. placebo	
		OR	4.67	
		95%-CI	(2.45, 8.86)	
		P-value	< 0.0001	
	Major clinical response	Comparison groups	Sarilumab 200 vs. placebo	
		OR	5.57	
		95%-CI	(2.95, 10.52)	
		P-value	< 0.0001	

Table 73: Summary of efficacy for trial EFC10832

Title: A randomized, double-blind, parallel, placebo-controlled study assessing the efficacy and safety of sarilumab added to non-biologic DMARD therapy in patients with rheumatoid arthritis who are inadequate responders to or intolerant of TNF-α antagonists			
Study identifier	EFC10832 - SARIL-RA-TARGET		
Design	Randomized, double-blind, parallel, placebo-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks until anticipated commercial availability of sarilumab or until 2020 at the latest when the study will be closed.
Hypothesis	Superiority		
Treatments groups	Sarilumab		Sarilumab 150 mg q2w+ DMARD Sarilumab 200 mg q2w +DMARD
	PBO		+ MTX
Endpoints and definitions	Primary endpoint	ACR20	ACR20 is defined as achieving at least 20% improvement in both TJC and SJC, and at least 20% improvement in at least 3 of the 5 other assessments (CRP level, patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, HAQ-DI).
		HAQ-DI (week 12)	Health Assessment Question-Disability Index. The HAQ-DI is a standardized questionnaire developed for use in RA with a scoring range between 0 and 3. A high HAQ-DI score has been found to be a strong predictor of morbidity and mortality in RA. A 0.22 unit difference is considered clinically meaningful.
	Secondary ranked endpoint (in hierarchical order)	DAS28-CRP	Disease Activity Score (DAS) 28- C reactive protein (CRP). The DAS28-CRP is a composite score that includes 4 variables: • TJC (based on 28 joints) • SJC (based on 28 joints) • general health assessment: defined as the patient's global assessment of disease activity • marker of inflammation: assessed by CRP (mg/L).
		ACR50	ACR50 is defined similarly to ACR20 with at least a 50% improvement.
		ACR70	ACR70 is defined similarly to ACR20 with at least a 70% improvement.
		DAS28-CRP remission	DAS28-CRP remission is defined as a DAS28-CRP score <2.6.

		CDAI	The clinical disease activity index (CDAI) is a composite index constructed to measure clinical remission in RA that does not include a laboratory test, and is a numerical summation of 4 of the components of the SDAI (tender and SJC [based on 28 joints] as well as patient's and physician's global disease activity). Scores range from 0 to 76.
		HAQ-DI (week 24)	See above.
		SF-36 Physical	The SF-36 is a 36 item questionnaire that measures eight multi-item dimensions of health: physical functioning (10 items) social functioning (2 items) role limitations due to physical problems (4 items), role limitations due to emotional problems (3 items), mental health (5 items), energy/vitality (4 items), pain (2 items), and general health perception (5 items). For each dimension, item scores are coded, summed, and transformed on to a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state). Two standardised summary scores can also be calculated from the SF-36; the physical component summary (PCS) and the mental health component summary (MCS).
		SF-36 Mental	See SF-36 Physical.
		FACIT fatigue	The FACIT-Fatigue is a 13-item questionnaire rated 0 to 4 developed to measure fatigue. The patient will be asked to answer to 13 questions rated 0 to 4 (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much) (see Appendix J). The total score ranges from 0 to 52.
		Morning stiffness	Rheumatoid arthritis is associated with stiffness of joints, especially in the morning after prolonged stationery state. The degree of stiffness can be an indicator of disease severity. The effect of sarilumab on the severity of morning stiffness was assessed on a visual analog scale (VAS) scale from 0 mm (no problem) to 100 mm (major problem).
		WPS-RA	Rheumatoid arthritis-work productivity survey (WPS-RA) The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer administered and is based on patient self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items).

		RAID	RA impact of disease (RAID) (RAID) score is a composite measure of the impact of RA on patients that takes into account 7 domains: pain, functional disability, fatigue, physical and emotional wellbeing, quality of sleep, and coping. The RAID is calculated based on 7 numerical rating scales (NRS) questions. Each NRS is assessed as a number between 0 and 10, which correspond to the domains mentioned above. The values for each of these domains were weighted by patient assessment of relative importance and combined in a single score.
		EQ-5D-3L	It is a standardized, generic measure of health outcome. The EQ-5D was specifically included to address concerns regarding the health economic impact of RA, which have been considered in cost effectiveness arguments (~xr38i). The EQ-5D-3L comprises 5 questions on mobility, self-care, pain, usual activities, and psychological status with 3 possible answers for each item (1=no problem, 2=moderate problems, 3=severe problems) and a vertical visual analog scale that allows the patients to indicate their health state today that can range from 0 (worst imaginable) to 100 (best imaginable) (22).
Database lock			

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT, 24 weeks			
Effect estimate per comparison	Treatment group	Placebo + DMARD	Sarilumab 150 mg q2w+ DMARD	Sarilumab 200 mg q2w + DMARD
	Number of subject	181	181	184
	Co-primary endpoints:			
	ACR20 at Week 24, n. responders (%)	61 (33.7)	101(55.8)	112 (60.9)
	OR vs placebo		2.711	3.284
	CI		(1.730, 4.247)	(2.108, 5.115)
	p-value vs placebo (two-sided CMH test)		<0.0001	<0.0001
	HAQ-DI at Week 12 LS mean (SE)	-0.26(0.043)	-0.46(0.044)	-0.47(0.043)
	LS mean difference		-0.202	-0.210
	CI		(-0.318,-0.086)	(-0.325,-0.095)

	p-value vs placebo (MMRM)		0.0007	0.0004
	Secondary ranked endpoints:			
	DAS28-CRP – Week 24 p-value vs placebo	-1.38(0.119)	-2.35(0.111) <0.0001	-2.82(0.108) <0.0001
	ACR50 – week 24 p-value vs placebo	33 (18.2%)	67 (37.0%) <0.0001	75 (40.8%) <0.0001
	ACR70– week 24 p-value	13 (7.2%)	36 (19.9%) 0.0002	30 (16.3%) 0.0056
	DAS28-CRP <2.6 – Week 24 p-value vs placebo	13 (7.2%)	45 (24.9%) <0.0001	53 (28.8%) <0.0001
	CDAI – Week 24 p-value vs placebo	-16.35(1.195)	-23.65(1.136) <0.0001	-26.08(1.109) <0.0001
	HAQ-DI – Week 24	-0.34(0.051)	-0.52(0.049) 0.0078	-0.58(0.048) 0.0004
	SF-36 Physical – Week 24 p-value vs placebo	4.40(0.692)	7.65(0.653) 0.0004	8.48(0.630) <0.0001
	SF-36 Mental – Week 24 p-value vs placebo	4.74(0.902)	6.26(0.848) 0.2026	6.76(0.817) 0.0854
	FACIT Fatigue – week 24 p-value vs placebo	6.82(0.863)	9.86(0.802) 0.0078	10.06(0.778) 0.0040
	Morning Stiffness – Week 24 p-value vs placebo	-21.66(2.390)	-32.30(2.231) 0.0008	-33.79(2.148) 0.0001
	WPS-RA– Week 24 p-value vs placebo		0.0004	0.0003
	RAID – Week 24 p-value vs placebo	-1.8(0.203)	-2.55(0.189) 0.0057	-2.80(0.183) 0.0002
	EQ-5D-3L – Week 24 p-value vs placebo	0.19(0.024)	0.29(0.023) 0.0034	0.34(0.022) <0.0001
Notes	Values presented are number and percent of responders for binary variables and LS mean change from baseline with standard error for continuous variables. The study results indicate a statistical significant superiority of sarilumab for each dose with regard to ACR20 and HAQ-DI.			
Analysis description				

Table 74: Summary of efficacy for trial EFC14092

Title: A randomized, double-blind, parallel-group study assessing the efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy in patients with rheumatoid arthritis			
Study identifier	EFC14092		
Design	Multicenter, randomized, double-blind, parallel group, active comparator-controlled, double dummy study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 months NA until anticipated commercial availability of sarilumab or until 2020 at the latest when the study will be closed.
Hypothesis	Superiority		
Treatments groups	Sarilumab (or matching adalimumab PBO)		200 mg q2w SC, 24 weeks, N=184 (q2w SC)
	Adalimumab (or matching sarilumab PBO)		40 mg q2w SC, 24 weeks, N=185 (q2w SC)
Endpoints and definitions	Primary endpoint	DAS28-ESR	Change from baseline in Disease Activity Score (DAS) 28- Erythrocyte Sedimentation Rate (ESR) at 24 weeks. DAS28 is a composite score that includes 4 variables: TJC (based on 28 joints); SJC (based on 28 joints); general health assessment (GH) by the patient assessed from the ACR RA core set questionnaire (patient global assessment) in 100 mm VAS; marker of inflammation assessed by the CRP in mg/L or ESR in mm/hr.
	Secondary ranked endpoint (in hierarchical order)	DAS28-ESR remission	DAS28-ESR remission is defined as a DAS28-ESR score <2.6 at Week 24.
		ACR50	ACR50 is defined as achieving at least 50% improvement in both TJC and SJC, and at least 50% improvement in at least 3 of the 5 other assessments (CRP level, patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, HAQ-DI).
		ACR70	ACR70 is defined similarly to ACR50 with at least a 70% improvement.
		ACR20	ACR20 is defined similarly to ACR50 with at least a 20% improvement.
		HAQ-DI	Health Assessment Question-Disability Index. The HAQ-DI is a standardized questionnaire developed for use in RA with a scoring range between 0 and 3. A high HAQ-DI score has been found to be a strong predictor of morbidity and mortality in RA. A 0.22 unit difference is considered clinically meaningful.

		SF-36 Physical	The SF-36 is a 36 item questionnaire that measures eight multi-item dimensions of health: physical functioning (10 items) social functioning (2 items) role limitations due to physical problems (4 items), role limitations due to emotional problems (3 items), mental health (5 items), energy/vitality (4 items), pain (2 items), and general health perception (5 items). For each dimension, item scores are coded, summed, and transformed on to a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state). Two standardised summary scores can also be calculated from the SF-36; the physical component summary (PCS) and the mental health component summary (MCS).
		FACIT fatigue	The FACIT-Fatigue is a 13-item questionnaire rated 0 to 4 developed to measure fatigue. The patient will be asked to answer to 13 questions rated 0 to 4 (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much) (see Appendix J). The total score ranges from 0 to 52.
		SF-36 Mental	See SF-36 Physical.
Database lock	January 20th, 2016.		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT, 24 weeks		
Descriptive statistics and estimate variability	**Treatment group**	**Adalimumab 40 mg q2w**	**Sarilumab 200 mg q2w**
	Number of subjects	185	184
	Primary endpoint: DAS28-ESR (Change LS mean)	-2.20	-3.28
	SE	0.106	0.105
	Secondary ranked endpoint: DAS-28 ESR remission – week 24 (Incidence)	7.0%	26.6%
	Secondary ranked endpoint: ACR50 response – week 24 (Incidence)	29.7%	45.7%

	Secondary ranked endpoint: ACR70 response – week 24 (Incidence)	11.9%	23.4%
	Secondary ranked endpoint: ACR20 response – week 24 (Incidence)	58.4%	71.7%
	Secondary ranked endpoint: HAQ-DI – week 24 (Change LS mean)	-0.43	-0.61
	SE	0.045	0.045
	Secondary ranked endpoint: SF-36 Physical – week 24 (Change LS mean)	6.09	8.74
	SE	0.555	0.555
	Secondary ranked endpoint: FACIT FATIGUE – week 24 (Change LS mean)	8.41	10.18
	SE	0.709	0.701
	Secondary ranked endpoint: SF-36 Mental – week 24 (Change LS mean)	6.83	7.86
	SE	0.774	0.773
Effect estimate per comparison	Primary endpoint: DAS28-ESR	Comparison groups	Sarilumab 200 mg q2w vs. Adalimumab 40 mg q2w
		LS mean difference	-1.077
		95%CI	(-1.361, -0.793)

		P-value vs. Adalimumab (Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model=baseline, treatment, region, visit, and treatment-by-visit interaction)	<0.0001
	Secondary ranked endpoints: DAS28-ESR (remission) – week 24	Comparison groups	Sarilumab 200 mg q2w vs. Adalimumab 40 mg q2w
		OR (Mantel-Haenszel estimate)	4.879
		CI	(2.536, 9.389)
		P-value (CMH test stratified by region)	<0.0001
	Secondary ranked endpoint: ACR50 response – week 24	Comparison groups	Sarilumab 200 mg q2w vs. Adalimumab 40 mg q2w
		OR (Mantel-Haenszel estimate)	1.976
		CI	(1.289, 3.028)
		P-value (CMH test stratified by region)	0.0017
	Secondary ranked endpoint: ACR70 response – week 24	Comparison groups	Sarilumab 200 mg q2w vs. Adalimumab 40 mg q2w
		OR (Mantel-Haenszel estimate)	2.286
		CI	(1.300, 4.020)
		P-value (CMH test stratified by region)	0.0036
	Secondary ranked endpoint: ACR20 response – week 24	Comparison groups	Sarilumab 200 mg q2w vs. Adalimumab 40 mg q2w
		OR (Mantel-Haenszel estimate)	1.800
		CI	(1.168, 2.773)
		P-value (CMH test stratified by region)	0.0074
	Secondary ranked endpoint: HAQ-DI – week 24	Comparison groups	Sarilumab 200 mg q2w vs. Adalimumab 40 mg q2w
		LS mean difference	-0.182
		95%CI	(-0.305, -0.059)
		P-value vs. Adalimumab (Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model=baseline, treatment, region, visit, and treatment-by-visit interaction)	0.0037
	Secondary ranked endpoint: SF36 Physical – week 24	Comparison groups	Sarilumab 200 mg q2w vs. Adalimumab 40 mg q2w
		LS mean difference	2.650
		95%CI	(1.147, 4.153)
		P-value vs. Adalimumab (Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model=baseline, treatment, region, visit, and treatment-by-visit interaction)	0.0006
	Secondary ranked endpoint:	Comparison groups	Sarilumab 200 mg q2w vs. Adalimumab 40 mg q2w
		LS mean difference	1.768

	FACIT FATIGUE – week 24	95%CI	(-0.137, 3.674)
		P-value vs. Adalimumab (Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model=baseline, treatment, region, visit, and treatment-by-visit interaction)	0.0689
	Secondary ranked endpoint: SF36 Mental – week 24	Comparison groups	Sarilumab 200 mg q2w vs. Adalimumab 40 mg q2w
		LS mean difference	1.036
		95%CI	(-1.061, 3.132)
		P-value vs. Adalimumab (Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model=baseline, treatment, region, visit, and treatment-by-visit interaction)	0.3319

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

Comparative analyses between EFC11072 Part B, Cohort 2 and EFC10832 studies

Signs and symptoms of rheumatoid arthritis

Table 75: Proportion of patients with ACR20, 50, and 70 responses - EFC11072 Part B, Cohort 2 and EFC10832

Proportion of patients	EFC11072 Part B, Cohort 2			EFC10832		
	Placebo + MTX (N=398)	Sarilumab 150 mg q2w + MTX (N=400)	Sarilumab 200 mg q2w + MTX (N=399)	Placebo + DMARD (N=181)	Sarilumab 150 mg q2w + DMARD (N=181)	Sarilumab 200 mg q2w + DMARD (N=184)
Week 12						
ACR20	34.7%	54.0%	64.9%	37.6%	54.1%	62.5%
Odds ratio (95% CI) vs placebo[a]		2.219 (1.668, 2.952)	3.504 (2.616,4.693)		2.019 (1.314, 3.102)	2.964 (1.909, 4.602)
p-value vs placebo[b]		<0.0001	<0.0001		0.0013	<0.0001
ACR50	12.3%	26.5%	36.3%	13.3%	30.4%	33.2%
Odds ratio (95% CI) vs placebo[a]		2.586 (1.780, 3.756)	4.124 (2.867, 5.934)		3.105 (1.777, 5.426)	3.590 (2.067, 6.236)
p-value vs placebo[b]		<0.0001	<0.0001		<0.0001	<0.0001
ACR70	4.0%	11.0%	17.5%	2.2%	13.8%	14.7%
Odds ratio (95% CI) vs placebo[a]		2.953 (1.638, 5.326)	5.106 (2.908, 8.964)		7.556 (2.526, 22.602)	8.090 (2.730, 23.972)
p-value vs placebo[b]		0.0002	<0.0001		<0.0001	<0.0001
Week 24						
ACR20	33.4%	58.0%	66.4%	33.7%	55.8%	60.9%
Odds ratio (95% CI) vs placebo[a]		2.773 (2.077, 3.703)	3.975 (2.957, 5.344)		2.711 (1.730, 4.247)	3.284 (2.108, 5.115)
p-value vs placebo[b]		<0.0001	<0.0001		<0.0001	<0.0001
ACR50	16.6%	37.0%	45.6%	18.2%	37.0%	40.8%
Odds ratio (95% CI) vs placebo[a]		2.966 (2.125, 4.140)	4.269 (3.064, 5.948)		2.958 (1.764, 4.959)	3.374 (2.045, 5.566)
p-value vs placebo[b]		<0.0001	<0.0001		<0.0001	<0.0001

Proportion of patients	EFC11072 Part B, Cohort 2			EFC10832		
	Placebo + MTX (N=398)	Sarilumab 150 mg q2w + MTX (N=400)	Sarilumab 200 mg q2w + MTX (N=399)	Placebo + DMARD (N=181)	Sarilumab 150 mg q2w + DMARD (N=181)	Sarilumab 200 mg q2w + DMARD (N=184)
ACR70	7.3%	19.8%	24.8%	7.2%	19.9%	16.3%
Odds ratio (95% CI) vs placebo[a]		3.174 (2.016, 4.996)	4.280 (2.743, 6.678)		3.607 (1.774, 7.332)	2.653 (1.308, 5.383)
p-value vs placebo[b]		<0.0001	<0.0001		0.0002	0.0056
Week 52						
ACR20	31.7%	53.5%	58.6%	NA	NA	NA
Odds ratio (95% CI) vs placebo[a]		2.487 (1.863, 3.320)	3.086 (2.305, 4.131)			
p-value vs placebo[b]		<0.0001	<0.0001			
ACR50	18.1%	40.0%	42.9%	NA	NA	NA
Odds ratio (95% CI) vs placebo[a]		3.023 (2.185, 4.183)	3.377 (2.446, 4.663)			
p-value vs placebo[b]		<0.0001	<0.0001			
ACR70	9.0%	24.8%	26.8%	NA	NA	NA
Odds ratio (95% CI) vs placebo[a]		3.323 (2.200, 5.020)	3.691 (2.453, 5.554)			
p-value vs placebo[b]		<0.0001	<0.0001			

CI = confidence interval; DMARD = disease-modifying anti-rheumatic drugs; NA = not available; MTX = methotrexate
Source: 5.3.5.3 Study EFC11072 Part B appendix 16-2-6-eff-response-data [16.2.6.1.1.3], [16.2.6.1.7.4], and [16.2.6.1.8.4]; Study EFC10832 appendix 16-2-6-eff-response-data [16.2.6.1.3], [16.2.6.3.4], and [16.2.6.4.4]
a Mantel-Haenszel estimate.
b Cochran-Mantel-Haenszel test stratified by prior biologic use (EFC11072)/number of previous anti-TNFs (EFC10832) and region.

Disease activity

Table 76: Mean change from baseline in DAS28-CRP - EFC11072 Part B, Cohort 2 and EFC10832

	EFC11072 Part B, Cohort 2			EFC10832		
	Placebo + MTX (N=398)	Sarilumab 150 mg q2w + MTX (N=400)	Sarilumab 200 mg q2w + MTX (N=399)	Placebo + DMARD (N=181)	Sarilumab 150 mg q2w + DMARD (N=181)	Sarilumab 200 mg q2w + DMARD (N=184)
Week 12						
Mean (SD)	-1.07 (1.18)	-2.06 (1.38)	-2.44 (1.30)	-1.08 (1.31)	-2.20 (1.40)	-2.55 (1.41)
LS mean difference versus placebo (95% CI)		-0.953 (-1.130, -0.776)	-1.350 (-1.527,-1.173)		-1.157 (-1.437,-0.876)	-1.475 (-1.753,-1.197)
p-value versus placebo[a]		<0.0001	<0.0001		<0.0001	<0.0001
Week 24						
Mean (SD)	-1.62 (1.44)	-2.68 (1.40)	-3.02 (1.26)	-1.96 (1.21)	-2.62 (1.34)	-3.18 (1.30)
LS mean difference versus placebo (95% CI)		-1.282 (-1.493,-1.071)	-1.652 (-1.863,-1.441)		-0.971 (-1.283,-0.658)	-1.444 (-1.752,-1.135)
p-value versus placebo[a]		<0.0001	<0.0001		<0.0001	<0.0001
Week 52						
Mean (SD)	-1.91 (1.27)	-3.12 (1.40)	-3.25 (1.29)			
LS mean difference versus placebo (95% CI)		-1.424 (-1.648,-1.199)	-1.589 (-1.814,-1.365)	NA	NA	NA
p-value versus placebo[a]		<0.0001	<0.0001			

CI = confidence interval; CRP = C-reactive protein; DAS = Disease Activity Scale; DMARD = disease-modifying anti-rheumatic drugs; LS = least squares; MMRM = mixed model for repeated measures; MTX = methotrexate; NA = not available; SD = standard deviation
Source: 5.3.5.1 Studies EFC11072 Part B appendix 16-2-6-eff-response-data [16.2.6.1.15.4] and EFC10832 appendix 16-2-6-eff-response-data [16.2.6.11.4]
Note: Number = Number of patients with assessment at both baseline and the corresponding week.
a Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, prior biological use (EFC11072)/ number of previous anti-TNFs (EFC10832), region, visit, and treatment by visit interaction.

Table 77: Proportion of patients with DAS28-CRP <2.6 at Week 12, Week 24, and Week 52 - EFC11072 Part B, Cohort 2 and EFC10832

	EFC11072 Part B, Cohort 2			EFC10832		
	Placebo + MTX (N=398)	Sarilumab 150 mg q2w + MTX (N=400)	Sarilumab 200 mg q2w + MTX (N=399)	Placebo + DMARD (N=181)	Sarilumab 150 mg q2w + DMARD (N=181)	Sarilumab 200 mg q2w + DMARD (N=184)
Week 12						
Number of patients (proportion)	19 (4.8%)	72 (18.0%)	92 (23.1%)	7 (3.9%)	31 (17.1%)	33 (17.9%)
OR, 95% CI versus placebo[a]		4.530 (2.662, 7.709)	6.101 (3.628, 10.260)		5.409 (2.288, 12.786)	5.713 (2.428, 13.441)
p-value[b]		<0.0001	<0.0001		<0.0001	<0.0001
Week 24						
Number of patients (proportion)	40 (10.1%)	111 (27.8%)	136 (34.1%)	13 (7.2%)	45 (24.9%)	53 (28.8%)
OR, 95% CI versus placebo[a]		3.551 (2.382, 5.292)	4.690 (3.176, 6.926)		4.622 (2.339, 9.132)	5.801 (2.948, 11.413)
p-value[b]		<0.0001	<0.0001		<0.0001	<0.0001
Week 52						
Number of patients (proportion)	34 (8.5%)	124 (31.0%)	136 (34.1%)	NA	NA	NA
OR, 95% CI versus placebo[a]		4.866 (3.218, 7.357)	5.525 (3.673, 8.310)			
p-value[b]		<0.0001	<0.0001			

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CRP = C-reactive protein; DAS = Disease Activity Scale; DMARD = disease-modifying anti-rheumatic drugs; MTX = methotrexate; OR = odds ratio relative to placebo

Source: 5.3.5.1 Study EFC10832 appendix 16-2-6-eff-response-data [16.2.6.11.6] and [16.2.6.11.5]; 5.3.5.3 Supporting analyses for SCE [1.4.18.1.2] and [1.4.18.1.3],

a Mantel-Haenszel estimate.

b CMH test stratified by prior biologic use (EFC11072) / number of previous anti-TNFs (EFC10832) and region.

Comparison of results in subpopulations

Sarilumab + DMARDs - placebo-controlled studies

Data from the 2 placebo-controlled studies were pooled to evaluate potential influence of demographic factors (gender, race, ethnicity, region, age, weight, BMI, and smoking history), baseline disease characteristics (duration of RA, baseline CRP, DAS28-CRP, serological status), prior medication history (number of prior DMARDs, number of prior TNF antagonists [only collected in EFC10832], type of concomitant DMARD treatment [MTX, non-MTX, only in EFC10832]) on the key efficacy outcomes: ACR20 response rates and changes in HAQ-DI, as well as changes in DAS28-CRP. Subgroup analyses for radiographic endpoints were only available from patients treated in EFC11072 Part B, Cohort 2.

The efficacy results were consistent across subgroups based on age, gender, race, ethnicity, region, duration of RA, number of prior DMARDs, baseline DMARD treatment (specific to EFC10832), number of prior anti-TNFs (specific to EFC10832), baseline CRP or baseline DAS28-CRP.

Monotherapy

The subgroup analyses for EFC14092 were based on the subgroups defined for the pooled analysis of the 2 placebo-controlled studies as well as on the additional subgroups of patients who had either an inadequate response to or an intolerance of MTX and baseline ESR. In all of these subgroup analyses, sarilumab 200 mg q2w was consistently superior to adalimumab 40 mg q2w when administered as monotherapy. Potential interactions with baseline BMI and CRP were identified. However, these interactions were not observed in the related subgroups of weight and ESR, respectively, and the efficacy results in these subgroups were consistent with the main results.

Persistence of efficacy

For long-term analyses, data from 901 patients initially randomized into EFC11072 Part B, Cohort 2 and from 456 patients initially randomized into EFC10832 were pooled longitudinally with data from the open-label long-term extension study, LTS11210. Patients initially randomized into EFC11072 Part B, Cohort 2 had up to approximately 196 weeks of continuous treatment with sarilumab, and patients initially randomized into

EFC10832 had up to approximately 108 weeks of continuous treatment with sarilumab. From the time of entry into LTS11210, patients were treated with sarilumab 200 mg q2w with dose reductions to 150 mg q2w for laboratory abnormalities (decreases in ANC, platelets or increases in transaminases).

Clinical studies in special populations

No studies in paediatric patients, renal and hepatic impaired patients were conducted.

A summary of the number of elderly patients from Phase 2 and Phase 3 studies in different age group (age ≥ 65) is presented in Table 78.

Table 78: Summary of number of elderly patients by age group in the Phase 2 / 3 studies in rheumatoid arthritis

	Age 65-74	Age 75-84	Age 85+
Controlled Trials (N=2590)	344 (13.3%)	25 (1.0%)	2 (0.1%)
Non Controlled Trials (N=932)	141 (15.1%)	26 (2.8%)	1 (0.1%)

Note: Controlled Trials include EFC11072 Part A and B, EFC10832, and EFC14092. Uncontrolled studies include EFC13752, MSC12665, SFY13370, EFC11574, and ACT11575

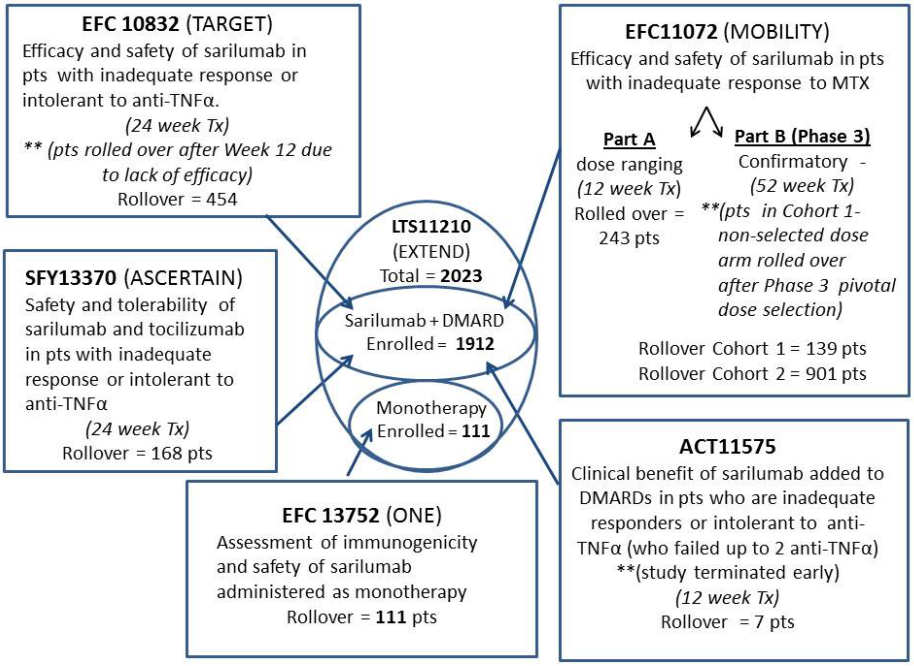
Supportive study

The OL long term study LTS11210

LTS11210 is a multicenter, multinational, open-label, uncontrolled long-term study with the primary objective to evaluate sarilumab long-term safety and the secondary objective to assess sarilumab efficacy in patients with RA.

The figure below summarizes the patient population, and number of patients from the initial studies that enrolled into LTS11210 and represented the overall safety population, N=2023 [(sarilumab + DMARD safety population, n=1912) + (monotherapy safety population, n=111)].

Figure 15: Schematic of patient population with RA who entered from the initial studies



Upon entry into LTS11210, the patients all received sarilumab 200 mg q2w, with reductions to 150 mg q2w for certain laboratory abnormalities (with a stable dose of one or a combination of the conventional synthetic DMARDs they were receiving, except for patients from EFC13752 who were only receiving sarilumab monotherapy).

Study duration: the study is ongoing. The treatment duration for a patient in the study is at least 264 weeks from the first IMP administration in LTS11210. In addition, patients may continue to be treated beyond 264 weeks until sarilumab is commercially available or until 2020, at the latest, when the study will be closed.

Number of patients

Planned: Approximately 2000 patients
Enrolled: 1912 (sarilumab + DMARD); 111 (sarilumab monotherapy)
Treated: 1910 (sarilumab + DMARD); 111 (sarilumab monotherapy). All treated subjects were evaluated for the efficacy and safety endpoints.

Data extraction date: 25 January 2016.

Evaluation of the efficacy data will be focused on the subjects from the placebo-controlled Phase 3 studies (*i.e.*, EFC11072 Part B, Cohort 2 EFC10832) that entered the LTS11210 study.

Results

- ACR20/50/70

The ACR20/50/70 responses for the overall sarilumab+DMARD and sarilumab monotherapy groups are shown in the table below.

Table 79: Percentage of patients with an ACR20, ACR50, ACR70 response by every 24 weeks – Safety Population

Study Week	ACR20	ACR50	ACR70
Sarilumab + DMARD			
Week 0	1318/1898 (69.4%)	824/1897 (43.4%)	435/1901 (22.9%)
Week 24	1482/1787 (82.9%)	1078/1782 (60.5%)	690/1781 (38.7%)
Week 48	1379/1662 (83.0%)	1037/1656 (62.6%)	673/1654 (40.7%)
Week 96	975/1146 (85.1%)	749/1145 (65.4%)	493/1144 (43.1%)
Week 144	519/599 (86.6%)	391/596 (65.6%)	268/594 (45.1%)
Week 192	179/204 (87.7%)	141/204 (69.1%)	102/203 (50.2%)
Week 216	163/183 (89.1%)	132/183 (72.1%)	88/180 (48.9%)
Week 240	110/125 (88.0%)	89/125 (71.2%)	64/122 (52.5%)
Week 264	37/41 (90.2%)	25/43 (58.1%)	18/42 (42.9%)
Sarilumab monotherapy			
Week 0	91/111 (82.0%)	65/11 (58.6%)	36/11 (32.4%)
Week 24	96/109 (88.1%)	70/109 (64.2%)	40/107 (37.4%)
Week 48	27/30 (90.0%)	22/30 (73.3%)	12/28 (42.9%)

Note: The number (n) represents the subset of the total number of patients who had the response. The denominator (/N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed.

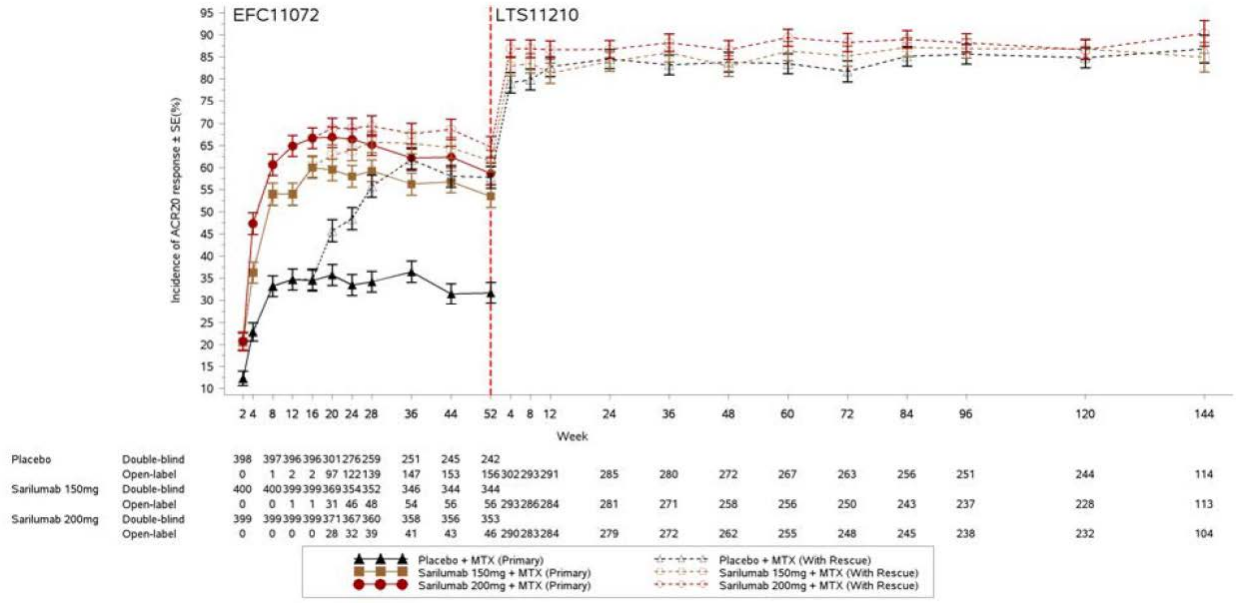
ACR20/50/70 response = at least 20%/50%/70% improvements from baseline in both TJC and SJC, and in at least 3 of the 5 components (HAQ-DI score, CRP and 3 VAS assessments). A patient was not counted at a visit if there were insufficient information to determinate ACR20/50/70 response or non-response.

PGM=POOPS/SAR153191/LTS11210/CSR_03/REPORT/PGM/eff_resp_pct_year_int_i_t.sas OUT=REPORT/OUTPUT/eff_resp_pct_year_int_i_t_i.rtf (05FEB2016 - 7:19)

EFC11072 part B and EFC10832 studies

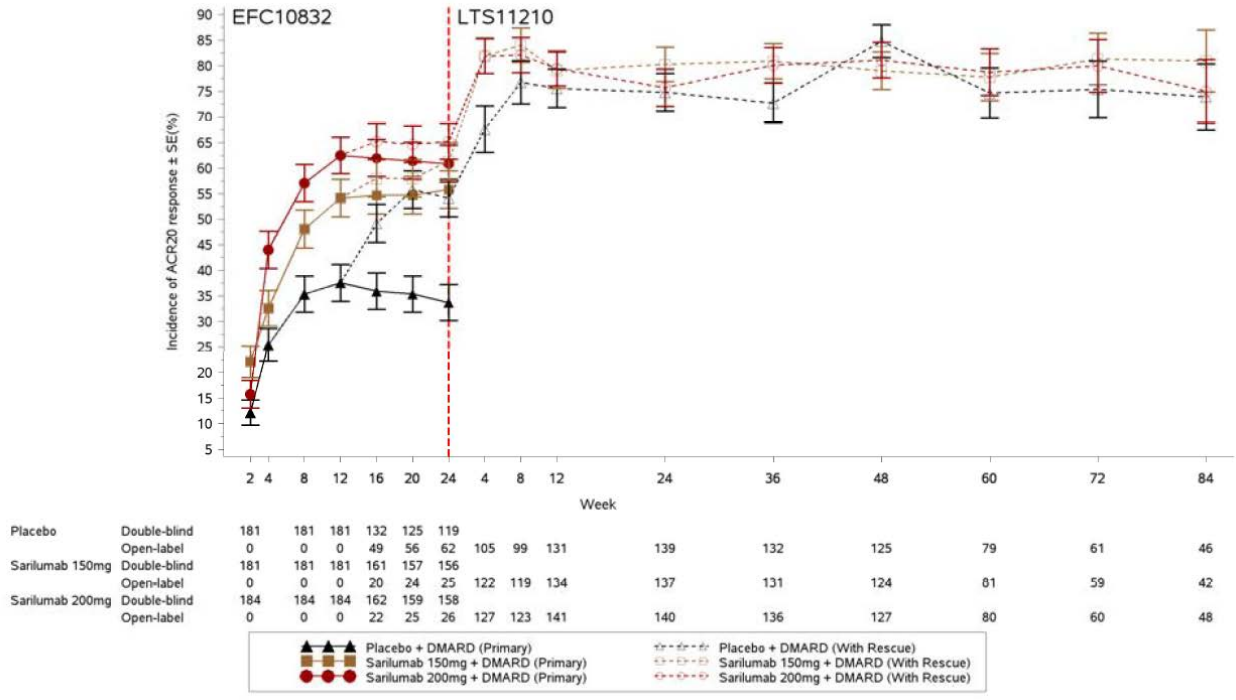
The efficacy of sarilumab 200 mg administered concomitantly with DMARDs on ACR20 seen in the placebo-controlled studies is shown below with data up to 3.8 and 2.1 years from initial randomization in EFC11072 Part B and EFC10832, respectively.

Figure 16: Incidence of ACR20 response for patients originally randomized into EFC11072 Part B, Cohort 2 and those who continued into LTS11210



Placebo	Double-blind	398	397	396	396	301	276	259	251	245	242											
	Open-label	0	1	2	2	97	122	139	147	153	156	302	293	291	285	280	272	267	263	256	251	244	114
Sarilumab 150mg	Double-blind	400	400	399	399	369	354	352	346	344	344											
	Open-label	0	0	1	1	31	46	48	54	56	56	293	286	284	281	271	258	256	250	243	237	228	113
Sarilumab 200mg	Double-blind	399	399	399	399	371	367	360	358	356	353											
	Open-label	0	0	0	0	28	32	39	41	43	46	290	283	284	279	272	262	255	248	245	238	232	104

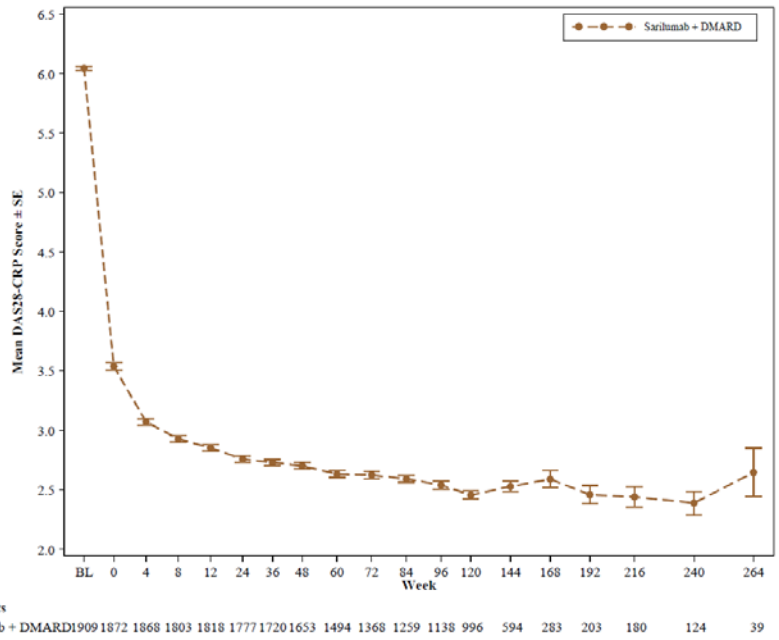
Figure 17: Incidence of ACR20 response for patients originally randomized into EFC10832 and those who continued into the LTS11210 study



Placebo	Double-blind	181	181	181	132	125	119															
	Open-label	0	0	0	49	56	62	105	99	131	139	132	125	79	61	46						
Sarilumab 150mg	Double-blind	181	181	181	161	157	156															
	Open-label	0	0	0	20	24	25	122	119	134	137	131	124	81	59	42						
Sarilumab 200mg	Double-blind	184	184	184	162	159	158															
	Open-label	0	0	0	22	25	26	127	123	141	140	136	127	80	60	48						

- DAS28 CRP and DAS28 CRP remission

Figure 18: DAS28-CRP at each visit - Sarilumab + DMARD



DAS28-CRP: Disease Activity Score for 28 Joints based on C-reactive protein

PGM=PRODOPS/SAR153191/LTS11210/CSR_03/REPORT/PGM/eff_das28_byvis_i_g.sas OUT=REPORT/OUTPUT/eff_das28_byvis_int_i_g_i.rtf (05FE 7:09)

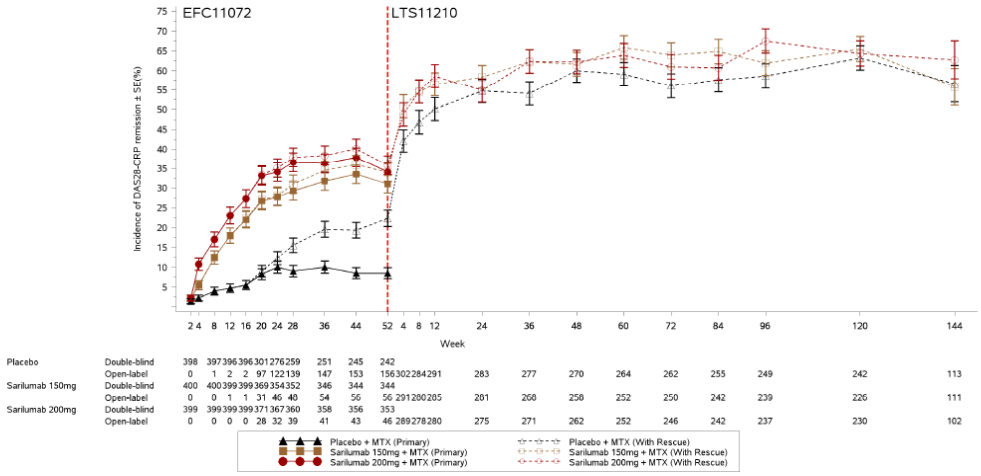
Table 80: Percentage of patients with DAS28 remission (DAS28-CRP<2.6) response by every 24 weeks – Safety Population

Study Week	DAS28 remission
Sarilumab + DMARD	
Week 0	569/1873 (30.4%)
Week 24	899/1778 (50.6%)
Week 48	887/1654 (53.6%)
Week 96	658/1139 (57.8%)
Week 144	335/594 (56.4%)
Week 192	123/203 (60.6%)
Week 216	114/180 (63.3%)
Week 240	85/124 (68.5%)
Week 264	23/39 (59.0%)
Sarilumab monotherapy	
Week 0	51/110 (46.4%)
Week 24	65/109 (59.6%)
Week 48	16/30 (53.3%)

EFC11072 part B and EFC10832 studies

The results are shown below.

Figure 19: Incidence of DAS28-CRP remission (DAS28-CRP < 2.6) at each visit - EFC11072-LTS11210 combination - ITT population



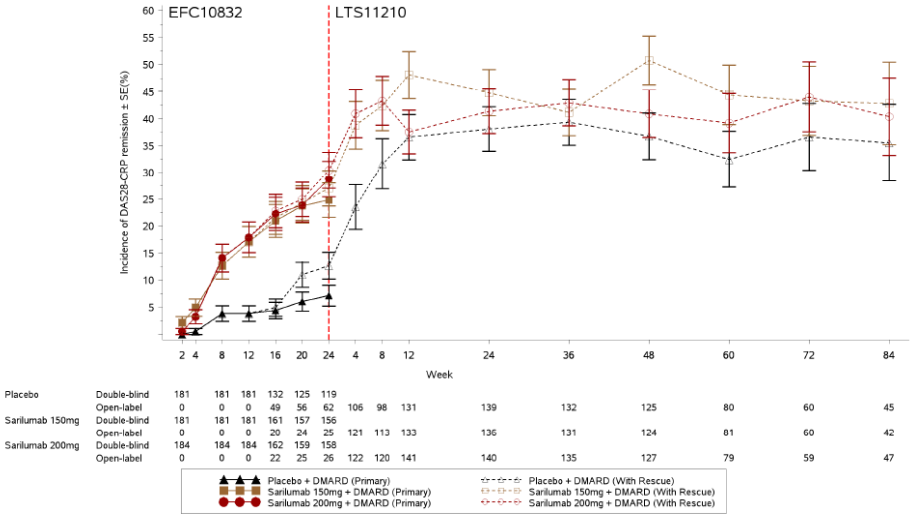
Placebo	Double-blind	398	397	396	396	301	276	259	251	245	242													
	Open-label	0	1	2	2	97	122	139	147	153	156	302	284	291	283	277	270	264	262	255	249	242	113	
Sarilumab 150mg	Double-blind	400	400	399	399	369	354	352	346	344	344													
	Open-label	0	0	1	1	31	46	40	54	56	56	291	280	285	281	268	258	252	250	242	239	226	111	
Sarilumab 200mg	Double-blind	399	399	399	399	371	367	360	358	356	353													
	Open-label	0	0	0	0	28	32	39	41	43	46	289	278	280	275	271	262	252	246	242	237	230	102	

Three patients (ID: 040001202, 040001203, 840016209) initiated non-study rescue medication prior to week 16 and were classified in open-label from the time the non-study rescue medication was initiated.

PGM=PRODOPS/SAR153191/OVERALL/CSE_EU/REPORT/PGM/eff_das_inci_i_g.sas OUT=REPORT/OUTPUT/eff_das28_inci_mb_i_g_x.rtf (19MAR2016 - 6:28)

DAS28 CRP change at each visit had a similar trend.

Figure 20: Incidence of DAS28-CRP remission (DAS28-CRP < 2.6) at each visit - EFC10832-LTS11210 combination - ITT population



Placebo	Double-blind	181	181	181	132	125	119										
	Open-label	0	0	0	49	56	62	106	98	131	139	132	125	80	60	45	
Sarilumab 150mg	Double-blind	181	181	181	161	157	156										
	Open-label	0	0	0	20	24	25	121	113	133	136	131	124	81	60	42	
Sarilumab 200mg	Double-blind	184	184	184	162	159	158										
	Open-label	0	0	0	22	25	26	122	120	141	140	135	127	79	59	47	

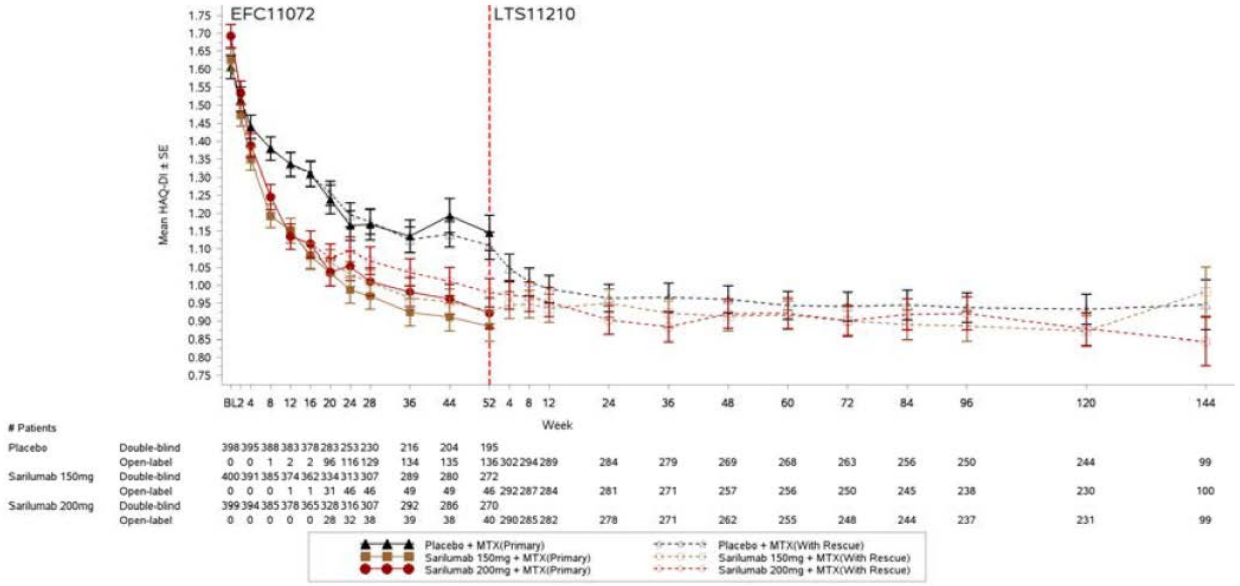
PGM=PRODOPS/SAR153191/OVERALL/CSE_EU/REPORT/PGM/eff_das_inci_i_g.sas OUT=REPORT/OUTPUT/eff_das28_inci_tg_i_g_x.rtf (19MAR2016 - 6:30)

DAS28 CRP change at each visit had a similar trend.

- Physical function

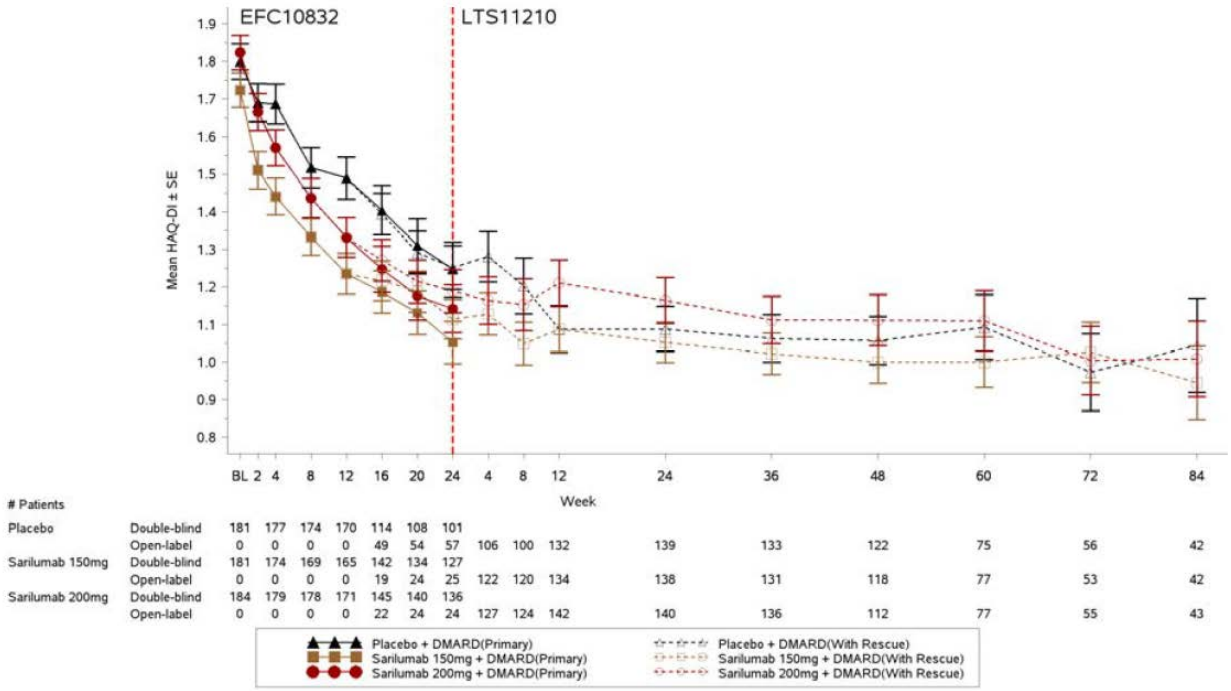
The results are shown in the figures below.

Figure 21: HAQ-DI over time for patients originally randomized into EFC11072 Part B, Cohort 2 and those who continued into the LTS11210 study



Source: 5.3.5.3 Supporting analyses for SCE [1.4.1.4.1]

Figure 22: HAQ-DI over time for patients originally randomized into EFC10832 and those who continued into the LTS11210 study



Source: 5.3.5.3 Supporting analyses for SCE [1.4.2.4.1]

- Radiographic progression (EFC11072 study)

- Analysis of 2 years radiographic data

The results are reported in the tables below.

Table 81: Mean changes from baseline in radiographic parameters at Week 52 and Week 100 for patients originally randomized into EFC11072 Part B, Cohort 2 who continued into the LTS11210 study

	EFC11072		
	Placebo + MTX (N=398)	Sarilumab 150 mg q2w + MTX (N=400)	Sarilumab 200 mg q2w + MTX (N=399)
van de Heijde mTSS			
Week 52			
Mean change from baseline (SD)	2.37 (5.63)	0.45 (3.24)	0.15 (3.93)
p-value versus placebo		<0.0001	<0.0001
Week 100			
Mean change from baseline (SD)	2.47 (5.62)	1.05 (5.61)	0.23 (3.56)
p-value versus placebo[a]		0.0021	<0.0001
Erosion score (0-280)			
Week 52			
Mean change from baseline (SD)	1.11 (2.68)	0.24 (1.81)	0.04 (1.67)
p-value versus placebo[a]	-	<0.0001	<0.0001
Week 100			
Mean change from baseline (SD)	1.17 (3.11)	0.54 (3.78)	0.09 (1.79)
p-value versus placebo[a]		0.0004	<0.0001
Joint space narrowing score			
Week 52			
Mean change from baseline (SD)	1.25 (3.72)	0.21 (2.04)	0.12 (2.57)
p-value versus placebo[a]		0.0019	<0.0001
Week 100			
Mean change from baseline (SD)	1.30 (3.31)	0.51 (2.80)	0.14 (2.30)
p-value versus placebo[a]		0.0166	<0.0001

mTSS = modified total Sharp score; MTX = methotrexate; SD = standard deviation;
Source: 5.3.5.3 Supporting analyses for SCE [1.4.1.22.6], [1.4.1.25.6], and [1.4.1.28.6]
a Rank ANCOVA model stratified by prior biologic use and region.
Modified total Sharp score = the sum of bone erosion scores from 44 joints and joint space narrowing scores from 42 joints, with a maximum score 448.
Data collected after treatment discontinuation or starting rescue medication are used as observed. Linear extrapolation is used to impute missing modified total Sharp scores.
Note: Number = Number of patients with assessment at both baseline and the corresponding week.

Table 82: Number and proportion of patients with no radiographic progression at Week 52 and Week 100 for patients originally randomized into EFC11072 Part B, Cohort 2 who continued into the LTS11210 study

	EFC11072 Part B, Cohort 2		
	Placebo + MTX (N=398)	Sarilumab 150 mg q2w + MTX (N=400)	Sarilumab 200 mg q2w + MTX (N=399)
N (%) of patients with change in mTSS ≤0[a]			
Week 52	115/285 (40.4%)	142/275 (51.6%)	180/277 (65.0%)
OR, 95% CI versus placebo[a]		1.635 (1.165, 2.293)	2.794 (1.979, 3.944)
p-value versus placebo[b]		0.0045	<0.0001
Week 100	126/285 (44.2%)	138/275 (50.2%)	168/277 (60.6%)
OR, 95% CI versus placebo[a]		1.287 (0.922, 1.797)	1.958 (1.396, 2.745)
p-value versus placebo[b]		0.1374	<0.0001
N (%) of patients with change in erosion score ≤0 [a]			
Week 52	129/285 (45.3%)	160/275 (58.2%)	191/277 (69.0%)
OR, 95% CI versus placebo[a]		1.760 (1.252, 2.474)	2.787 (1.964, 3.955)
p-value versus placebo[b]		0.0012	<0.0001
Week 100	140/285 (49.1%)	160/275 (58.2%)	181/277 (65.3.0%)
OR, 95% CI versus placebo[a]		1.493 (1.064, 2.094)	1.987 (1.410, 2.801)
p-value versus placebo[b]		0.0205	<0.0001
N (%) of patients with joint space narrowing score ≤0 [a]			
Week 52	166/285 (58.2%)	181/275 (65.8%)	223/277 (80.5%)
OR, 95% CI versus placebo[a]		1.402 (0.995, 1.976)	3.016 (2.056, 4.425)
p-value versus placebo[b]		0.0526	<0.0001
Week 100	165/285 (57.9%)	175/275 (63.6%)	206/277 (74.4%)
OR, 95% CI versus placebo[a]		1.278 (0.909, 1.796)	2.120 (1.479, 3.039)
p-value versus placebo[b]		0.1560	<0.0001

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; mTSS = modified total Sharp score; MTX = methotrexate
Source: 5.3.5.3 Supporting analyses for SCE [1.4.1.23.5], [1.4.1.26.5], and [1.4.1.29.5]
Note: Percentages are calculated using the number of ITT patients with available progression status at the corresponding time in the corresponding treatment group as denominator
No progression" is change in Sharp score ≤0
Data collected after treatment discontinuation or starting rescue medication are used as observed. Linear extrapolation is used to impute missing scores.
a Mantel-Haenszel estimate.
b CMH test stratified by prior biologic use (EFC11072) / number of previous anti-TNFs (EFC10832) and region.

Of note, in the sarilumab 200 mg group, the dose had been reduced to 150 mg q2w in 121 (15.1%) out of the 800 patients with radiographic data at Week 100 (Year 2).

- Analysis of 3 years radiographic data

The results are reported in the tables below.

Table 83: Change from baseline in the modified total Sharp score (mTSS) at week 148 (52+96) – Reading Campaign 2 in LTS11210 – ITT population

mTSS (0-448)	Placebo + MTX (N=307)	Sarilumab 150mg q2w + MTX (N=300)	Sarilumab 200mg q2w + MTX (N=294)
LTS11210 Week 96			
Number	237	228	239
Mean (SD)	52.77 (64.19)	51.06 (57.80)	47.03 (57.61)
SE	4.170	3.828	3.727
Median	33.00	26.00	24.57
Min : Max	0.0 : 344.5	0.5 : 266.5	0.0 : 283.5
Change			
Number	237	228	239
Mean (SD)	3.30 (7.18)	1.87 (6.76)	0.79 (5.38)
SE	0.466	0.448	0.348
Median	1.00	0.50	0.00
Min : Max	-9.5 : 62.7	-13.5 : 50.0	-23.5 : 32.7
P-value vs placebo[a]	-	0.0057	<0.0001

Modified total Sharp score = the sum of bone erosion scores from 44 joints and joint space narrowing scores from 42 joints, with a maximum score 448.
Data collected after treatment discontinuation or starting rescue medication are used as observed. The linear extrapolation method is used to impute missing modified total Sharp scores.
Note: Number = Number of patients with assessment at both baseline and the corresponding week.
[a]: Rank ANCOVA model stratified by prior biologic use and region.
PGM=PRODOPS/SAR153191/OVERALL/CSE_EU/REPORT/PGM/eff_chg_score_byvis_i_t.sas OUT=REPORT/OUTPUT/eff_chg_mtss_ex_byvis_i_t_x.rtf (22APR2016 - 10:38)

Table 84: Rates of no progression in the modified total Sharp score (change from baseline <= 0) at week 148 (52+96) – Approach 1 - Reading Campaign 2 in LTS11210 – ITT population

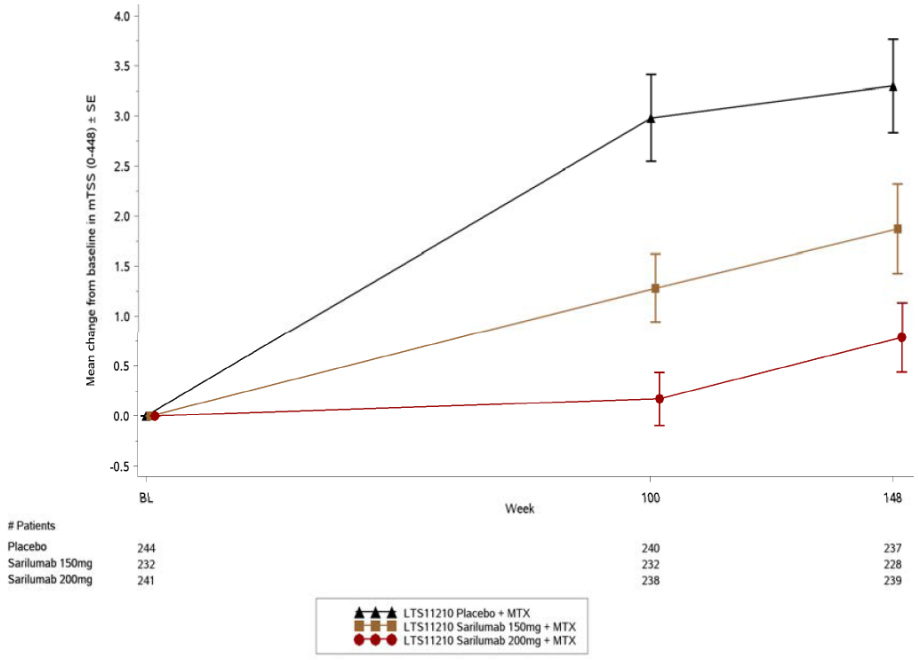
No progression in mTSS [n(%)]	Placebo + MTX (N=307)	Sarilumab 150mg q2w + MTX (N=300)	Sarilumab 200mg q2w + MTX (N=294)
LTS11210 Week 96			
Number	254	244	245
No progression	92 (36.2%)	109 (44.7%)	127 (51.8%)
Progression	162 (63.8%)	135 (55.3%)	118 (48.2%)
P-value vs placebo[a]	-	0.0540	0.0007
OR, CI vs placebo[b]	-	1.427 (0.994, 2.049)	1.870 (1.304, 2.681)

OR: odds ratio.
Modified total Sharp score = the sum of bone erosion scores from 44 joints and joint space narrowing scores from 42 joints, with a maximum score 448.
Data collected after treatment discontinuation or starting rescue medication are used as observed. The linear extrapolation method is used to impute missing modified total Sharp scores. Patients with missing modified total Sharp scores after the imputation are considered as progression.
Note: Percentages are calculated using the number of ITT patients with available progression status at the corresponding time in the corresponding treatment group as denominator.
[a]: CMH test stratified by prior biologic use and region. [b]: Mantel-Haenszel estimate.
PGM=PRODOPS/SAR153191/OVERALL/CSE_EU/REPORT/PGM/eff_prog_xray_ex_i_t.sas OUT=REPORT/OUTPUT/eff_prog_xray_mtss_0_ex_p1_i_t_x.rtf (22APR2016 - 10:39)

Of the patients scored at Week 148 (Year 3) there were 142 (19.6%) patients who had dose reduction from 200 mg to 150 mg sarilumab q2w between Week 52 (Year 1) and Week 148 (Year 3).

- Time-course of radiographic data (1, 2 and 3 years)

Figure 23: Figure of mean change from baseline in the modified total Sharp score (mTSS) at each visit – Reading Campaign 2 in LTS11210 – ITT population



PGM=PRODOPS/SAR153191/OVERALL/CSE_EU/REPORT/PGM/eff_xray_meanchg_i_g.sas
OUT=REPORT/OUTPUT/eff_meanchg_mtss_i_g_x.rtf (22APR2016 - 10:46)

SFY13370

This was a randomized, double-blind, double-dummy, 24-week study assessing the safety and tolerability of sarilumab and tocilizumab with the primary objective to assess the safety of sarilumab and tocilizumab in the same study.

SFY13370 was conducted in patients with RA based on the 2010 ACR/EULAR diagnostic criteria and defined as moderately to severely active based on joint counts and baseline CRP levels. These patients had to have an inadequate response to or an intolerance of at least 1 TNF antagonist and continued their treatment with conventional DMARDs (MTX, leflunomide, sulfasalazine, hydroxycholorquine) at baseline and continued these DMARDs during the study.

Sarilumab was administered subcutaneously (SC) 150 mg q2w or 200 mg q2w. Tocilizumab was administered intravenously with an initial dose regimen of 4 mg/kg every 4 weeks (q4w) with the option to increase the dose to 8 mg/kg q4w at the Investigator's discretion.

A total of 202 patients were randomized and treated (49, 51, and 102 in the sarilumab 150 mg q2w, sarilumab 200 mg q2w, and tocilizumab 4 mg/kg groups, respectively).

Baseline demographics and disease characteristics were well balanced among the treatment groups.

A total of 60.8% of tocilizumab patients had a dose increase from 4 mg/kg to 8 mg/kg during the treatment period; 42.4% of patients increased their dose at Week 4. Among the tocilizumab patients who up-titrated to 8 mg/kg; there were 4 patients who later reduced their dose to 4 mg/kg primarily due to adverse safety findings.

Within the limitations of this study, which was not designed to evaluate the comparative efficacy of sarilumab and tocilizumab, efficacy responses were similar between the treatment groups.

EFC13752

This was an open-label, parallel-group, 24-week study assessing the immunogenicity and safety of sarilumab as monotherapy in patients with RA. Patients were randomized to receive sarilumab 150 or 200 mg q2w.

A total of 132 patients were randomized and treated (65 in the sarilumab 150 mg q2w group and 67 in sarilumab 200 mg q2w group).

Baseline demographics and disease characteristics were well balanced among the treatment groups.

Within the limitations of this study, which was not designed to evaluate the comparative efficacy of the 2 dose regimens of sarilumab, efficacy responses were similar between the treatment groups.

MSC12665

MSC12665 was a multicenter study to evaluate the usability of a sarilumab AI device conducted in patients with RA based on the 2010 ACR/EULAR diagnostic criteria and defined as moderately to severely active based on joint counts and baseline CRP levels. Patients were on conventional DMARDs (MTX, leflunomide, sulfasalazine, hydroxycholorquine) at baseline and continued these DMARDs during the study. This study was divided into 2 parts: a multicenter, randomized, open-label, parallel-group, 12-week study in which patients were randomized to 1 of 4 arms to receive sarilumab 150 mg or 200 mg q2w delivered using the AI or prefilled syringe (PFS), and a 12-month extension part in which all patients received sarilumab 150 mg q2w delivered using the PFS. Only the 12-week data are presented in the CSR; the extension phase of this study is ongoing.

A total of 217 patients were randomized and treated (53 in the sarilumab 150 mg q2w PFS group, 56 in the sarilumab 150 mg q2w AI group, 56 in sarilumab 200 mg q2w PFS group, 52 in sarilumab 200 mg q2w AI group). Baseline demographics and disease characteristics were well balanced among the treatment groups.

The primary endpoint was the number of AI-associated product technical failures reported during that 12-week part. None occurred among the 600 injections performed in 108 patients, which confirmed the usability of this AI.

Within the limitations of this study, which was not designed to evaluate the comparative efficacy of the 2 dose regimens of sarilumab, efficacy responses were similar between the treatment groups.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Four Phase 3 efficacy studies, designed to assess the treatment responses of sarilumab in moderately to severely active RA, were conducted: EFC11072 (2-part study, Phase II/III), EFC10832, EFC14092, LTS11210.

The effect of sarilumab in add on to MTX/cDMARDs in c-DMARD-IR and b-DMARD-IR subjects, was assessed in studies EFC11072 and EFC10832.

EFC11072 was a 2-part, double-blind, placebo-controlled study conducted in patients with an inadequate response to MTX. In this study, sarilumab or placebo was administered in combination with MTX. This study is

completed. Part A was the 12-week Phase 2, dose-ranging part of the study; Part B was the 52-week, Phase 3 part of the study.

In the dose-ranging study EFC11072 Part A 306 patients with moderately to severely active RA who had an inadequate response to MTX were included. With regard to the in- and exclusion criteria the population defined was relevant for dose finding. Five dose regimens of sarilumab were tested, the study design was comprehensible. Baseline demographic and disease characteristics were well balanced among the treatment groups.

The primary endpoint ACR 20 at week 12 as well as the secondary endpoints (ACR50/70, change from baseline in each of the seven ACR components, change from baseline in DAS28, DAS28 remission, EULAR response, ACRn at week 12) are in line with the recommendations made in the "Points to Consider on the Clinical Investigation of Medicinal Products other than NSAIDs in Rheumatoid Arthritis".

EFC11072 Part B

After Part A of EFC11072 was fully enrolled, Part B was initiated and patients were randomly assigned using the same strategy as in Part A.

The inclusion criteria were identical to part A but comprised one bone erosion or anti-CCP positive status or RF positive status in addition. The 3 co-primary endpoints (ACR20, change of HAQ-DI, change in van der Heijde modified tSS) and the main secondary endpoint (Major clinical response defined as the event of achieving and maintaining an ACR 70 response for at least 24 consecutive weeks) reflect the objectives, namely to demonstrate that sarilumab added to MTX is effective in reduction of signs and symptoms, in the inhibition of progression of structural damage and in the improvement in physical function, adequately and are in line with the recommendations made in the "Points to Consider on the Clinical Investigation of Medicinal Products other than NSAIDs in Rheumatoid Arthritis".

EFC10832 was a 24-week, randomized, double-blind, placebo-controlled study in patients with a history of TNF-IR. In this study, sarilumab or placebo was administered in combination with MTX, sulfasalazine, hydroxychloroquine, or leflunomide. This study is completed.

In contrast to study EFC11072 and EFC10832 the duration of RA of the included patients had to be at least 6 months (instead of 3 months), the definition of moderate to severely active RA was comparable to that in these previous studies. Besides MTX other DMARDs such as Leflunomide, Sulfasalazine and Hydroxychloroquine were allowed. The objectives (reduction of signs and symptoms, improvement in physical function, improvement of disease activity score and of quality of life) were reflected by the primary (ACR20, HAQ-DI) and secondary endpoints.

Both studies, EFC11072 and EFC10832, in line with current guidelines for the management of moderately to severely active RA subjects, allowed rescue treatment in inadequate responders. However, the definition of non-responder is not based on disease sign and symptoms, and thus does not allow to fully characterize treatment efficacy. In addition, different treatment periods (16 and 12 weeks for the MTX-IR and TNF-IR subjects, respectively) were used to check for treatment response, further challenging the possibility to extrapolate clear information for potential recommendation in the SmPC.

The effect of sarilumab monotherapy in subjects who responded inadequately or were intolerant to MTX was assessed in study EFC14092. This study was designed to provide the evidence of sarilumab administered as monotherapy and to provide the context for the efficacy of sarilumab relative to that of an approved biologic DMARD. Adalimumab, a TNF-a-inhibitor, was chosen as a comparator. This was considered acceptable.

EFC14092 was a Phase 3, 2-part, study: Part 1 was a randomized, active-controlled, double-blind, double-dummy 24-week treatment period that enrolled patients who were either intolerant of, or considered inappropriate candidates for continued treatment with MTX, or who, after at least 12 weeks of continued treatment with MTX, were determined to be inadequate responders. In this study, sarilumab or adalimumab were administered as monotherapy. In Part 2, the open-label extension, all patients were to receive sarilumab as monotherapy. Part 1 is completed; Part 2 is ongoing. The final report for this study is expected no later than the end of 2021.

The duration of RA had to be at least 3 months; this inclusion criterion was the same as the one in study EFC11072. The choice of DAS28-ESR as a primary endpoint to demonstrate that sarilumab is superior to adalimumab monotherapy with respect to signs and symptoms is acceptable. Regarding the baseline data the population in the sarilumab group was a bit younger (-2.7 years) and regarding the baseline disease characteristics patients on sarilumab had a longer duration of RA and lower baseline CRP compared to adalimumab. However, DAS28-CRP and DAS28-ESR values, as well as HAQ-DI and CDAI scores were comparable between treatment groups.

Overall, the inclusion and exclusion criteria were similar in all three phase 3 trials, and are considered overall adequate to identify the patient population covered by the indication.

Co-primary efficacy endpoints of all Phase 3 studies are in compliance with the requirements of the relevant EMA guideline on medicinal products for the treatment of RA, as they aimed at evaluating treatment effect on signs and symptoms (ACR20 response), physical function (change from baseline in HAQ-DI), and for EFC11072 Part B only, progression in structural damage (mTSS). The endpoints were analysed in a step-down hierarchy to avoid multiplicity issues.

LTS11210 is an ongoing long-term, open-label, Phase 3, uncontrolled extension study. Patients from EFC11072 and EFC10832 were allowed to enter this study. Data from LTS11210 are provided up through the CTD cut-off date of 25 January 2016.

With regard to efficacy the study results have to be interpreted with caution as this is an open label trial without internal control. Furthermore, the efficacy analyses do not account for dropouts. Thus the efficacy results are likely to be biased.

Of note, the route of administration slightly differed between the different studies:

EFC14092: SC in abdomen or front of thigh, EFC10832: SC in abdomen, thigh or upper arm, EFC11072: SC in abdomen. However, this seems to be a minor difference that does not affect the outcomes of the studies.

Efficacy data and additional analyses

Sarilumab in add on to MTX/cDMARDs in c-DMARD-IR and b-DMARD-IR subjects

The enrolled patient population in both EFC11072 part B and EFC10832 studies is considered sufficiently representative of the target population of moderately to severely active RA subjects. However, the proportion of EU patients enrolled in the EFC11072 trial is very low (less than 20%), and could put into question the external validity of the study.

Further data was provided in order to support the broad comparability among the EU population and non EU-population of the the EFC11072, Part B, Cohort 2 study and the subjects (EU and not EU) enrolled in the

other pivotal studies (EFC10832 and EFC14092) in terms of baseline and disease characteristics as well in terms of efficacy outcomes. Therefore, the external validity of the study results for the EU population is confirmed.

Of note, roughly 30% of subjects in Study EFC11072 had previously received b-DMARD, without experiencing inadequate response leading to treatment interruption in the previous 3 months. The distribution of these patients in the 3 arms of the trial was provided during the evaluation procedure.

Similar proportion of patients completed the 2 studies. Rescued subjects were 3 fold higher in the PLB+MTX arm as compared to sarilumab+MTX arms (slightly higher in the sarilumab lower dose). Discontinuation ranged from 9% to 12% in PLB+MTX and from 14% to 20% in sarilumab+MTX arms, with the lower rates being observed in the TNF-ir patients; safety issues were the most common reason for discontinuation in all arms of both studies. Patients considered as non-responders (rescued or discontinued) were about 43% -50% in the PLB+MTX arms and 30% in sarilumab+MTX arms. The percentage of patients with insufficient data considered as non-responders was very low and therefore a potential impact on the estimation of treatment effect is excluded.

In the dose-ranging study EFC11072 Part A the highest ACR20 response rate occurred in the 150 mg qw treatment group, but with respect to the other endpoints, the 150 mg once weekly dose was not more effective than some of the lower doses evaluated. Only a trend was seen in the 150 mg q2w, 100 mg qw, and 200 mg q2w sarilumab treatment arms regarding the ACR20 response.

The ACR50 response rates were highest for the 100 mg qw (nominal p = 0.0062) and 200 mg q2w (nominal p = 0.0038) groups. The response rate of patients achieving ACR70 at Week 12 was also highest in the 200 mg q2w group with nominal p = 0.0078 compared with placebo.

In Part B of the study the dose of 200 mg q2w respectively 150 mg q2w was administered. With regard to the abovementioned findings in the dose-ranging Part A of the study the dose of 150 qw would have been suitable to use as this dose was the maximally effective dose based on the results of the ACR20 response. As a q2w-regimen compared to a qw-regimen allows fewer applications for the patients the choice of 200 mg q2w - which was the effective dose regarding the more clinically meaningful parameters ACR50 and ACR70 - is acceptable. The choice of 150 mg q2w as a second possible dose for a biweekly regimen is acceptable as well because there has been seen a trend for efficacy concerning ACR20, ACR50 and ACR70.

The ACR20 response rates of sarilumab 150 mg q2w and of 200 mg q2w were similar, but the response rates for ACR50 and ACR70 were numerically superior regarding the 200 mg q2w dose. In addition, results for certain components of the ACR score, specifically Pain and physician global assessment, were better for the 200 mg q2w dose. Therefore, the choice of the 200 mg q2w dose as the standard dose and 150 mg q2w as the other possible dose is acceptable

Both doses of sarilumab (150/200mg q2w) were statistically significant superior to placebo regarding all 3 co-primary endpoints (ACR20, HAQ-DI, mTSS) in study EFC11072 Part B.

A gain over placebo of 33% was observed in the first co-primary endpoint, ACR20 response, at week 24, in EFC11072 and EFC10832 studies respectively, with 66.4% of patients obtaining ACR20 response. The amelioration of signs and symptoms appeared early than 24 weeks and was maintained up to 52 weeks.

The data collected after treatment discontinuation or rescue were set to missing and the patients were considered as non-responders after that time. Since treatment discontinuation and rescue were, overall, more frequent in the control group, this approach tends to overestimate the treatment effect. The proposed sensitivity analysis using the LOCF method to impute missing data is not reassuring about the robustness of the estimation of treatment effect, given that the LOCF analysis, in such scenario, is likely to be anti-conservative,

especially if treatment discontinuation is observed earlier in the control group. A more conservative approach was considered to be required.

Sensitivity analysis based on a conservative approach was not provided. However, according to the Applicant explanation, as the majority of missing data was due to rescue therapy and lack of efficacy, it is agreed that such a conservative approach could be applied only to a small percentage of patients (discontinued due to adverse events). Therefore, a potential impact on the estimation of treatment effect should be negligible.

The sensitivity analyses were consistent with the primary results. Linear extrapolation was used to impute missing information or post rescue week 52 data, based on the assumption of linearity on bone damage over time. Different sensitivity analyses were performed, all supportive of the primary analysis. In addition to the sensitivity analyses performed in the CSR the Applicant conducted two additional sensitivity analyses of mTSS using pattern mixture models (PMM). In both analyses, all observed X-ray assessments after one year were analyzed including those after rescue. In the first of these analyses the data for patients who did not have a X-ray at one year, was imputed based on a 'switch to control' assumption in which the missing data was based on the observed one year results in the placebo group. In the second analysis, the multiple imputation procedure was based on a 'copy increment from reference' approach in which missing data due to efficacy and safety (ie discontinuations due to lack of efficacy, AE, or rescue) was imputed based on the placebo group, but the placebo progression was assumed to apply only from the point in time at which the last X-ray was observed, and not for the full one year. Missing data for other reasons (such as unreadable X-rays) was assumed missing at random.

These analyses confirmed the results of the primary analysis at week 52 and the secondary analysis at week 24.

However, none of the applied sensitivity analyses may completely overcome the potential for overestimation of treatment effect. Because of the high number of patients who discontinued or were rescued, the Applicant was asked to provide analyses of the time to rescue and time to withdrawal. The Applicant provided time-to-event analysis, were the initialization of rescue medication is considered as censoring in the time-to-discontinuation analysis.

Rescue medication is given for a much higher number of patients in the placebo group and a slightly higher number in the sarilumab 150mg q2w group. Especially in the placebo group, rescue medication is initiated in a substantial number of patients at each visit (after week 16) and only a few patients who initialize rescue medication in between scheduled visits. Overall, the frequency of rescue medication cumulates to over 40% in the placebo group and stays approximately at approximately 13% to 15% in the sarilumab groups. These estimates are slightly higher than raw frequencies and are considered more accurate as they appropriately take censoring into account.

Time dependent discontinuation rates and AE related discontinuation rates are higher (or at least not less) in sarilumab patients throughout the whole study period than in placebo patients. Discontinuation rates seem more or less constant over time. Overall discontinuation rates are over 20% for all study groups, and around 10% (placebo) to 17% (sarilumab) for AE related discontinuation. These estimates are slightly higher than raw frequencies and are considered more accurate as they appropriately take censoring into account.

Overall, the pattern is as expected. These findings concerning the probability of discontinuation seem to be reasonable due to the AEs that are connected with the sarilumab treatment compared to placebo. The findings regarding the probability of rescue seem to favour the efficacy of sarilumab, especially used in the higher dose.

Supportive evidence of a positive sarilumab effect on bone damage is provided by the greater ($p < 0.0001$) proportion of sarilumab-treated patients with no progression of structural damage compared to placebo, as shown by the conservative analysis evaluating treatment effect on the binary endpoint progression/no

progression. The effect on progressive structural damage was sustained upon continued treatment for up to 3 years. Of note, the evaluation of RX scans indicated a larger reduction of radiographic progression in bone structural damage in subjects initially randomized to sarilumab 200 mg q2w as compared to those who started treatment with sarilumab 150 mg q2w.

As it its mentioned in the" Points to Consider on the Clinical Investigation of Medicinal Products other than NSAIDs in Rheumatoid Arthritis" for agents which are claimed to prevent structural joint damage it is recommended to demonstrate radiological differences of hands and forefeet on the basis of before/after comparisons taken not less than one year apart, ideally for two years. Therefore the 1-year-data provided regarding mTSS could be regarded as sufficient but not as convincing as it could be. The main secondary endpoint, the proportion of patients achieving major clinical response, was met: The 200 mg q2w group was slightly better than the 150 mg q2w group of sarilumab (14,8%, 12,8%, placebo 3,0%). Sarilumab was in both doses superior to placebo ($p<0.0001$) regarding the other secondary endpoints in the hierarchy concerning the improvement of signs and symptoms (ACR50/70, DAS28-CRP, CDAI-scores).

No evidence of interaction was found for most subgroup analyses. However, the following interactions were found:

• The incidence of ACR20 interaction for the anti-CCP antibody subgroup (nominal p-value=0.001), indicating a lower ACR20 response in anti-CCP antibody negative patients

• The change from baseline in HAQ-DI, for the anti-CCP antibody subgroup (nominal p-value=0.0028), indicating a lower HAQ-DI change in anti-CCP antibody negative patients

• The change from baseline in HAQ-DI, for the rheumatoid factor subgroup (nominal p-value=0.0417), indicating a lower HAQ-DI change in rheumatoid factor negative patients

• The change from baseline in mTSS, for the smoking history subgroup (self-reported positive smoking history, current or former, versus negative smoking history) (nominal p-value=0.0412), indicating a greater change in mTSS in patients with a history of smoking

Study EFC10832 showed that both doses of sarilumab were superior to placebo when added to background DMARDs for the treatment of moderate to severe RA patients who had inadequate response to or were intolerant of anti-TNF-a therapies. Both primary endpoints (ACR20 response at week 24, change from baseline in HAQ-DI score at week 12) were met. Patients who were negative for autoantibodies (RF or anti-CCP) had a smaller treatment effect with regard to ACR20 and HAQ-DI. The secondary endpoints in the hierarchy (ACR50/70, decrease in DAS28-CRP, DAS28-CRP <2.6 (remission) were met, too. Results of all ACR core set components and quality of life analyses (PCS of SF-36) support the superiority of both doses of sarilumab to placebo.

This study was not powered to evaluate potential differences between doses, only a trend was observed regarding different efficacy parameters that 200 mg q2w are superior to the sarilumab dose of 150 mg q2w.

Subgroups analyses showed that in study EFC11072 autoantibody (i.e. RF and anti-CCP) positivity was a co-variate impacting on improvement in signs and symptoms (ACR20 for anti-CCP) and functional activity (for RF and anti-CCP). However, this was not confirmed in study EFC10832. Moreover, the lower ACR response in negative RF or anti-CCP subjects was not seen in radiologic outcomes for bone structural progression.

From a clinical perspective, it is remarkable the superiority of the combination sarilumab+MTX over PBL+MTX in achieving and maintaining ACR70 for at least 24 consecutive weeks during the 52-week period.

It is of note that, some secondary endpoints related to the evaluation of QoL were only met by the 150mg q2w sarilumab dose in both EFC11072 and EFC10832 studies.

Ancillary analyses taking into account other endpoints e.g. Boolean-based ACR/EULAR remission, SDAI and CDAI indexes, were in line with the results of the primary analysis.

In study EFC14092 the primary endpoint of change from baseline in DAS28-ESR at week 24 was met, therefore sarilumab 200 mg q2w administered as monotherapy was superior to adalimumab 40 mg q2w monotherapy. The results of the sensitivity analyses for the primary endpoint were consistent with those from the primary analyses. Treatment effect was seen already at 3 months post treatment. It is of note that although the total proportion of responders was higher in the sarilumab arm (49 subjects versus 13) a higher proportion of Adalimumab-treated subjects obtained 0 active joints (tender or swollen or both), likely meaning that in those few Adalimumab responders the anti-inflammatory effect exerted by the drug is more profound.

The secondary endpoint, incidence of DAS28-ESR remission (DAS28-ESR <2.6), was also met. That means that significantly more patients treated with sarilumab than adalimumab achieved DAS28-ESR remission (26.6% vs. 7%, p<0.0001). With regard to the other secondary endpoints ACR/2050/70 sarilumab demonstrated superiority to adalimumab. Sarilumab showed better improvement of physical function, measured by HAQ-DI, than adalimumab.

Partial improvements were seen in QoL measures (few endpoints were statistically superior others only numerically higher).

In all subgroups including those defined by autoantibody status, sarilumab monotherapy was superior to adalimumab monotherapy

The subgroup analyses revealed a possible interaction between baseline BMI and treatment group for both change from baseline in DAS28-ESR at Week 24; with the smallest between group differences appearing in the subgroup with a baseline body mass index (BMI) $\geq$ 30 kg/m^2. However, this category of patients was poorly represented, and no interaction with BMI or body weight was detected in the two add-on studies. No significant interaction was identified between baseline weight and treatment group for change from baseline in DAS28-ESR. In addition, regarding DAS28-ESR remission (DAS28-ESR <2.6) there was a statistically significant interaction between baseline BMI and treatment group at Week 24 (p=0.0094), where the smallest treatment effect was seen in patients with BMI $\geq$ 30 kg/m2.

In the analysis of ACR20 and DAS28 CRP responses using pooled data from EFC11072 and EFC10832 studies, the magnitude of treatment effect with sarilumab 150 mg dose was the lowest in the categories of both BMI$\geq$30 kg/m^2 and body weight >100 kg. Furthermore PK data showed that exposure to sarilumab varied across different groups of body weight, and population PK analyses indicated lower exposure to sarilumab at weights $\geq$100 kg. An exposure-response analysis was thus requested to substantiate or negate the clinical relevance of the observation (see PK section).

Exposure-response (E - R) analyses of ACR20 and DAS28-CRP change from baseline at Week 24 were conducted by pooling data from Study EFC11072, Part B, Cohort 2 and Study EFC10832.

Modeling approaches were similar to those used in the previous empirical E-R modeling of efficacy endpoints for each study (Study POH0455. The Pharmacokinetics (PK)/Pharmacodynamics (PD) model was used to provide model predictions with 95% CI for each dose (150 mg q2w and 200 mg q2w) difference from placebo in each bodyweight subgroup. The body weight and BMI were evaluated as covariates in the E-R analyses of ACR20 and DAS-CRP response using pooled data from EFC11072, Part B and EFC10832 studies. With the body weight effect in PK/PD accounted for in the PK model, the secondary effect of body weight on effect was not included in the E-R model or only had marginal effects, which is consistent with the previously submitted E-R analyses for these end points in Study POH0455

A larger between-group difference in change in DAS28-ESR from baseline at Week 24 appeared among patients with an average baseline CRP >15 mg/mL compared with patients with an average baseline CRP ≤ 15 mg/mL. No significant interaction between the subgroups of baseline CRP or ESR was identified for the incidence of DAS28-ESR remission. In all these subgroups, sarilumab was superior to adalimumab.

As study LTS11210 is an open label study, which is ongoing, the results must be evaluated with caution and are only preliminary. Data collected over 3 years (1 year in EFC11072 and 2 years in LTS11210) were evaluated.

In the group of patients who received sarilumab and DMARDs the proportion of patients with ACR20/50/70 responses and DAS28 remission was maintained (*i.e.*, the proportion of patients with ACR20 response kept increasing over time, reaching up to ~90% after 264 weeks of treatment in the safety population.). Throughout the treatment period and the effect of sarilumab on the ACR core set components was maintained over time. However, the results of this LTE study have to be evaluated with caution as the placebo effect in the data has to be taken into consideration.

Of note, patients originally randomized to receive sarilumab 150 mg q2w (study EFC11072, study EFC10832), upon switching to 200 mg q2w, achieved nearly comparable responses to those originally randomized to 200 mg q2w (LTS11210), although differences in radiographic progression of bone damage were still apparent both after 2 years (mTSS: 0.23, 200 mg q2w vs. 1.05, 150 mg q2w) and 3 years of treatment (mTSS: 0.79, 200 mg q2w vs. 1.87, 150 mg q2w).

In the 3 year analysis of mTSS the score increased by 2.14 units from baseline to year 3 and the rate of nonprogression from baseline was 44.2%.

Consistent results were obtained for the two populations of patients rolling over from the two studies EFC11072 and EFC10832, with a predictable trend of a lower percentage of responses in TNF-IR subjects (from study EFC10832) as compared to MTX-IR ones (from study EFC11072). However, study LTS11210 data interpretation is confounded by the use of both C1P2F2 DP in vials and C2P1F3 DP in PFS. Clarification on DPs comparability and on the potential impact of differences between the two DPs on LTS11210 study results was given by the Applicant supporting that the contribution of patients treated with C1P2F2 drug product in vials was limited (roughly 7.6% of cumulative exposure to sarilumab in LTS11210 derived from patients enrolled in EFC11072, Part A who received C1P2F2 drug product in vials; beyond 96 weeks, <0.001% of data can be attributed to patients who received C1P2F2 drug product in vials). Therefore, the potential impact on LTS11210 study could be reasonably excluded. Efficacy data for patients with sarilumab monotherapy were limited. The proportion of patients with ACR20/50/70 repsonses and DAS28 remission was improved or maintained and the effect of sarilumab on the ACR core set components was maintained.

The pooled analyses of EFC11072 Part B and EFC10832 showed that the response to sarilumab 150 mg is influenced by weight and BMI but not by other demographic characteristics.

Patients with weights ≥ 100 kg had the lowest ACR20 response rates with sarilumab 150 mg q2w and smallest change from baseline in DAS28-CRP while they generally responded to sarilumab 200 mg q2w. There was no significant association of weight with radiographic outcomes.

In analyses based on relatively small numbers of patients, patients who received sarilumab 150 mg q2w and who were negative regarding both autoantibodies were less likely to have had an improvement ACR20 and change from baseline in DAS28-CRP compared with patients randomized to sarilumab 200 mg q2w.

The starting dose of sarilumab 200 mg q2w seems to be acceptable from a point of view concerning the efficacy. The Applicant appropriately discussed the higher rate of fatal infections and sepsis cases at the high dose level of sarilumab with the longer duration of exposure to sarilumab treatment. Furthermore, the inhibition of

structural damage is better for the 200 mg q2w dose compared to the lower dose, especially a starting dose of 200 mg q2w leads to a better outcome regarding structural damage compared to the effects gained by a switch from the lower to the high dose. The post-hoc analysis of the data of study MSC12655 indicates that, for some patients, a switch from the high to the low dose of sarilumab did not result in maintenance of the disease remission (DAS28-CRP <2.6).

The possibility to decrease the dose of sarilumab in case of laboratory abnormalities (decreases in ANC or platelets or increased transaminases) is given (see section 4.2 of the SmPC).

The data derived from patients who decreased their sarilumab dose from 200 mg q2w to 150 mg q2w, although with some limitations, indicate maintenance of treatment effect up to 24 weeks. Unfortunately, no long-term data on bone damage is available following sarilumab dose reduction, and as such no conclusion on this aspect is at present possible. However, the observation that the rate of remissions is maintained and even numerically increased after 24 weeks from dose decrease is considered sufficiently reassuring to recommend dose decrease to 150 mg q2w in case of laboratory abnormalities.

The available evidence on sarilumab efficacy after dose increase from 150 mg q2w to 200 mg q2w, together with the overall efficacy data from the pivotal trials showing a trend towards a better performance of the 200 mg q2w dose vs 150 mg q2w dose, is considered sufficiently supportive to recommend, in the proposed SmPC, the increase in sarilumab dose after reduction to 150 mg q2w in case of laboratory abnormalities.

2.5.4. Conclusions on the clinical efficacy

The efficacy data of the two phase 3 placebo-controlled studies in patients who received background DMARDs showed that both dose regimens of sarilumab (150 mg q2w, 200 mg q2w) were superior to placebo regarding improvement of signs and symptoms (ACR20 responses), of physical function (change from baseline in HAQ-DI) and of progression in structural damage (mTSS, only study EFC11072).

The active-comparator study demonstrated the efficacy of sarilumab as monotherapy and relative to the biologic DMARD adalimumab.

Overall, data of the submitted studies are considered overall adequate to identify the patient population of the indication.

2.6. Clinical safety

Patient exposure

The safety assessment of sarilumab is mainly based on the integrated safety analysis of nine Phase 2 and 3 studies. The integrated safety database for sarilumab in RA includes patients enrolled in the global RA studies who received at least 1 dose of sarilumab with or without DMARDS.

A total of 3354 patients having received at least 1 dose of sarilumab±DMARD in the global Phase 2 and 3 RA clinical development program, providing 5981.0 patient-years of cumulative exposure, are included in the integrated safety analysis. Of these, 2887 patients were on background DMARD therapy; and 467 patients received sarilumab as monotherapy.

For the purpose of the analysis the patients were dived in 3 different pools: placebo-controlled population (Pool 1), sarilumab+DMARD long-term safety population (Pool 2), and sarilumab monotherapy population (Pool 3). The patients from the placebo-controlled population who were on sarilumab are also included in the sarilumab+DMARD long-term safety population (Pool 2). Pool 1 includes safety data collected during the double-blind treatment period. Once a patient entered the rescue period, defined as the day when the first open-label dose of sarilumab was administered, data were no longer included. Duration of treatment for Pool 1 is up to 52 weeks. Pool 2 consists of all patients who received any dose of sarilumab + DMARD; the maximum duration of treatment observed is 5.4 years. Pool 3 consists of patients who received sarilumab as monotherapy. The review of safety data in this population allows for an assessment of the safety of sarilumab when administered without concomitant DMARDs. The majority of the data are derived from patients treated with sarilumab 200 mg q2w.

In all Phase 2/3 studies (except monotherapy studies) patients received background therapy for RA. The background therapy varied among the combination studies and included MTX, a combination of MTX with other DMADRs e.g. leflunomide, sulfasalazine and hydrochloroquine or non-MTX DMADRs. The majority of patients in the combination therapy studies received MTX with or without other DMARDs as background therapy, only a small proportion of patients received concomitant “non-MTX DMARDS”.

The patients demographic and baseline characteristics were summarised in the efficacy section. Briefly, in all populations (placebo-controlled, sarilumab+DMARD long-term safety, and monotherapy) the majority of patients were female and Caucasian with a mean age of ~52 years. Prior biologic DMARD use was reported in 8.4% of patients in the monotherapy population, compared to 43% and 39% of patients in the placebo-controlled and sarilumab+DMARD long term safety populations, respectively.

Adverse events

An overview of TEAEs based on incidence and exposure-adjusted incidence rate (ie, patients/100 patient-years) is provided in tables below.

Table 85: Overview of Adverse Event Profile: Incidence and exposure-adjusted incidence rate during the entire TEAE period – All population pools

Treatment	Raw incidence rate n/N (%)	Exposure adjusted incidence rate[a] n/PY (rate per 100 PYs)
TEAE		
Any sarilumab monotherapy doses (Pool 3)	285/467 (61.0%)	285/139.3 (204.6)
Any sarilumab doses + DMARD (Pool 2)	2314/2887 (80.2%)	2314/1340.1 (172.7)
Sarilumab 200 mg q2w + DMARD (Pool 1)	488/661 (73.8%)	488/193.6 (252.0)
Sarilumab 150 mg q2w + DMARD (Pool 1)	465/660 (70.5%)	465/215.5 (215.7)
Placebo + DMARD (Pool 1)	278/661 (57.2%)	278/218.2 (173.3)
Serious TEAE		
Any sarilumab monotherapy doses (Pool 3)	26/467(5.6%)	26/295.2 (8.8)
Any sarilumab doses + DMARD (Pool 2)	438/2887 (15.2%)	438/4157.2 (10.5)
Sarilumab 200 mg q2w + DMARD (Pool 1)	59/661 (8.9%)	59/426.5 (13.8)
Sarilumab 150 mg q2w + DMARD (Pool 1)	42/660 (6.4%)	42/433.8 (9.7)
Placebo + DMARD (Pool 1)	31/661 (4.7%)	31/375.4 (8.3)
TEAE leading to death		
Any sarilumab monotherapy doses (Pool 3)	3/467 (0.6%)	3/303.3 (1.0)
Any sarilumab doses + DMARD (Pool 2)	19/2887 (0.7%)	19/4481.4 (0.4)
Sarilumab 200 mg q2w + DMARD (Pool 1)	1/661 (0.2%)	1/442.8 (0.2)
Sarilumab 150 mg q2w + DMARD (Pool 1)	2/660 (0.3%)	2/442.1 (0.5)
Placebo + DMARD (Pool 1)	3/661 (0.5%)	3/383.9 (0.8)
TEAE leading to permanent treatment discontinuation		
Any sarilumab monotherapy doses (Pool 3)	26/467 (5.6%)	26/300.3 (8.7)
Any sarilumab doses + DMARD (Pool 2)	538/2887 (18.6%)	58/4390.8 (12.3)
Sarilumab 200 mg q2w + DMARD (Pool 1)	83/661 (12.6%)	83/428.4 (19.4)
Sarilumab 150 mg q2w + DMARD (Pool 1)	72/660 (10.9%)	72/429.8 (16.8)
Placebo + DMARD (Pool 1)	31/661 (4.7%)	31/379.8 (8.2)

PY: Patient-years, TEAE: Treatment-emergent adverse event, SAE: Serious adverse event.
n (%) = number and percentage of patients with at least one TEAE.
[a] Number of patients with at least one event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration.
b The 95% confidence interval was calculated using the exact method.

Common adverse events and adverse drug reactions

The TEAEs by SOC and PT that were reported in ≥2% of patients in at least 1 treatment group in the placebo-controlled population (Pool 1) are summarized in table below.

Table 86: Number (%) of patients with TEAE(s) and number of events (per 100 patient-years) by primary SOC and PT (>= 2% in at least 1 treatment group) - Placebo-controlled safety population (Pool 1)

		Sarilumab			Sarilumab	
	Placebo + DMARD	150 mg q2w + DMARD	200 mg q2w + DMARD	Placebo + DMARD	150 mg q2w + DMARD	200 mg q2w + DMARD
Primary System Organ Class Preferred Term	(N=661) n (%)	(N=660) n (%)	(N=661) n (%)	(PY=382.3) n_E (n_E/100 PY)	(PY=440.7) n_E (n_E/100 PY)	(PY=441.4) n_E (n_E/100 PY)
Any class	378 (57.2%)	465 (70.5%)	488 (73.8%)	994(260.0)	1490(338.1)	1703(385.8)
Infections and infestations	191 (28.9%)	226 (34.2%)	233 (35.2%)	289 (75.6)	356 (80.8)	373 (84.5)
Upper respiratory tract infection	32 (4.8%)	42 (6.4%)	47 (7.1%)	39 (10.2)	54 (12.3)	55 (12.5)
Urinary tract infection	28 (4.2%)	29 (4.4%)	38 (5.7%)	30 (7.8)	31 (7.0)	48 (10.9)
Nasopharyngitis	31 (4.7%)	36 (5.5%)	28 (4.2%)	35 (9.2)	41 (9.3)	30 (6.8)
Bronchitis	19 (2.9%)	17 (2.6%)	25 (3.8%)	21 (5.5)	23 (5.2)	26 (5.9)
Influenza	19 (2.9%)	17 (2.6%)	16 (2.4%)	22 (5.8)	20 (4.5)	17 (3.9)
Pharyngitis	14 (2.1%)	15 (2.3%)	16 (2.4%)	15 (3.9)	15 (3.4)	18 (4.1)
Sinusitis	11 (1.7%)	14 (2.1%)	16 (2.4%)	11 (2.9)	17 (3.9)	16 (3.6)
Blood and lymphatic system disorders	20 (3.0%)	77 (11.7%)	122 (18.5%)	20 (5.2)	133 (30.2)	207 (46.9)
Neutropenia	3 (0.5%)	65 (9.8%)	94 (14.2%)	3 (0.8)	101 (22.9)	137 (31.0)
Leukopenia	0	11 (1.7%)	22 (3.3%)	0 (0.0)	18 (4.1)	34 (7.7)
Metabolism and nutrition disorders	29 (4.4%)	43 (6.5%)	38 (5.7%)	35 (9.2)	54 (12.3)	49 (11.1)
Hypertriglyceridaemia	5 (0.8%)	19 (2.9%)	12 (1.8%)	5 (1.3)	20 (4.5)	14 (3.2)
Nervous system disorders	40 (6.1%)	42 (6.4%)	46 (7.0%)	47 (12.3)	53 (12.0)	64 (14.5)
Headache	24 (3.6%)	22 (3.3%)	22 (3.3%)	27 (7.1)	30 (6.8)	24 (5.4)
Vascular disorders	30 (4.5%)	29 (4.4%)	32 (4.8%)	32 (8.4)	35 (7.9)	36 (8.2)
Hypertension	20 (3.0%)	19 (2.9%)	21 (3.2%)	21 (5.5)	19 (4.3)	21 (4.8)
Gastrointestinal disorders	64 (9.7%)	62 (9.4%)	94 (14.2%)	92 (24.1)	101 (22.9)	138 (31.3)
Diarrhoea	16 (2.4%)	15 (2.3%)	25 (3.8%)	18 (4.7)	17 (3.9)	30 (6.8)
Nausea	12 (1.8%)	10 (1.5%)	15 (2.3%)	13 (3.4)	10 (2.3)	17 (3.9)
Musculoskeletal and connective tissue disorders	85 (12.9%)	47 (7.1%)	68 (10.3%)	104 (27.2)	59 (13.4)	92 (20.8)
Rheumatoid arthritis	27 (4.1%)	7 (1.1%)	18 (2.7%)	29 (7.6)	8 (1.8)	21 (4.8)
Back pain	9 (1.4%)	10 (1.5%)	15 (2.3%)	9 (2.4)	10 (2.3)	15 (3.4)
General disorders and administration site conditions	33 (5.0%)	74 (11.2%)	88 (13.3%)	43 (11.2)	228 (51.7)	242 (54.8)
Injection site erythema	6 (0.9%)	35 (5.3%)	35 (5.3%)	6 (1.6)	129 (29.3)	105 (23.8)
Injection site pruritus	1 (0.2%)	17 (2.6%)	16 (2.4%)	2 (0.5)	41 (9.3)	41 (9.3)
Investigations	47 (7.1%)	86 (13.0%)	104 (15.7%)	64 (16.7)	111 (25.2)	139 (31.5)
Alanine aminotransferase increased	17 (2.6%)	44 (6.7%)	45 (6.8%)	17 (4.4)	51 (11.6)	48 (10.9)
Transaminases increased	3 (0.5%)	12 (1.8%)	18 (2.7%)	3 (0.8)	12 (2.7)	20 (4.5)
Injury, poisoning and procedural complications	77 (11.6%)	72 (10.9%)	82 (12.4%)	94 (24.6)	108 (24.5)	125 (28.3)
Accidental overdose	34 (5.1%)	36 (5.5%)	40 (6.1%)	38 (9.9)	45 (10.2)	55 (12.5)

PY: Patient-years, TEAE: Treatment-emergent adverse event.
SOC: System organ class, PT: Preferred term.
MEDDRA 18.1
n (%) = number and percentage of patients with at least one TEAE.
n_E(n_E /100 PY) = number of events and number of events per 100 patient-years.
PY for a treatment group is the total treatment duration of the treatment group.
Note: Table sorted by SOC internationally agreed order and decreasing frequency of PT in the sarilumab 200mg q2w treatment group.
PGM=PRODOPS/SAR153191/OVERALL/CSS_EU/REPORT/PGM/ae_socpt_2pct_s_t_p1.sas OUT=REPORT/OUTPUT/ae_socpt2cut_s_t_p1_i.rtf (15MAR2016 - 6:38)

A comparison of common adverse events between the sarilumab and placebo groups that occurred in the time period prior to the potential initiation of rescue therapy (Week 0-12), was performed as showed in table below.

Table 87: Number (%) of patients with TEAE(s) by primary SOC and PT (>=2% in at least one treatment group) during the TEAE period (0-12 weeks) - Placebo-controlled safety population (Pool 1)

Primary System Organ Class Preferred Term	Placebo + DMARD (N=661)	Sarilumab 150 mg q2w + DMARD (N=660)	Sarilumab 200 mg q2w + DMARD (N=661)
Any class	278 (42.1%)	326 (49.4%)	350 (53.0%)
Infections and infestations	103 (15.6%)	118 (17.9%)	134 (20.3%)
Upper respiratory tract infection	16 (2.4%)	19 (2.9%)	21 (3.2%)
Nasopharyngitis	15 (2.3%)	18 (2.7%)	16 (2.4%)
Urinary tract infection	13 (2.0%)	16 (2.4%)	16 (2.4%)
Blood and lymphatic system disorders	12 (1.8%)	40 (6.1%)	77 (11.6%)
Neutropenia	1 (0.2%)	38 (5.8%)	64 (9.7%)
Metabolism and nutrition disorders	10 (1.5%)	27 (4.1%)	20 (3.0%)
Hypertriglyceridaemia	3 (0.5%)	16 (2.4%)	5 (0.8%)
Nervous system disorders	29 (4.4%)	27 (4.1%)	25 (3.8%)
Headache	15 (2.3%)	16 (2.4%)	11 (1.7%)
Gastrointestinal disorders	45 (6.8%)	36 (5.5%)	54 (8.2%)
Diarrhoea	13 (2.0%)	9 (1.4%)	15 (2.3%)
Musculoskeletal and connective tissue disorders	51 (7.7%)	23 (3.5%)	32 (4.8%)
Rheumatoid arthritis	15 (2.3%)	2 (0.3%)	9 (1.4%)
General disorders and administration site conditions	21 (3.2%)	53 (8.0%)	59 (8.9%)
Injection site erythema	4 (0.6%)	22 (3.3%)	20 (3.0%)
Investigations	25 (3.8%)	50 (7.6%)	50 (7.6%)
Alanine aminotransferase increased	9 (1.4%)	25 (3.8%)	28 (4.2%)
Injury, poisoning and procedural complications	46 (7.0%)	29 (4.4%)	42 (6.4%)
Accidental overdose	21 (3.2%)	16 (2.4%)	21 (3.2%)

TEAE: Treatment-emergent adverse event.
SOC: System organ class, PT: Preferred term.
MEDDRA 18.1
n (%) = number and percentage of patients with at least one TEAE.
Note: Table sorted by SOC internationally agreed order and decreasing frequency of PT in the sarilumab 200mg q2w treatment group.

Table 88: Number (%) of patients with TEAE(s) and number of events (per 100 patient-years) by primary SOC and PT >/= 2%) - Sarilumab+DMARD long-term safety population (Pool 2)

	Sarilumab+DMARD	
Primary System Organ Class	**Any Dose**	**Any Dose**
	(N=2887)	**(PY=5844.9)**
Preferred Term	**n (%)**	**n_E (n_E/100 PY)**
Any class	2418 (83.8%)	13922(238.2)
Infections and infestations	1428 (49.5%)	3348 (57.3)
Upper respiratory tract infection	325 (11.3%)	480 (8.2)
Urinary tract infection	252 (8.7%)	362 (6.2)
Nasopharyngitis	237 (8.2%)	305 (5.2)
Bronchitis	196 (6.8%)	257 (4.4)
Sinusitis	110 (3.8%)	130 (2.2)
Influenza	107 (3.7%)	128 (2.2)
Pharyngitis	104 (3.6%)	119 (2.0)
Cellulitis	85 (2.9%)	97 (1.7)
Pneumonia	80 (2.8%)	88 (1.5)
Gastroenteritis	76 (2.6%)	83 (1.4)
Blood and lymphatic system disorders	670 (23.2%)	1399 (23.9)
Neutropenia	507 (17.6%)	991 (17.0)
Leukopenia	111 (3.8%)	180 (3.1)
Thrombocytopenia	80 (2.8%)	98 (1.7)
Metabolism and nutrition disorders	338 (11.7%)	477 (8.2)
Hypertriglyceridaemia	97 (3.4%)	143 (2.4)
Hypercholesterolaemia	79 (2.7%)	85 (1.5)
Dyslipidaemia	65 (2.3%)	69 (1.2)
Nervous system disorders	311 (10.8%)	437 (7.5)
Headache	115 (4.0%)	139 (2.4)
Vascular disorders	279 (9.7%)	330 (5.6)
Hypertension	204 (7.1%)	215 (3.7)
Gastrointestinal disorders	553 (19.2%)	972 (16.6)
Diarrhoea	135 (4.7%)	166 (2.8)
Nausea	83 (2.9%)	106 (1.8)
Musculoskeletal and connective tissue disorders	599 (20.7%)	1024 (17.5)
Rheumatoid arthritis	175 (6.1%)	241 (4.1)
Back pain	116 (4.0%)	133 (2.3)
Arthralgia	68 (2.4%)	77 (1.3)
Osteoarthritis	66 (2.3%)	84 (1.4)
General disorders and administration site conditions	474 (16.4%)	1929 (33.0)
Injection site erythema	214 (7.4%)	957 (16.4)
Injection site pruritus	105 (3.6%)	333 (5.7)

Primary System Organ Class Preferred Term	Sarilumab+DMARD Any Dose (N=2887) n (%)	 Any Dose (PY=5844.9) n_E (n_E/100 PY)
Investigations	571 (19.8%)	919 (15.7)
Alanine aminotransferase increased	289 (10.0%)	371 (6.3)
Transaminases increased	75 (2.6%)	89 (1.5)
Aspartate aminotransferase increased	53 (1.8%)	58 (1.0)
Injury, poisoning and procedural complications	644 (22.3%)	1099 (18.8)
Accidental overdose	316 (10.9%)	453 (7.8)
Fall	98 (3.4%)	106 (1.8)

Those events with overall frequency ≥2% in any treatment group and for which there was a numerically higher incidence in both sarilumab groups compared to placebo were considered ADRs. Adverse events which met these criteria were infections (ie, upper respiratory tract infection, urinary tract infection and nasopharyngitis), the IL-6 associated laboratory changes (neutropenia, hypertriglyceridemia, ALT increased), and injection site erythema.

In order to determine if there were specific AEs to be considered as ADRs, a statistical review was performed and the clinical assessment of each AE term identified were:

- Thrombocytopenia
- Injection site reaction
- Transaminases increased
- Oral herpes (in addition to the infections by preferred term)
- Hypercholesterolemia

Monotherapy population

Table 89: Number (%) of patients with TEAE(s) and number of events (per 100 patient-years) by primary SOC and PT (>=2% in the any dose group) - Sarilumab monotherapy safety population (Pool 3)

Primary System Organ Class Preferred Term	Sarilumab Any Dose (N=467) n (%)	 Any Dose (PY=303.4) n_E (n_E/100 PY)
Any class	285 (61.0%)	934(307.8)
Infections and infestations	135 (28.9%)	196 (64.6)
Nasopharyngitis	28 (6.0%)	31 (10.2)
Bronchitis	16 (3.4%)	20 (6.6)
Upper respiratory tract infection	16 (3.4%)	20 (6.6)
Urinary tract infection	15 (3.2%)	20 (6.6)
Blood and lymphatic system disorders	82 (17.6%)	157 (51.7)
Neutropenia	73 (15.6%)	139 (45.8)

Primary System Organ Class Preferred Term	Sarilumab Any Dose (N=467) n (%)	 Any Dose (PY=303.4) n_E (n_E/100 PY)
Nervous system disorders	32 (6.9%)	42 (13.8)
Headache	15 (3.2%)	19 (6.3)
Vascular disorders	18 (3.9%)	20 (6.6)
Hypertension	11 (2.4%)	11 (3.6)
Musculoskeletal and connective tissue disorders	51 (10.9%)	74 (24.4)
Rheumatoid arthritis	11 (2.4%)	13 (4.3)
General disorders and administration site conditions	49 (10.5%)	163 (53.7)
Injection site erythema	29 (6.2%)	109 (35.9)
Investigations	36 (7.7%)	42 (13.8)
Alanine aminotransferase increased	15 (3.2%)	15 (4.9)
Injury, poisoning and procedural complications	45 (9.6%)	57 (18.8)
Accidental overdose	22 (4.7%)	26 (8.6)

Serious adverse event/deaths/other significant events

The most frequent SAEs in the sarilumab + DMARD treatment groups were those associated with IL-6 blockade, specifically infections and laboratory abnormalities (changes in ANC and ALT). The exposure-adjusted SAE rate did not increase over time in the sarilumab+DMARD long-term safety population (Pool 2). Infections remained the most frequent SAEs.

As of the data extraction dates (25 January 2016 for the sarilumab+DMARD population and 17 February 2016 for the sarilumab monotherapy population), a total of 27 deaths were reported in the patients receiving sarilumab in the Phase 2/3 RA clinical studies, including 3 deaths in the sarilumab monotherapy population. The most common causes of death were CV, infections, and malignancies. The exposure-adjusted rate of death did not increase over time in the sarilumab+DMARD long-term safety population.

Adverse events of special interest

Specific adverse events, referred to as adverse events of special interest (AESIs), are analysed. These AESIs were selected based on the biologic activity of IL-6 and the associated effects of IL-6 inhibition, as well as the safety profile of other biologics used in the treatment of RA. The AESIs consistent with IL-6 blockade and potential clinical outcomes were: infections particularly serious and opportunistic infections), neutropenia with or without infection, thrombocytopenia with or without bleeding, elevations in hepatic transaminases with or without hepatic impairment, elevations in lipids, and cardiovascular outcomes or pancreatitis. The AESIs based on the safety profiles of other biologic treatments for RA were: events of GI perforation (observed in clinical trials of tocilizumab, primarily as complications of diverticulitis in RA patients), malignancy, autoimmunity and lupus-like syndrome (observed with TNF antagonists), demyelinating disorders (observed with TNF antagonists). The AESIs based on safety findings observed with other subcutaneously administered protein

based therapeutics were: injection site reactions, hypersensitivity (particularly anaphylaxis) and immunogenicity.

Infections were the most common AEs across treatment groups, and occurred more frequently with sarilumab+DMARD compared to placebo+DMARD. During the entire treatment period in the placebo-controlled population, the rate of infections in the 200 mg q2w and 150 mg q2w sarilumab groups was 84.5 and 81.0 events/100 patient-years, resp., compared to 75.1 events/100 patient-years in the placebo group. The most commonly reported infections (5% to 7% of patients) were upper respiratory tract infections, urinary tract infections, and nasopharyngitis. The rate of serious infections in the entire placebo controlled population in the 200 mg q2w and 150 mg q2w sarilumab groups was 4.3 events (95% CI: 2.59, 6.72) and 3.0 events/100 patient-years (95% CI: 1.57, 5.04), resp. compared to 3.1 events/100 patient-years (95% CI: 1.62, 5.48) in the placebo group. The rate of infections (57.3 events/100 patient-years) and serious infections (3.4 events/100 patient-years) with sarilumab+DMARD in the long-term safety population was consistent with rates in the controlled periods of the studies. The rates of any infection and discontinuation due to infection were similar between both doses of sarilumab. There was a numeric difference in the incidence of serious infections between the 200 mg q2w and 150 mg q2w sarilumab treatment groups (1.1%) but the 95% CI for the rate difference included zero (95% CI: -0.6, 2.7). While a statistical difference between doses was not detected, based on the 95% CI, if a difference does exist it is likely to be small (<3%). Exposure-adjusted rate of serious infection (95% CI) by 6-month intervals during the entire TEAE period was provided for sarilumab+DMARD long-term safety population, the rate was constant over time.

There were 6 patients who had a fatal infection in sarilumab+DMARD long-term safety population, with 5 patients on 200 mg q2w and 1 patient on 150 mg q2w at the time of the fatal event. In addition, there were 4 reports of non-fatal sepsis or septic shock, of which 1 occurred in EFC11072 and the remaining occurred in LTS11210. All of these patients were on 200 mg q2w.

Absolute neutrophil and leukocyte counts over time ranged widely and were fluctuating. Neutrophil count was in general above the threshold 1.5 G/L for Grade 1 neutropenia (one patient at a single timepoint a marked reduced leucite and neutrophil count). The last neutrophil counts prior to onset of events were all above 1.5 G/L. In most case (7/10) the event occurred less than 12 days after the last sarilumab dose. Evaluation of exposure-adjusted rate of all infections shows that the event rate was highest in the first 6 months followed by a continued decrease stabilising on a low level until Month 60, after which there fewer data available are limiting the assessment.

The exposure-adjusted incidence rate of infections in the monotherapy population (59.0/100 patient-years) was generally similar to the concomitant DMARD populations with the exposure-adjusted incidence rate of serious infections slightly lower in the monotherapy population (1.3/100 patient-years). The most frequent infections, occurring in at least 2% of patients receiving sarilumab monotherapy, were nasopharyngitis, bronchitis, upper respiratory tract infection, and urinary tract infections. Six patients developed herpes zoster that required hospitalization and herpes zoster was the AE by PT that more frequently led to permanent treatment discontinuation (0.5%). Moreover, herpes zoster was the only OI reported also in the monotherapy population, although only in two patients.

Opportunistic infections (OIs) were reported both in pool 1 and pool 2 populations with Herpes zoster being the most represented event (0.7 events/100 PYs in long-term population). Data on OIs by subgroups of use of corticosteroids at baseline, previous biologic DMARD use and lowest absolute neutrophil count (ANC) at any time in the study have been provided.

Data provided from pool 1 do not allow drawing firm conclusion due to the very small number of patients developing OIs in this safety population.

In the long-term safety population (pool 2), 54 patients experienced OIs and the incidence of OIs was numerically higher in patients with prior baseline steroid use in the sarilumab any dose group (2.1% in patients with baseline steroid use vs.1.6% in patients with no baseline steroid use). However, data coming from an additional analysis by calculating exposure adjusted event rates of OI in pool 2, showed that the exposure-adjusted event rate of OIs in patients with baseline corticosteroid use in sarilumab+DMARD group [1.0/100 patient-year (PY)s] appears to be quite similar to the exposure-adjusted event rate of OIs in the group of patients with no baseline corticosteroid use (0.9/100 PYs). A less clear pattern was observed in patients with prior biologic DMARD use both in pool 1 and pool 2. Regarding the incidence of OIs by lowest ANC, a clear association between Grade 3-4 neutropenia and an increased risk of OIs was not possible to identify. In the placebo-controlled population, no patients with an ANC <1.0 Giga/L experienced an opportunistic infection. In the long-term safety population, of the 340 patients with an ANC <1.0, only 3 patients had an opportunistic infection and 1 of these had an opportunistic infection that was concurrent with ANC <1.0.

Mean baseline ANC in the 52-week placebo-controlled population (Pool 1) was at the upper end of the normal range. Mean decreases in ANC were observed in the sarilumab + DMARD groups (Pool 2), although the mean values remained within the normal range; ANC values remained at the upper end of the normal range in the placebo + DMARD group. The decrease in ANC reached a plateau at Week 4 and was stable thereafter. In the monotherapy population (Pool 3) a decrease in ANC was observed, which was transient for most patients.

Baseline platelet counts in the placebo-controlled population (Pool 1) were at the upper end of the normal range. A mean decrease from baseline in platelet count was observed in the sarilumab + DMARD groups (Pool 2), although mean values remained in the normal range. Platelet counts in the placebo group remained at the upper end of the normal range. The decrease in platelet count reached a plateau at Week 4 and was stable thereafter.

Mean increases in ALT and AST were observed in the sarilumab treatment groups (Pool 1 and Pool 2) compared to the placebo group. On average, an increase was observed at 2 weeks after initiation of therapy. Changes in liver enzymes reached a plateau at Week 4 and were stable thereafter.

Lipid parameters (LDL, HDL, and triglycerides) were first assessed at 4 weeks following initiation of sarilumab in the placebo-controlled population (Pool 1). In the sarilumab + DMARD groups at Week 4, the mean LDL increased by ~14 mg/dL; mean triglycerides increased by ~23 mg/dL; and mean HDL increased by ~3 mg/dL. After Week 4, no additional increase was observed. In the long-term safety population, the differences from baseline in lipid parameters were consistent with what was observed in the placebo-controlled clinical trials. There were no reports of pancreatitis secondary to increase in triglycerides. The observed rate of confirmed major adverse cardiovascular events (MACE) was low.

In the placebo-controlled population (Pool 1), at baseline, the mean creatinine (Cr) was 65.18-66.14 umol/L (0.74-0.75 mg/dL) [normal range: 35.36 -97.24 umol/L (0.40-1.10 mg/dL)]. In the patients on sarilumab, an initial increase in serum Cr was observed which plateaued after Week 24 with a mean Cr of ~70 umol/L (~0.79 mg/dL) [normal range: 35.36-97.24 umol/L (0.40-1.10 mg/dL)].

A total of 8 patients on sarilumab+DMARD had either complicated diverticulitis or GI perforation not secondary to surgical complication. All but 1 patient were on concomitant NSAIDs (including low dose aspirin) or steroids. No events occurred in a patient on placebo.

In the placebo-controlled population, the exposure adjusted rate of malignancies was similar in both sarilumab + DMARD q2w groups (0.9 and 1.1 events/100 patient years, respectively) and placebo + DMARD groups (1.0

event/100 patient years). The rates were similar in the long-term safety population (0.8 events/100 patient years [95% CI: 0.55, 1.01]). Based on standardized incidence ratios (SIRs) using the SEER database (1.16 events/100 patient-years) (Howlader N et al: SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016), an increased rate of malignancy was not observed in patients receiving sarilumab compared to the general population or patients with RA.

The incidence of ANA positivity was similar between sarilumab groups and placebo groups and only few patients developed positivity to anti-ds DNA antibodies. 4 adverse events of cutaneous lupus were reported in the long-term safety population, but there were no events suggestive of Lupus-like disorders. There was no evidence that sarilumab treatment was associated with lupus-like syndrome.

Two cases suggestive of demyelinating disorders were identified in patients receiving sarilumab with concomitant DMARDs: one case of transverse myelitis occurred 7 months post-study in which the assessment of a causal relationship with the study drug was confounded by prior and concomitant use of anti-TNFs, and one case reported as Multifocal Motor Neuropathy (MMN) for which a definitive diagnosis of MMN and/or a causal relation with sarilumab, have not been confirmed by the Applicant.

A higher incidence of injection site reactions were observed in sarilumab treatment groups compared to placebo, the reactions were mild in severity for the majority (90.6%) of patients.

No cases of severe systemic hypersensitivity reaction or anaphylaxis were observed in the placebo-controlled population or in the long-term safety population before the cut-off date for the CTD.

Comparison of sarilumab and tocilizumab

The sarilumab clinical development program included 2 studies with sarilumab SC and the marketed IL-6 inhibitor tocilizumab IV, both in patients receiving concomitant MTX. One study (6R88-RA-1309) was a single-dose study with the primary objective of assessing PD parameters (including ANC) and the other study (SFY13370) was a 24-week safety calibrator study.

Among the PD parameters in Study 6R88-RA-1309, ANC was also considered a safety parameter. The mean change and mean percent change from baseline in ANC values were similar across treatment groups for the first week of the study. The return of ANC values to baseline values was the main difference observed between the sarilumab and tocilizumab treatment groups. The timing of the trend for return to baseline was consistent with the dosing interval for both sarilumab (q2w) and tocilizumab (q4w).

With regard to other safety parameters no clinically meaningful differences were observed between sarilumab and tocilizumab in either of these studies.

Comparison of sarilumab and adalimumab

The EFC14092 study compared sarilumab 200 mg q2w to adalimumab 40 mg q2w administered as monotherapy. Safety data for patients who received sarilumab in the study were included in the monotherapy population described previously.

Infections were the most frequent TEAE by SOC and occurred in at a similar frequency in the adalimumab and sarilumab groups (27.7% and 28.8%, respectively). The incidence of neutropenia was higher in the sarilumab group than in the adalimumab group (13.6% compared to 0.5%, respectively), although the rate of infections, including serious and opportunistic infections was similar in the 2 groups. Injection site erythema was also observed more frequently in the sarilumab group (7.6% compared to 3.3% in the adalimumab group). TEAEs of headache and rheumatoid arthritis were among the AEs reported more frequently in the adalimumab group

(6.5% and 3.8%, respectively, in the adalimumab group compared to 3.9% and 0.5%, respectively, in the sarilumab group).

Mean decreases in ANC and platelet count and mean increases in ALT, and LDL were observed in the sarilumab group compared to the adalimumab group, with all mean values remaining in the normal range. No increased incidence of infection overall, serious infection or opportunistic infection was observed.

Immunological events

Pool 1

In placebo-controlled population ADA were positive in 14% of patients in sarilumab 200 mg q2w group, 19.3% in sarilumab 150 mg q2w group and 3.5% in placebo group. 1.8%, 3.3% and 0.2% of patients respectively, were positive for neutralizing antibodies. The majority of positive responses in the ADA assay were transient and the median titer was ≤60; the lowest titer is 30.

Pool 2

The percentage of patients positive in the ADA assay in the long-term safety population was 17.1% with a median titer of 30.

Table 90: Number (%) of patients with lack of efficacy or loss of efficacy by persistent ADA status during the entire TEAE period Sarilumab+DMARD- immunogenicity population (Pool 2)

		ADA positive[a]			
n(%)	ADA negative (N=2131)	Persistent[d] (N=120)	Transient[e] (N=316)	Treatment-boosted (N=3)	All (N=439)
Lack of efficacy[b]	71(3.3%)	3(2.5%)	15(4.7%)	0	18(4.1%)
Loss of efficacy[c]	31(1.5%)	1(0.8%)	8(2.5%)	0	9(2.1%)

Only patients with at least one non-missing post-baseline ADA status are included.

[a] Patient with a positive ADA status is defined as no positive assay response at baseline but with a positive assay response during the entire TEAE period (ie, treatment-emergent positive ADA) or a positive ADA assay response at baseline and also have at least a 4-fold increase in titer during the entire TEAE period (treatment-boosted positive ADA).

[b] Lack of efficacy is defined as treatment discontinuation due to lack of efficacy.

[c] Loss of efficacy is defined as treatment discontinuation due to lack of efficacy after achieving an ACR50 or EULAR Good response

[d] Persistent positive response: treatment-emergent positive ADA detected at 2 or more consecutive sampling time points during the TEAE period, where the first and last ADA positive samples are separated by a period of at least 16 weeks. Also persistent in case last sample analyzed is positive.

[e] Transient positive response is defined as any positive ADA assay response that is not considered persistent.

Table 91: Number (%) of patients with lack of efficacy or loss of efficacy by neutralizing ADA status during the entire TEAE period Sarilumab+DMARD - immunogenicity population (Pool 2)

		ADA positive		
n(%)	ADA negative (N=2131)	Neutralizing (N=54)	Non-neutralizing (N=385)	All (N=439)
Lack of efficacy[b]	71(3.3%)	0	18(4.7%)	18(4.1%)
Loss of efficacy[c]	31(1.5%)	0	9(2.3%)	9(2.1%)

Only patients with at least one non-missing post-baseline ADA status are included.
[a] Patient with a positive ADA status is defined as no positive assay response at baseline but with a positive assay response during the entire TEAE period or a positive ADA assay response at baseline and also have at least a 4-fold increase in titer during the entire TEAE period. Patient is defined as with a positive neutralizing ADA status if he/she had at least one post-baseline ADA measurement classified as neutralizing positive during the entire TEAE period.
[b] Lack of efficacy is defined as treatment discontinuation due to lack of efficacy.
[c] Loss of efficacy is defined as treatment discontinuation due to lack of efficacy after achieving an ACR50 or EULAR Good response

Table 92: Number (%) of patients with hypersensitivity adverse events by ADA status during the entire TEAE period - Sarilumab+DMARD immunogenicity population (Pool 2)

n(%)	ADA negative (N=2131)	ADA positive[a] (N=439)
Hypersensitivity reaction[b]	198 (9.3%)	26 (5.9%)
Anaphylaxis[c]	0	0

Only patients with at least one non-missing post-baseline ADA status are included (ie, N).
[a] Patient with a positive ADA status is defined as no positive assay response at baseline but with a positive assay response during the entire TEAE period or a positive ADA assay response at baseline and also have at least a 4-fold increase in titer during the entire TEAE period. ADA titer category is defined based on the patient's maximum titer.
[b] SMQ Hypersensitivity (narrow). [c] SMQ Anaphylactic reaction (narrow).

Laboratory findings

In the sarilumab+DMARD long-term safety population (Pool 2), a total of 14 patients reported an adverse event in the HLT Renal failure and Impairment with reported PTs of acute kidney injury (4 patients), renal failure (4 patients), renal impairment (3 patients), chronic kidney disease (2 patients), and pre-renal failure (1 patient). In the monotherapy pool (Pool 3) 2 patients reported an adverse event in the HLT Renal failure and impairment. In 14 patients with reported PT of acute kidney injury, pre-renal failure, renal impairment, or renal failure, there were concurrent illnesses (e.g., infection, dehydration due to hyperglycemia) which could have attribute to the renal failure. Two additional cases were reported during the evaluation procedure. These patients did not have a concurrent illness. In one of these patients concomitant medications included those with potential renal side effects (MTX, NSAID, diuretic and angiotensin-converting enzyme inhibitor). In the other patient without a concurrent illness, laboratory values were in the normal range (Cr, CrCl, and BUN) with urinalysis showing trace protein. Concurrent disease and concomitant medications provide alternative explanation for the events.

A low incidence of lymphopenia was reported. No adverse events related to other specific white cell types were observed.See also adverse events of special interest.

Data about Immunoglobulins titers were not collected during the clinical development program. In order to identify the occurrence of those infections more commonly associated to humoral immunodeficiency in sarilumab treated subjects, a table reporting events of bacterial upper respiratory tract and pulmonary infections in placebo-controlled safety population (pool 1) has been provided (see table below).

Table 93

	Placebo + DMARD (N=661) (PY= 382.3)	Sarilumab 150 mg q2w + DMARD (N=660) (PY = 440.7)	Sarilumab 200 mg q2w + DMARD (N=661) (PY = 441.4)
	Patients with event / number of events	**Patients with event / number of events**	**Patients with event / number of events**
Upper Respiratory Tract Infection	32/39	42/54	47/55
Bronchitis	19/21	17/23	25/26
Bronchitis bacterial	1/1	1/1	0/0
Pharyngitis	14/15	15/15	16/18
Pharyngitis streptococcal	0/0	1/1	0/0
Sinusitis	11/11	14/17	16/16
Chronic sinusitis	0/0	0/0	1/1
Acute sinusitis	2/2	0/0	1/2
Sinusitis bacterial	1/1	1/1	0/0
Pneumonia	3/3	7/7	8/8
Pneumonia bacterial	1/1	0/0	0/0
Pneumonia streptococcal	0/0	1/1	0/0

Safety in special populations

Studies have not been conducted in pregnant and lactating women on sarilumab. The clinical development program excluded enrolment of pregnant or breast feeding women and sexually active women of childbearing potential were required to practice adequate contraception during the study. Per protocol, IMP was to be discontinued in female participants who became pregnant.

In the sarilumab+DMARD long-term safety population, there were 13 patients who became pregnant and 2 male patients whose partner became pregnant. Of these 13 patients who became pregnant seven women had miscarriage (i.e., spontaneous abortion, missed abortion, imminent abortion, blighted ovum); 1 occurred early in the second trimester and the rest occurred during the first trimester.

Both pregnant partners of male sarilumab patients delivered a healthy child.

Table 94: Number (%) of patients with TEAE(s) by AE categories and by age group - Any sarilumab dose group in the sarilumab+DMARD long-term safety population (Pool 2)

	Age <65 (N=2464) n(%)	Age 65-74 (N=378) n(%)	Age 75-84 (N=42) n(%)	Age 85+ (N=3) n(%)
Total TEAEs	2051 (83.2)	328 (86.8)	36 (85.7)	3 (100)
Serious TEAEs – Total	404 (16.4)	114 (30.2)	11 (26.2)	0
- Fatal	12 (0.5)	10 (2.6)	0	0
- Hospitalization/prolong existing hospitalization	335 (13.6)	98 (25.9)	8 (19.0)	0
- Life-threatening	13 (0.5)	11 (2.9)	1 (2.4)	0
- Disability/incapacity	16 (0.6)	0	0	0
- Other (medically significant)	101 (4.1)	33 (8.7)	5 (11.9)	0
TEAEs leading to drop-out	476 (19.3)	108 (28.6)	10 (23.8)	1 (33.3)
Psychiatric disorders (SOC)	137 (5.6)	14 (3.7)	1 (2.4)	0
Nervous system disorders (SOC)	254 (10.3)	50 (13.2)	7 (16.7)	0
Accidents and injuries (SMQ)	258 (10.5)	57 (15.1)	3 (7.1)	1 (33.3)
Cardiac disorders (SOC)	66 (2.7)	31 (8.2)	1 (2.4)	0
Vascular disorders (SOC)	230 (9.3)	40 (10.6)	10 (23.8)	0
Central nervous system haemorrhages and cerebrovascular conditions (SMQ)	14 (0.6)	7 (1.9)	2 (4.8)	0
Infections and infestations (SOC)	1221 (49.6)	185 (48.9)	21 (50.0)	1 (33.3)
Anticholinergic syndrome (SMQ)	0	0	0	0
Quality of life decreased (PT)	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures (PTs)	159 (6.5)	37 (9.8)	5 (11.9)	1 (33.3)
Serious infections (SOC)	144 (5.8)	38 (10.1)	2 (4.8)	0

Note: the same adverse event might be counted several times in different AE categories.
MEDDRA 18.1
Postural hypotension was searched using prefer term (PT) orthostatic hypotension; fracture was searched using PTs contains 'fracture'; fall, blackout, syncope, dizziness and ataxia were searched using PTs.
PGM=PRODOPS/SAR153191/OVERALL/CSS_EU/REPORT/PGM/ae_newcat_s_t.sas OUT=REPORT/OUTPUT/ae_newcat_s_t_p2_i.rtf (17APR2017 - 15:14)

Safety related to drug-drug interactions and other interactions

A specific clinical pharmacology study to assess the effect of sarilumab on simvastatin, a sensitive CYP3A4 substrate, was conducted in patients with RA. Exposure of simvastatin decreased by 45% when administered to patients with RA as a single 40 mg oral dose, 1 week after a single 200 mg SC dose of sarilumab. These reductions in the exposure of simvastatin suggest that sarilumab may reverse IL-6 mediated suppression of CYP3A4 activity in patients with active RA.

Discontinuation due to adverse events

In the placebo-controlled population (Pool 1), during the entire treatment period, a higher incidence of TEAEs leading to permanent discontinuation was reported in the sarilumab treatment groups compared to placebo. In the placebo-controlled population (Pool 1), during the entire treatment period, a higher incidence of TEAEs leading to permanent discontinuation was reported in the sarilumab treatment groups compared to placebo. The SOCs in which TEAEs were most frequently reported as leading to treatment discontinuation for sarilumab (both doses) were Infections and infestations; Blood and lymphatic system disorders; and Investigations. The most frequently reported PTs were neutropenia, ALT increased and herpes zoster.

The exposure-adjusted discontinuation rate did not increase in the sarilumab+DMARD long-term safety population (Pool 2). Neutropenia, increased ALT, and herpes zoster remained the most frequent TEAEs leading to discontinuation. Prior to the implementation of the above-mentioned protocol amendment in LTS11210, herpes zoster was specified as an opportunistic infection that should lead to treatment discontinuation.

In the monotherapy pool (Pool 3) highest incidence of discontinuation due to adverse events occurred during the first 12 weeks of sarilumab monotherapy. The SOCs in which TEAEs were most frequently reported as leading to treatment discontinuation, in decreasing frequency, were Blood and lymphatic system disorders; Infections and infestations; and General disorders and administrative conditions. The most frequently reported PTs (for the monotherapy population defined as occurring in 2 or more patients) were neutropenia, herpes zoster, and ALT increased, although ALT increased leading to treatment discontinuation occurred less frequently in the monotherapy population. Rheumatoid arthritis and injection site erythema leading to treatment discontinuation also occurred in 2 or more patients in the monotherapy population.

2.6.1. Discussion on clinical safety

A total of 3354 patients have received at least 1 dose of sarilumab±DMARD in the global Phase 2 and 3 RA clinical development program are included in the integrated safety analysis.

In all Phase 2/3 studies (except monotherapy studies) patients received background therapy for RA. In several studies the patients received MTX while in other studies permitted background therapy also includes one or a combination of e.g. MTX, leflunomide, sulfasalazine and hydrochloroquine). The Applicant submitted an analysis for any TEAE, any infection, serious TEAE, and discontinuation due to any adverse event (AE) in the placebo controlled safety population (Pool 1) and for the population that received MTX concomitantly either alone or in combination with other non-biologic DMARDs and those that were non-MTX-treated in the long-term safety population (Pool 2). The majority of the patients received an MTX based background therapy. No differences between the MTX and non-MTX based background regimen were observed. The new analyses provided by the Applicant do not fully address the concern; it would have been of interest to analyse at least MTX vs. MTX+DMARDs background therapy. However given the benign safety profile of the treatment further analysis of the data deems not of added value.

Demographic and baseline patient characteristics in the placebo-controlled population were well-balanced among the three treatment groups. Baseline RA characteristics were generally similar between all populations studied and between treatment groups.

An overview of the incidence and exposure –adjusted incidence rate for was provided of TEAEs, serious TEAES, TEAEs leading to death and TEAEs leading to permanent discontinuation were provided for the different population pools.

Based on exposure-adjusted incidence rates, no clinically meaningful differences between the sarilumab+DMARD long-term safety population (Pool 2) and the placebo-controlled population (Pool 1) was observed. In the Pool 2 population the exposure adjusted incidence rates of TEAEs, SAEs, and discontinuations due to TEAE were generally similar or slightly lower than the rates observed in the placebo-controlled population. The exposure-adjusted incidence rate for death was similar to the rate observed in the placebo-controlled population.

The majority of patients in the sarilumab monotherapy population any dose group reported at least 1 TEAE during the treatment-emergent period. The exposure-adjusted incidence rate of TEAEs in the sarilumab monotherapy group was consistent with what was observed in the sarilumab+DMARD placebo-controlled and long-term safety populations. The exposure-adjusted incidence rates of SAEs and discontinuations due to TEAEs were slightly numerically lower in the monotherapy population than in the sarilumab+DMARD populations and were generally consistent with the rates observed in the placebo+DMARD group. This is not unexpected since the safety profile of sarilumab might be biased to some extent by the concomitant medication i.e. DMARDs. The

exposure-adjusted incidence rate of TEAEs leading to death in the sarilumab monotherapy population was consistent with what was observed in the concomitant DMARD populations.

However, the events were not reported broken down to the dose e.g. the data are reported for the entire Pool 2 but not according the two different dose groups Analyses for the sarilumab + DMARD long-term safety population (Pool 2) were performed on the sarilumab 150 mg and 200 mg q2w initial dose groups and the "any dose group". To supplement these data the Applicant reviewed the data for the non-selected dose groups. There were 364 patients exposed to at least 1 dose of a sarilumab non-selected dose regimen (i.e., 100 mg once in 2 weeks [q2w], 100 mg every week [qw], or 150 mg qw). The contribution of the 100 mg q2w and 100 mg qw doses is limited in both the number of patients and the follow-up time. The 150 mg qw dose group contributed the most data to the data among the non-selected dose. Although the data on the 150 mg qw dose group is limited relative to the data available on the selected doses, the type of events observed were consistent with effects of IL-6 inhibition and subcutaneous route of administration and with the overall safety database.

An analysis of the exposure adjusted-rate of TEAEs by 6-month intervals during the entire TEAE period and an exposure-adjusted rate of TEAEs leading to permanent discontinuation by 6-month intervals during the entire TEAE period was submitted. The analysis of the exposure adjusted TEAE rate showed that the event rate was highest in the first 6 month with a continuous decline thereafter. Similar the exposure-adjusted rate of TEAEs leading to permanent discontinuation showed that the event rate was highest in the first 6 months followed by a continued decrease stabilising on a low level.

In the placebo controlled population (Pool 1) the most frequent TEAEs were infection and infestation, a higher incidence was observed in sarilumab + DMARD group compared to the placebo +DMARD group. In general those TEAEs associated with IL-6 blockade, specifically infection, and laboratory abnormalities occurred at a higher incidence in either sarilumab + DMARD group compared to the placebo + DMARD group. A numerically higher incidence of TEAEs was observed in the 200 mg q2w group compared to the 150 mg q2w group, primarily due to a higher incidence of neutropenia and leukopenia.

In the monotherapy population (Pool 3) the most frequently reported adverse events were infections and infestations, followed by neutropenia, injection site erythema, and nasopharyngitis. Consistent with administration in the absence of MTX or other DMARDs, which have the potential for hepatotoxicity, the monotherapy population had a lower occurrence of ALT increased compared to the sarilumab+DMARD population; the exposure-adjusted event rate for ALT increased was comparable to the placebo+DMARD group in the placebo-controlled population.

Safety data in bDMARDs-Inadequate Responders (IR) subjects from sarilumab monotherapy population (pool 3) have been provided. There were very few subjects in pool 3 (7 and 5 patients in the 150 mg and 200 mg q2w initial dose groups, respectively) who discontinued prior biologic DMARD. The majority of patients in any dose treatment experienced TEAEs [9 subjects (75%)]. Infections were reported in 33.3% of patients and only 1 patient had a serious TEAE. Among AEs of special interest (AESIs), infections and injection site reactions were the most represented (33.3% and 25%, respectively).

The applicant selected placebo-controlled population as most appropriate population for identification of common AEs. However this population provides only data up to 52 weeks of treatment. An analysis of Pool 2 should allow analysis of the long-term profile up to 5 years. The applicant was requested to provide the AE profile for Pool 2, including an evaluation over time. The Applicant supplement the data submitted with the MAA i.e. AESIs, and time course of discontinuations for AEs for Pool 2 by an analysis of the exposure adjusted-rate of TEAEs by 6-month intervals during the entire TEAE period and an exposure-adjusted rate of TEAEs leading to permanent discontinuation by 6-month intervals during the entire TEAE period.

The analysis of the exposure adjusted TEAE rate showed that the event rate was highest in the first 6 month with a continuous decline thereafter.

Similar the exposure-adjusted rate of TEAEs leading to permanent discontinuation showed that the event rate was highest in the first 6 months followed by a continued decrease stabilising on a low level.

In the sarilumab+DMARD long-term safety population (Pool 2), a total of 14 patients reported an adverse event in the HLT Renal failure and Impairment with reported PTs of acute kidney injury (4 patients), renal failure (4 patients), renal impairment (3 patients), chronic kidney disease (2 patients), and pre-renal failure (1 patient). In the monotherapy pool (Pool 3) 2 patients reported an adverse event in the HLT Renal failure and impairment. In 14 patients with reported PT of acute kidney injury, pre-renal failure, renal impairment, or renal failure, there were concurrent illnesses (e.g., infection, dehydration due to hyperglycemia) which could have attribute to the renal failure.

Adverse events of special interest (AESIs) based on the biologic activity of IL-6 were reported separately.

Infections were the most common AESIs across treatment groups, and occurred more frequently with sarilumab+DMARD compared to placebo+DMARD.

Absolute neutrophil and leukocyte counts over time ranged widely and were fluctuating. Neutrophil count was in general above the threshold 1.5 G/L for Grade 1 neutropenia (one patient at a single timepoint a marked reduced leucite and neutrophil count). The last neutrophil counts prior to onset of events were all above 1.5 G/L. However the neutrophil count was in all cases either prior to the sarilumab dose or at the timepoint of the dosage. In most case (7/10) the event occurred less than 12 days after the last sarilumab dose. Both events i.e. neutropenia and serious infections are known risk of treatment with IL-6 inhibitors and adequately described in the SPC. Evaluation of exposure-adjusted rate of all infections shows that the event rate was highest in the first 6 months followed by a continued decrease stabilising on a low level until Month 60, after which there fewer data available are limiting the assessment. Thus the data do not suggest an increased incidence of infection over time.

The exposure-adjusted incidence rate of infections in the monotherapy population was generally similar to the concomitant DMARD populations with the exposure-adjusted incidence rate of serious infections slightly lower in the monotherapy population. The observed rates are consistent with the general RA population (Tran TN et al: Incidence density of serious infection, opportunistic infection, and tuberculosis associated with biologic treatment in patients with rheumatoid arthritis – a systematic evaluation of the literature. Open Access Rheumatology: Research and Reviews. 2013;5:21-32).

Exposure-adjusted rate of serious infection by 6-month intervals during the entire TEAE period was provided for sarilumab+DMARD long-term safety population, however not for all infections. The applicant provided such analysis all infections. Evaluation of exposure-adjusted rate of all infections shows that the event rate was highest in the first 6 months followed by a continued decrease stabilising on a low level until Month 60, after which there fewer data available are limiting the assessment. Thus the data do not suggest an increased incidence of infection over time.

Consistent with the presence of a chronic inflammatory condition, mean baseline ANC and platelet counts were at the upper end of the normal range at baseline. A decrease of the values was observed in all sarilumab treatment groups. However the mean values remained within the normal range. The decrease in ANC reached a plateau at Week 4 and was stable thereafter. No meaningful differences were observed between the two sarilumab dose groups. Due to previous experience with tocilizumab, patients with platelet counts <150 Giga/L were not included in the sarilumab clinical trials, therefore similarly to what required for ANC decrease, a

warning recommending to not initiate sarilumab in patients with platelet counts <150 X103/µl has been added in section 4.2 of the SmPC.

Data about Immunoglobulins titers were not collected during the clinical development program. Clinical data provided seem to not identify a clear difference in the incidence of bacterial infections between sarilumab and placebo arms. Moreover, taking into account the role of IL-6 in inducing B cells differentiation and data coming from non-clinical animal studies reporting reversible changes in IgG responses and concentrations, "Immunoglobulins levels following sarilumab treatment" has been added to the RMP as missing information.

Mean increases in ALT and AST were observed in the sarilumab treatment groups compared to the placebo group, with no clinically meaningful differences between doses. Changes in liver enzymes reached a plateau at Week 4 and were stable thereafter. No cases of liver enzyme elevations met Hy's Law criteria. Lower incidence of ALT in the sarilumab monotherapy population than in the sarilumab + DMARD population was observed. This is not unexpected and can be attributed to the absence of DMARDs. As expected, a better safety profile in terms of transaminases elevation was observed when sarilumab was administered as monotherapy, due to of the absence of the combined effects of MTX or other c-DMARDs on liver functionality.

Increase in lipid parameters (LDL, HDL, and triglycerides) were observed in the sarilumab + DMARD groups at Week 4, while the values for placebo group patients remain largely constant. After Week 4, no additional increase was observed. In the long-term safety population, the differences from baseline in lipid parameters were consistent with what was observed in the placebo-controlled clinical trials. There were no reports of pancreatitis secondary to increase in triglycerides. The observed rate of confirmed major adverse cardiovascular events (MACE) was low. Consistent with the data of the sarilumab + DMARDs population, a increase from baseline in LDL, HDL, and triglycerides was observed at 4 weeks after initiation of sarilumab in the monotherapy population (Pool 3). However mean values remained in the normal range. None of these patients experienced pancreatitis.

The exposure adjusted rate of malignancies was similar in Pool 1 for both sarilumab + DMARD q2w groups and placebo + DMARD groups. The rates in the long-term safety population were consistent with this finding. An increased rate of malignancy was not observed in patients receiving sarilumab compared to the general population or patients with RA (Howlader N et al: SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016.).

From available data, there was no evidence that sarilumab treatment was associated with lupus-like syndrome or demyelinating disorder.

The safety profile of sarilumab in monotherapy was generally consistent with the safety profile of sarilumab with concomitant DMARDs. The exposure-adjusted incidence rates of SAEs and of TEAEs leading to treatment discontinuations were slightly lower in the monotherapy population than in the sarilumab concomitant DMARD populations and similar to the placebo+DMARD group. Also consistent with what was observed in the concomitant DMARD populations, few fatal events were reported.

Overall, regarding the sarilumab safety profile of monotherapy population in bDMARDs-Inadequate Responders (IR) subjects, no firm conclusion can be drawn due to the very limited number of subjects (12 subjects in total). However, safety profile is not expected to be worse when sarilumab is used as monotherapy compared to MTX combination therapy in this subpopulation.

No clinically meaningful differences were observed with regard to safety between sarilumab and tocilizumab in either of these studies performed.

Comparable safety profiles of sarilumab and adalimumab were observed with differences primarily due to the anticipated laboratory changes associated with IL-6 inhibition, i.e. a higher incidence of patients with decreased ANC and neutropenia which was not associated with infection.

The Applicant was required to provide data on immunogenicity, including the impact on efficacy and safety, according to 1% error rate confirmatory cut point. Overall, data provided did not show important differences in lack and loss of efficacy between all patients who were ADA positive (3.8% and 1.7%, respectively) and those who were ADA negative (3.4% and 1.5%). With regard to safety, the incidence rate of hypersensitivity reactions analyzed with the 1% error rate were similar in ADA positive (6.5%) or negative (9.4%) patients, as previously observed with the 0.1% error rate.

In the sarilumab+DMARD long-term safety population, there were 13 patients who became pregnant. Of these women 7 patients had a miscarriage. The Applicant provided data from the Medical Birth Registry of Norway. Data on women with RA were collected with regard to the risk of pregnancy loss, including early miscarriages (before gestational Week 12), late miscarriages (Weeks 12–22), and stillbirths (Wallenius et al 2015). Further data from Roche database on women who were exposed to tocilizumab shortly before or during pregnancy, pregnancy outcomes (Hoeltzenbein 2016) were discussed. The data suggest a relative high incidence of miscarriage in the RA population compared to the general population.

The Applicant will participate in the North America pregnancy registry (OTIS) to evaluate the risk of birth defects and other pregnancy outcomes in women exposed to sarilumab during pregnancy in real-world clinical setting (see below section RMP) to address this missing information.

No studies in paediatric patients, elderly patients, renal impaired patients or hepatic impaired patients were conducted. Only 14% of patients were older than 65 years. In total, age ranged from 18 – 88 years. This has been adequately addressed in the SmPC.

Patients with known HIV infection as well as patients infected with Hepatitis B and / or hepatitis C were excluded from the study. This has been adequately reflected reflected in the SmPC and the RMP.

The effect of sarilumab on CYP enzymes may be clinically relevant for a CYP substrate with narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of sarilumab in patients being treated with these types of medicinal products, therapeutic monitoring of effects (e.g., for warfarin) or drug concentration (e.g., for theophylline) should be performed, and the individual dose of the medicinal product should be adjusted as needed. Caution should be exercised when sarilumab is co-administered with CYP3A4 substrates (e.g. oral contraceptives or statins) as there may be a reduction in exposure which may reduce the effectiveness of the CYP3A4 substrate.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety observation is based on a total of 3354 patients exposed to at least 1 dose of sarilumab for a total of 5981.0 patient-years of exposure. Sarilumab is associated with infections (including serious infections), decrease in ANC and platelet count, and increase in ALT and lipids, all of which are events consistent with the known effect of IL-6 inhibition, and with injection site reactions, consistent with a SC route of administration. No new safety concerns were identified during the development program in the clinical trial population.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Serious infections
	Hypersensitivity reactions
	Neutropenia
	Gastrointestinal perforations
Important potential risks	Thrombocytopenia and potential risk of bleeding
	Clinically evident hepatic injury
	Lipid abnormalities and increased risk of major cardiovascular events
	Malignancy
Missing information	Use in pregnant and lactating women
	Use in pediatric patients
	Use in elderly
	Use in Hepatitis B/Hepatitis C infected patients
	Use in HIV infected patients
	Immunoglobulins levels following sarilumab treatment
	Use of vaccination in patients receiving sarilumab

HIV: Human Immunodeficiency Virus; IgE: Immunoglobulin E.

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Safety surveillance program using existing EU RA registries Cat. 3	To evaluate the long-term safety of patients exposed to sarilumab in real-world clinical practice	Serious infections Lipid abnormalities and increased risk of major cardiovascular events Gastrointestinal perforations Malignancy Use in pregnant women	Planned	Protocol submission planned date: Within 6 months after approval 1st interim report planned date: 1 year after first patient enrolled Final report planned date: 1 year after final patient's last visit

EU: European Union; RA: Rheumatoid Arthritis.

Risk minimisation measures

Safety concern	Routine risk minimization activities	Additional risk minimization activities
Important identified risks		
Serious infections	Appropriate SmPC statements/information; PL	Patient Alert Card
Hypersensitivity reactions	Appropriate SmPC statements/information, PL	None
Neutropenia	Appropriate SmPC statements/information; PL	Patient Alert Card
Gastrointestinal perforations	Appropriate SmPC statements/information; PL	Patient Alert Card
Important potential risks		
Thrombocytopenia and potential risk of bleeding	Appropriate SmPC statements/information; PL	None
Clinically evident hepatic injury	Appropriate SmPC statements/information; PL	None
Lipid abnormalities and increased risk of major cardiovascular events	Appropriate SmPC statements/information; PL	None
Malignancy	Appropriate SmPC statements/information	None
Missing information		
Use in pregnant and lactating women	Appropriate SmPC statements/information	None
Use in pediatric patients	Appropriate SmPC statements/information	None
Use in elderly	Appropriate SmPC statements/information	None

Safety concern	Routine risk minimization activities	Additional risk minimization activities
Use in Hepatitis B/Hepatitis C infected patients	Appropriate SmPC statements/information	None
Use in HIV infected patients	Appropriate SmPC statements/information	None
Immunoglobulins levels following sarilumab treatment	Appropriate SmPC statements/information	None
Use of vaccination in patients receiving sarilumab	Appropriate SmPC statements/information	None

SmPC: Summary of Product Characteristics; HCP: Healthcare Professional; HIV: Human Immunodeficiency Virus; PL: Patient Leaflet.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

2.9. New Active Substance

The applicant declared that sarilumab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers sarilumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet does not entirely meet the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

The applicant's response package has not addressed all aspects adequately as requested, in particular related to the mock-ups.

However, the readability test is be considered acceptable with the applicant's commitment to perform a new reduced testing with the adopted version of the package leaflet within the next upcoming variation impacting the content of the PL/IFU. The abridged testing should be carried out with ten participants and should cover all QRD aspects as previously mentioned.

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kevzara (sarilumab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The initially claimed indication was: “Kevzara is indicated in combination with disease-modifying anti-rheumatic drugs (DMARDs) or as monotherapy for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who responded inadequately or were intolerant to DMARDs or tumour necrosis factor (TNF) antagonists. Kevzara has been shown to inhibit progression of joint damage and to improve physical function”.

The final approved indication is:

“Kevzara in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs. Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate (see section 5.1)”.

Treatment of the disease is aimed at: the amelioration of signs and symptoms and disease activity (including remission), improvement in physical function and prevention of the progression of structural damage.

3.1.2. Available therapies and unmet medical need

Available therapies consist of conventional disease-modifying antirheumatic drugs (c-DMARDs). Among these, methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine, are the first line of therapy for RA, methotrexate (MTX) being the preferred option in either DMARD-naïve early RA (<6 months duration) or established RA.

Biologic DMARDs (b-DMARDs) including tumour necrosis factor inhibitors (etanercept, infliximab, and adalimumab) and other classes of biologics (eg, antagonists or inhibitors of IL-1, IL-6, CD20, or T-cell activation), are used either in combination with c-DMARDs or as monotherapy.

A substantial number of patients fail to achieve RA treatment goals with current therapies, and there remains a continuing unmet medical need for an alternative and effective therapy.

Indeed, ~66% of DMARD-naïve patients with RA have been reported to discontinue MTX after 2 years of treatment due to insufficient response or toxicity (van der Kooij SM et al, Ann Rheum Dis. 2007 Oct; 66(10):1356-62). A substantial proportion of patients (between 30% and 40%) fail to respond to or become intolerant of anti-TNF-α therapies (Smolen & Aletaha, Nat Rev Rheumatol. 2015 May;11(5):276-89).

There is some evidence that suggests these patients may ultimately derive clinical benefit when they switch to a mechanistically different drug.

3.1.3. Main clinical studies

Sarilumab in add on to MTX/cDMARDs in c-DMARD-IR and b-DMARD-IR subjetcs

-EFC11072 was an operationally seamless Phase 2/3 study aimed to demonstrate that sarilumab on top of MTX is effective on reduction of signs and symptoms RA at 12 weeks and to define the best dose/dosage regimen for further development **(part A)** and to demonstrate sarilumab efficacy in MTX-IR patients (superiority over PLB+MTX of sarilumab 200mgq2w or 150mgq2w).

Part B is considered a pivotal study for demonstrating efficacy in MTX-IR patients. It is a PLB controlled study of 52 weeks, consisting of two cohorts. Cohort 2 included patients after doses were selected from part A and thus having the following arms: sarilumab 150mg q2w+MTX, sarilumab 200mg q2w+MTX and PLB+MTX, which is considered the primary population.

-EFC10832 was a 24-week, double-blind, placebo-controlled study in patients with a history of TNF-IR. In this study, sarilumab or placebo was administered in combination with MTX or other c-DMARDs i.e. sulfasalazine, hydroxychloroquine, or leflunomide.

Sarilumab monotherapy in subjects who responded inadequately or were intolerant to MTX

EFC14092 was a 2-part study: Part 1 (completed) was a randomized, active-controlled (adalimumab), double blind, double-dummy (due to different formulations) 24-week treatment period that enrolled patients who were either intolerant of, or considered inappropriate candidates for continued treatment with MTX, or who, after at least 12 weeks of continued treatment with MTX, were determined to be inadequate responders. In Part 2, the open-label extension, all patients were to receive sarilumab as monotherapy (ongoing).

Long-term study. Among others, patients from from EFC11072 and EFC10832 were allowed to enter the long-term OL **LTS11210** study, an ongoing (cut-off date of 25 January 2016), open-label, uncontrolled extension study.

3.2. Favourable effects

The overall benefit is demonstrated by ACR20, ACR50 and ACR70 responses. Favourable results were also demonstrated for the secondary endpoints, e.g. individual ACR components, DAS28 and patient reported outcomes.

The key favourable effects are:

- Improvement of signs and symptoms: ACR20 response rates in EFC11072 and EFC10832 were better for sarilumab compared to placebo
- A gain over placebo of 33% and 27% was observed in the first co-primary endpoint, **ACR20 response,** at week 24, in EFC11072 and EFC10832 studies respectively, with 66.4% and 60.9% of patients

obtaining ACR20 response. The amelioration of disease signs and symptoms appeared early than 24 weeks and, in the EFC11072 study, was maintained up to 52 weeks.

- Major clinical response (i.e. achieving and maintaining ACR70 for at least 24 consecutive weeks) shown in EFC11072 Part B
- Improvement in physical function: Change from baseline in HAQ-DI in EFC11072 Part B and EFC10832 was statistically significant for sarilumab compared to placebo
- Results showed statistically superiority of both sarilumab doses, with a slight larger gain in the sarilumab higher dose (-0.58 and -0.49 for sarilumab 200 mg q2w; -0.54 and -0.50 for sarilumab 150 mg q2w; and of -0.30 and -0.29 for placebo). The magnitude of improvement in HAQ-DI was clinically meaningful according to both definitions (>0.22 and >0.3) used in the supportive analyses. Maintenance of treatment effect was observed up to 52 and 24 weeks, in EFC11072 and EFC10832 studies, respectively
- Improvement regarding progression in structural damage (reduction of progression): change from baseline in mTSS in EFC11072 Part B was statistically significant better for sarilumab compared to placebo. Study results showed superiority of sarilumab+c-DMARD compared to PBL-c-DMARD, with the largest effect seen with the sarilumab 200mg q2w dose (0.25 for sarilumab 200 mg q2w; 0.90 for sarilumab 150 q2w, and 2.78 for placebo). Supportive evidence of a positive sarilumab effect on bone damage is provided by the greater ($p < 0.0001$) proportion of sarilumab-treated patients with no progression of structural damage compared to placebo, as shown by the conservative analysis evaluating treatment effect on the binary endpoint progression/no progression. The effect on progressive structural damage was sustained upon continued treatment for up to 3 years. Of note, the evaluation of RX scans indicated a larger reduction of radiographic progression in bone structural damage in subjects initially randomized to sarilumab 200 mg q2w as compared to those who started treatment with sarilumab 150 mg q2w.
- In both studies evaluating sarilumab efficacy in combination with c-DMARDs, there was a consistent trend favouring the 200mg dose over the 150mg for all explored outcomes, and in particularly for the reduction of the rate of bone damage progression.
- Superiority of sarilumab to placebo (in EFC11072 and EFC10832) regarding secondary endpoints (ACR50, ACR70), all components of ACR response, the proportion of patients achieving a remission (DAS28 remission <2.6), improvement in health status (SF-36 PCS, FACIT-Fatigue)
- Maintenance of treatment effect: Improvement of RA-associated signs and symptoms (ACR 20/50/70) responses upon prolonged sarilumab administration was observed in the OL Long term LTS11210 study. The ACR20 response incidence kept increasing over the time, reaching up to ~90% after 264 weeks of treatment in the safety population. Moreover, disease activity as well as physical function supported the persistency of sarilumab effect in MTX- and TNF-IR patients (slightly lower). Consistent results are obtained when the two EFC11072 study EFC10832 studies are seen separately, with a predictable trend of a lower incidence of response in TNF-IR subjects as compared to MTX-IR ones.
- Superiority of sarilumab (200 mg q2w) to adalimumab (40 mg q2w) regarding DAS28-ESR, DAS28-ESR remission, ACR20, ACr50. ACR70, HAQ-DI.
- The 200 mg q2w dose demonstrated improvement in the change from baseline in joint space narrowing relative to placebo at 24 weeks (EFC11072 Part B)

Posology: There was a consistent trend favouring the 200mg dose over the 150mg for all explored outcomes and in particularly for the reduction of the rate of bone damage progression. Of note, in the OL LTS11210 study, patients originally randomized to receive sarilumab 150 mg q2w, upon switching to 200 mg q2w, achieved nearly comparable responses to those originally randomized to 200 mg q2w, with the exception of treatment effect on radiographic progression of bone damage that remained larger in patients originally randomised to sarilumab 200 mg q2w both after 2 years (mTSS: 0.23, 200 mg q2w vs. 1.05, 150 mg q2w) and 3 years of treatment (mTSS: 0.79, 200 mg q2w vs. 1.87, 150 mg q2w). Maintenance of the treatment effect up to 24 weeks was seen in subjects who decreased their sarilumab dose from 200 mg q2w to 150 mg qw2.

3.3. Uncertainties and limitations about favourable effects

Sarilumab in add on to MTX/cDMARDs in c-DMARD-IR and b-DMARD-IR subjects

Given that no active control arm with a b-DMARD was included in the 2 pivotal studies, it is not possible at present to contextualise the benefit of sarilumab treatment in the present therapeutic armamentarium available for the treatment of c-DMARD-IR patients. Although superiority of sarilumab doses was shown for HAQ-DI endpoint, some secondary endpoints related to QoL measure were only met by the 150mg q2w sarilumab dose in both second line and third line settings.

Sarilumab monotherapy in bDMARDs-IR subjects

No efficacy data were available for sarilumab monotherapy in b-DAMRDs-IR patients

Inconsistency among add-on and monotherapy studies.

Exposure to sarilumab varies across different groups of body weight (<60 kg, 60 to >100 kg and >100 Kg), however, inconsistent results from add-on and monotherapy efficacy studies, probably due to the limited number of observations, do not allow to clinically characterize the impact of BMI≥30 kg/m2 on sarilumab efficacy.

Posology

No long-term data on bone damage is available following sarilumab dose reduction.

Regarding long term study LTS11210: With regard to efficacy the study results have to be interpreted with caution as this is an open label trial without internal control. Furthermore, the efficacy analyses do not account for dropouts. Thus the efficacy results are likely to be biased

3.4. Unfavourable effects

Overall, a larger number of patients treated with sarilumab (17%-18%) compared to the placebo group (10%) discontinued treatment. The reasons for discontinuation were mostly adverse events, of which the most common were neutropenia, elevation of ALT levels and herpes zoster infections.

Roughly 70% of patients treated with sarilumab in combination with cDMARDs experienced **TEAEs** compared to 57% of the placebo+c-DMARD group. The differences between sarilumab in combination with c-DMARDs and placebo+c-DMARDs were primarily due to differences in **infections** (about 35% in sarilumab+c-DMARDs patients, and 29% in placebo+c-DMARDs), with a greater involvement of the upper respiratory and urinary tract, **injection site erythema and pruritus** as well as **laboratory changes** (in particular neutropenia, hypertriglyceridemia, ALT, or transaminase increased).

Infections and transaminase increase were more specifically related to c-DMARD (mainly MTX) administration, whereas neutropenia seems to be more sarilumab-related. However, 6 patients developed herpes zoster that required hospitalization.

Most frequently observed TEAEs and AESI were infections with a higher incidence in the sarilumab group

Elevations in lipids were reported for LDL, HDL and triglycerides during sarilumab treatment. The increase occurred in the first 4 weeks and remained stable thereafter. However, the majority of patients did not have a shift in NCEP ATPIII and of those patients who did, the majority shifted up 1 level.

Two cases suggestive of **demyelinating disorders** were identified in patients receiving sarilumab with concomitant DMARDs.

There was a higher dose dependent (200mg q2w) incidence of neutropenia in the sarilumab group (40.6%) compared to placebo (4.9%). **Neutropenia** occurred generally early during treatment (first 4 weeks) with sarilumab and then plateaued.

Higher dose dependent (200mg q2w) incidence of serious infections in the sarilumab group compared to placebo.

Gastrointestinal perforations occurred only in the sarilumab group.

There was a higher incidence of injection site reactions in sarilumab treatment groups compared to placebo

Hypersensitivity reactions, following sarilumab sc injection, were principally of mild or moderate grade. However, serious hypersensitivity events were also observed, although rarely.

Subgroups analysis showed that elderly patients (≥65 years old) seem to be at higher risk for infections and that subjects with a low weight (< 60 Kg) are at higher risk of developing ANC <1.0 Giga/L.

3.5. Uncertainties and limitations about unfavourable effects

There is uncertainty regarding long-term safety profile of Pool 2. Placebo population only provides AE data up to 52 weeks of treatment. Although available data do not seem to indicate an increased risk of malignancies and MACE with sarilumab long-term exposure, only 523 out of 2887 patients were exposed for >192 weeks to sarilumab treatment, making difficult to conclusively evaluate the long-term risk of **malignancies and MACEs**.

Regarding infections, although a **correlation between ANC decrease and infections** have not been reported during clinical studies, it is difficult to exclude a potential increased risk of infections and serious infections in patients with low neutrophil count due to sarilumab treatment.

In the long-term safety population (pool 2), 54 patients experienced **Opportunistic infections** and the incidence of OIs was numerically higher in patients with prior baseline steroid use in the sarilumab any dose group (2.1% in patients with baseline steroid use vs. 1.6% in patients with no baseline steroid use). However, data coming from an additional analysis by calculating exposure adjusted event rates of OI in pool 2, showed that the exposure-adjusted event rate of OIs in patients with baseline corticosteroid use in sarilumab+DMARD group [1.0/100 patient-year (PY)s] appears to be quite similar to the exposure-adjusted event rate of OIs in the group of patients with no baseline corticosteroid use (0.9/100 PYs). A less clear pattern was observed in patients with prior biologic DMARD use both in pool 1 and pool 2.

Taking into account the role of IL-6 in inducing B cells differentiation and data coming from non-clinical animal studies reporting reversible changes in IgG responses and concentrations, although the effect of these changes

on responses to vaccination was not studied, concerns about patient's ability to generate a sufficient humoral immune response remain.

From available data, there was no evidence that sarilumab treatment was associated with demyelinating disorder. Two cases suggestive of **demyelinating disorders** were identified: one case of transverse myelitis occurred 7 months post-study in which the assessment of a causal relationship with the study drug was confounded by prior and concomitant use of anti-TNFs, and one case reported as Multifocal Motor Neuropathy, for which, however, a definitive diagnosis of MMN and/or a causal relation with sarilumab, have not been confirmed by the Applicant.

3.6. Effects Table

Table 99 - Effects Table for sarilumab (indication: rheumatoid arthritis)

Effect	Short Description	Unit	Treatment	Placebo	Uncertainties / Strength of evidence
Favourable Effects					
ACR20	Response (≥ 20% improvement) at week 24 Co-primary endpoint (EFC11072 Part B)	N (%)	**Week 24:** 150 mg q2w: 232 (58.0%) 200 mg q2w: 265 (66.4%)	Placebo+MTX: 133 (33.4%)	Co-primary endpoint was met
	Co-primary endpoint (EFC10832)	N (%)	**Week 24:** 150 mg q2w: 101 (55.8%) 200 mg q2w: 112 (60.9%)	Placebo+DMARD: 61 (33.7%)	Co-primary endpoint was met
HAQ-DI (change from baseline)	Health Assessment Question-Disability Index, questionnaire scoring range 0-3 Co-primary endpoint (EFC11072 Part B)	Mean change (SD), LS mean difference, 95% CI	150 mg q2w: -0.54 (0.55) -0.235 (-0.312,-0.157) 200 mg q2w: -0.58 (0.63) -0.258 (-0.336,-0.181)	Placebo+MTX: -0.30 (0.58)	Co-primary endpoint was met
	Co-primary endpoint (EFC10832)		150 mg q2w: -0.50 (0.64) -0.202 (-0.318,-0.086) 200 mg q2w: -0.49 (0.56)	Placebo+DMARD: -0.29 (0.54)	

			-0.210 (-0.325,-0.095)			
mTSS (change from baseline to Week 52)	Radiologic progression Co-primary endpoint (EFC11072 Part B)	Change mean (SD)	150 mg q2w: 0.90 (4.66) 200 mg q2w: 0.25 (4.61)	2.78 (7.73)	Co-primary endpoint was met P-value vs placebo: 150 mg q2w <0.0001 200 mg q2w <0.0001	
DAS28-ESR at week 24 (Change from baseline)	Disease activity score regarding 28 joints using erythrocyte sedimentation rate Primary endpoint (EFC14092)	Change mean (SD) LS mean (LS) LS mean diff, 95% CI	Sarilumab 200 mg q2w: -3.35 (1.37) -3.28 (0.105) -1.077 (-1.361,-0.793)	Adalimumab 40 mg q2w: -2.22 (1.36) -2.20 (0.106)	Primary endpoint was met	
Unfavourable Effects						
SAE	Serious infections	Rate	4.3 /100 patient years	3.0 / 100 patient years	Dose dependent (2OO mg q2w)	
SAE	Gastrointestinal perforations	Event	8	0		
SAE	Serious hypersensitivity reactions		4/ 100 pt-years		Any dose; no placebo data presented Known AE/SAE for all biologicals	
	Neutropenia	Decrease below LLN	40.6 %	4.9 %	Dose dependent (2OO mg q2w)	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Overall, available evidence supports the benefit of sarilumab in the treatment in moderately to severely active RA adult patients who responded inadequately or were intolerant to one or more DMARDs. Treatment effect resulted in the amelioration of disease signs and symptoms, improvement of physical function, and reduced progression of bone structural damage, the latter effect being demonstrated only in c-DMARD-IR patients in combination with MTX. Importantly, treatment effect was maintained over time with a persistent improvement of RA-associated signs and symptoms upon prolonged sarilumab administration. The magnitude of the effect is overall considered clinically relevant in a patient population for which there still the need for further effective alternative treatments. This is particularly true for the c-DMARD-IR patients, where sarilumab monotherapy was clearly superior to the anti TNFa drug, adalimumab, on all measured endpoints. Conversely, no efficacy data were available for sarilumab monotherapy in RA patients inadequately responders or intolerant to b-DMARD,

and as such the evidence of benefit of sarilumab treatment as monotherapy was limited to patients intolerant or irresponsive to c-DMARDs.

Rheumatoid arthritis is a heterogenous disease, and even though demographic data may be comparable, patients that do not respond adequately to TNF-inhibitors are considered to have a disease that is more difficult to treat.

The fact that the results for monotherapy in the MTX-IR population showed a better trend than combination therapy in the TNFi-IR population cannot support a claim that monotherapy would be effective in the latter group. Current data does not support RA indication for both monotherapy in bDMARDs-IR patients and combination therapy with cDMARDs.

Unfortunately, no direct comparative data with b-DMARDs have been generated for the combination sarilumab+c-DMARD, which is expected to be the most common use of sarilumab in the clinical practice. The full appreciation of the relative benefit of sarilumab-cDMARD treatment in the context of the available therapeutic scenario was thus hampered.

A limited number of subjects received other cDMARDs than MTX in the pivotal study where non-MTX DMARDs were allowed as background therapy (115 subjects in Study 10832). CHMP considered that the data was therefore too limited to support for a broad indication of conventional DMARDS and that combination therapy should not include conventional DMARDs as a group. The different DMARDs are not to be regarded as equivalent, neither for mode of action nor in terms of safety. Therefore there is not enough data to support other combinations than with MTX.

Therefore the wording of the indication was changed as recommended by the CHMP and it now read:

“Kevzara in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs. Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate (see section 5.1)”.

Treatment effect appeared to be dose dependent, with a consistent trend favouring the 200mg dose over the 150mg for all explored outcomes, and in particularly for the reduction of the rate of bone damage progression. The sarilumab posology recommended in the proposed SmPC is thus supported by sufficiently clear data. There is, however, at present incompletely understanding of the effect of BMI on sarilumab efficacy, as inconsistent evidence of a potential decrease of treatment efficacy in patients with BMI≥30 kg/m^2 is derived by the pivotal studies. It is thus at present not known whether sarilumab dose adjustment is required in patients with BMI≥30 kg/m2. Patients with a higher body weight (>100kg) are expected to gain a less beneficial therapeutic effect, especially when the dose of sarilumab is lowered from 200 mg q2w to 150 mg q2w due to safety reasons. A statement regarding possibly impaired efficacy of sarilumab in overweight patients was included in the SmPC.

The safety profile of sarilumab is principally characterized by the occurrence of: i. hypersensitivity and injection site reactions, generally of mild to moderate grade, not requiring discontinuation in the majority of cases, ii. infections (including serious and opportunistic infections), and iii. laboratories abnormalities, in particular ANC decrease and ALT increase, without any apparent correlation between neutropenia and infections. Both neutropenia and ALT elevations appear to be reversible and fairly manageable with dose decrease or treatment interruption. Although available data do not seem to indicate an increased risk of malignancies and MACE with sarilumab over time, the limited number of patients with long-term exposure prevents any sound conclusion on these risks. There is a potential risk of demyelinating disorders that is at present incompletely characterized, and also occurrence of gastrointestinal perforations, reported as complications of diverticulitis.

3.7.2. Balance of benefits and risks

The evidence of sarilumab efficacy in combination with MTX in moderately to severely active RA adult patients who responded inadequately or were intolerant to DMARDs is considered statistically convincing and supported by a good concordance among efficacy endpoints. The uncertainties that at present affect the estimation of the magnitude of treatment benefit, although need further investigations, are not considered to substantially revert the overall sarilumab benefit that has been consistently shown across the two pivotal studies and supported by a number of secondary analyses in this patient population.

Similarly, the efficacy of sarilumab monotherapy in patients intolerant or irresponsive to MTX is considered soundly demonstrated, as well.

Conversely no direct evidence of efficacy is at present available for sarilumab monotherapy in moderately to severely active RA adult patients who responded inadequately or were intolerant to b-DMARs. The Applicant extrapolated the use of monotherapy in TNF-IR subjects. Although an extrapolation approach might be favourable and comprehensible in some cases this approach seemed not to be acceptable in the current situation.

Rheumatoid arthritis is a heterogenous disease, and even though demographic data may be comparable, patients that do not respond adequately to TNF-inhibitors are considered to have a disease that is more difficult to treat.

The fact that the results for monotherapy in the MTX-IR population showed a better trend than combination therapy in the TNFi-IR population cannot support a claim that monotherapy would be effective in the latter group. Current data does not support RA indication for both monotherapy in bDMARDs-IR patients and combination therapy with cDMARDs.

A limited number of subjects received other cDMARDs than MTX in the pivotal study where non-MTX DMARDs were allowed as background therapy (115 subjects in Study 10832). CHMP considers that the data is therefore too limited to support for a broad indication of conventional DMARDS and that combination therapy should not include conventional DMARDs as a group. The different DMARDs are not to be regarded as equivalent, neither for mode of action nor in terms of safety. Therefore there is not enough data to support other combinations than with MTX.

In addition, considering the large number of treatment options that have become available for RA, and as the choice and the order of treatments may differ between prescribers/centers, it may not be feasible anymore to exactly define the second line indication in the labelling. As such the indication should be further modified to rephrase the specific indication of RA patients irresponsive/intolerant to c-DMARDs or biologic DMARDs into a more general second line indication: one or more DMARDs.

The applicant amended the wording of the indication accordingly into:

“Kevzara in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs. Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate”.

The most important favourable effects are the improvements in signs and symptoms (ACR20/50/70), improvement in physical function measured as the change from baseline in HAQ-DI and the reduction of progression in structural damage measured until week 52(mTSS) and the efficacy of sarilumab monotherapy (measured regarding DAS28-ESR) in comparison with adalimumab monotherapy. The evidence of efficacy was

statistically convincing. Improvement in signs and symptoms and concerning physical function is clinically important for patients. A reduction of progression is important as RA is an ongoing disease, slowing down the progression of the disease is important for the quality of life of the patients who suffer from this life-long, not curable disease.

Overall the safety profile of sarilumab both as monotherapy and in combination with cDMARDs appears sufficiently characterised in the population of the claimed indication, with the notable exception of sarilumab monotherapy in patients b-DMARD-IR, for which the few available data have not been presented and discussed. Most of the more frequently reported AEs appear of mild, moderate grade, manageable in the clinical setting, and reversible upon dose decrease or treatment interruption. In general, adequate information on serious AEs, dose reduction and treatment interruption is already included in the SmPC. Hypersensitivity reactions are a known unfavourable effect for all biologicals.

However, serious hypersensitivity reactions were also reported, albeit rarely, following sarilumab sc injection, as such appropriate information has been added in the SmPC The most important risks of the treatment with sarilumab are serious infections and neutropenia, both dose-dependent, and gastrointestinal perforations as well as serious hypersensitivity reactions. Serious infections and neutropenia were dose dependent effect. As a lower dose of sarilumab is available these effects could be managed by dose reductions. The occurrence of infections, and serious infections, including opportunistic infections, observed in sarilumab-treated patients, is considered an important safety issue, particularly because, patients with treatment-induced low neutrophil count could be at higher risk of severe infections. Although the available evidence does not suggest a direct correlation between neutropenia and infections, the risk needs to be taken into account. A warning has been included in section 4.4 of the SmPC.

Gastrointestinal disorders only occurred in the patients treated with sarilumab. The occurrence could be due to the effect of the IL6-antagonist in the gastrointestinal tract.

Taking into account the role of IL-6 in inducing B cells differentiation and data coming from non-clinical animal studies reporting reversible changes in IgG responses and concentrations, although the effect of these changes on responses to vaccination was not studied, concerns about patient's ability to generate a sufficient humoral immune response remain. In this regard, "use of vaccination in patients receiving sarilumab" and "Immunoglobulins levels following sarilumab treatment" have been added as missing information in the RMP.

The uncertainties that characterise the long-term safety, namely the risk of malignancy and MACEs, derive from the mechanism of action of the drug, as no direct indication of an increased risk of CV risk or malignancy is retrieved from the available clinical data, and the indirect comparison with literature and patient database. However, due to the known higher risk of RA patients to develop malignancies compared to the general population and the status of immunosuppression in these patients, malignancies are considered a potential risk. It is although acknowledged that all biological drugs already marketed for the treatment of RA have faced this long-term risk,that has been managed with its inclusion in the RMP and appropriate information reflected in the SmPC. Similarly, a relationship between lipid increase and CV risk during sarilumab treatment cannot be ruled out at present, considering that the RA population is at higher risk of CV diseases compared to the general population. Although not resolvable at present, this risk may be taken into account by including a warning on the increased risk of cardiovascular disorders in patients with RA in section 4.4 of the SmPC.

The potential risk of demyelinating disorders has been already highlighted at the time the first IL-6 drug was approved for the treatment of RA, albeit central and peripheral inflammatory demyelinating diseases were rarely reported.

However, from available data, there was no evidence that sarilumab treatment was associated with demyelinating disorder. Two cases suggestive of demyelinating disorders were identified: one case of transverse myelitis occurred 7 months post-study in which the assessment of a causal relationship with the study drug was confounded by prior and concomitant use of anti-TNFs, and one case reported as Multifocal Motor Neuropathy, for which, however, a definitive diagnosis of MMN and/or a causal relation with sarilumab, have not been confirmed by the Applicant.

3.8. Conclusions

The overall Benefit/Risk of Kevzara is positive.

4. Recommendations

Outcome

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

Kevzara in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Kevzara in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of patient alert card, including communication media, distribution modalities, and any other aspects, with the National Competent Authority.

The MAH shall ensure that in each Member State where Kevzara is marketed, all healthcare professionals who are expected to prescribe Kevzara have access to the patient alert card.

- **The patient alert card** shall contain the following key messages:
    - A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using Kevzara.
    - That Kevzara treatment may increase the risks of serious infections, neutropenia and intestinal perforation.
    - Educate patients on signs or symptoms that could represent serious infections or gastrointestinal perforations to seek for medical attention immediately.
    - Contact details of the prescriber for Kevzara

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

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that sarilumab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.