FDA Briefing Document

Arthritis Advisory Committee Meeting

August 2, 2017

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought biologics license application (BLA) 761057 for sirukumab for rheumatoid arthritis to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Division Director Memorandum/Division Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medication Error Prevention and Risk Management
M E M O R A N D U M

Date:	July 6, 2017
From:	Badrul Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products
To:	Chair, Members and Invited Guests Arthritis Advisory Committee (AAC)
Subject:	Division Summary for the August 2, 2017 AAC meeting, biologics license application (BLA) 761057 for sirukumab injection for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have an inadequate response or are intolerant to one or more disease modifying anti-rheumatic drugs (DMARDs)

During the August 2, 2017, Arthritis Advisory Committee (AC) meeting, the committee will discuss biologics license application (BLA) 761057, for sirukumab injection (proposed trade name PLIVENSIA), submitted by Janssen Biotech, Inc., for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or are intolerant to one or more disease modifying anti-rheumatic drugs. The proposed dose is 50 mg subcutaneous (SC) every 4 weeks (q4w).

Patients with RA have a chronic progressive disease that is associated with morbidity and mortality. Drugs that slow down disease progression in RA, otherwise called disease-modifying anti-rheumatic drugs (DMARDs), are widely used in the treatment of RA. Multiple small molecule drugs and large molecule biologic products belonging to the DMARD category are approved for the treatment of RA. It would be desirable to add another treatment option for RA. The product under review, sirukumab, is a monoclonal antibody that inhibits interleukin (IL)-6. There are two other approved monoclonal antibody products, tocilizumab and sarilumab, that target the IL-6 pathway for the treatment of patients with RA. The difference between the products is that sirukumab targets IL-6, whereas tocilizumab and sarilumab target IL-6 receptor. The proposed indication for sirukumab is similar to that of

tocilizumab and sarilumab.

The efficacy and safety of sirukumab were assessed in one phase 2 dose ranging study, and three pivotal phase 3 studies (plus an additional study conducted in Japanese patients). The phase 2 dose ranging study was small with approximately 30 patients per treatment arm. Two adequately sized phase 3 studies compared sirukumab 100 mg q2w and 50 mg q4w to placebo (all treatment arms included background conventional DMARD (cDMARD) treatment, typically methotrexate), and one adequately sized phase 3 study compared the same two sirukumab doses to adalimumab (all as monotherapy, with no cDMARD background). The one phase 3 study that assessed radiographic progression had a placebo control for 52 weeks with early (week 18) and late (week 40) escapes based on <20% improvement baseline in both swollen and tender joint counts. Janssen's intent early in the development program appeared to be to provide support primarily for the 100 mg q2w dose and secondarily for the 50 mg q4w dose over placebo and over adalimumab.

The results of the submitted studies showed efficacy of sirukumab at doses of 100 mg q2w and 50 mg q4w (two doses studied in phase 3 studies) for reducing signs and symptoms of RA based on the proportion of patients achieving American College of Rheumatology (ACR) response criteria and reduction in DAS28-CRP, for improvement of physical function as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI), and for structural progression reduction as assessed by the van der Heijde modified Sharp score (vdH-S). In general, the efficacy of the sirukumab 100 mg q2w dose and the 50 mg q4w dose over placebo was similar, and the sirukumab doses were not superior to adalimumab.

The major safety findings of sirukumab were related to immunosuppression that are consistent with other DMARDs, but a signal for a safety finding was a trend of increased overall mortality with sirukumab over placebo. The common causes of mortality were MACE, infection, and malignancy. The increased mortality was seen with both sirukumab doses at comparable rates. Sirukumab was associated with increased risk of serious infection, and there were reports of opportunistic infection and tuberculosis. Sirukumab treatment was associated with laboratory abnormalities including neutrophil count decrease, liver function test values increase, and increase in lipid parameters of LDL, HDL, and triglyceride. These changes were comparable for the sirukumab 100 mg q2w and 50 mg q4w doses. While these immunosuppression-related adverse events and laboratory parameter changes were in qualitative terms similar to other products targeting the IL-6 pathway, the observation of the trend of increased overall mortality seen within the controlled time period of registration studies seems unique for the sirukumab program.

Based on the efficacy and safety data, Janssen has proposed sirukumab 50 mg q4w as the only dose for the treatment of patients with RA.

At the upcoming AC meeting, we would like the Committee to discuss the adequacy of the phase 2 study in general for selection of dose or doses for the phase 3 program, noting that historically the phase 2 studies for such RA development programs have been relatively small and in general not very different than what was done for sirukumab. We would also like the Committee to discuss the conduct of a relatively long-term, such as 52-week, placebo-

controlled study in RA patients to assess radiographic progression in the current time and in the future, given the multiple treatment options available for the treatment of RA, and the interest expressed by the community relatively recently to limit long-term placebo exposure in clinical trials to avoid unacceptable harm to patients. At the AC meeting, the ultimate focus will be to discuss the efficacy findings, safety findings, and the overall benefit-risk profile of sirukumab for the treatment of patients with RA. Under consideration will be the data presented by Janssen and the FDA, and how that data impacts the approach to the management of RA based upon the Committee's view on the seriousness of RA, treatment options currently available to patients with RA, and anything else that the Committee considers relevant. Below are specific topics for discussion at the meeting.

Draft Points to Consider:

1. Discuss the safety findings in the phase 3 program, with particular consideration of the imbalance in death between sirukumab and placebo.

2. Discuss the dose selection for the phase 3 program. Consider whether the evaluated doses were reasonable given the safety profile in the phase 3 studies.

3. Discuss the design of the 52-week placebo-controlled radiographic study, ARA3002. Consider the optimal study design for assessment of radiographic progression in rheumatoid arthritis.

4. Overall, do the data provide substantial evidence that sirukumab provides a clinically meaningful benefit in the treatment of rheumatoid arthritis?

5. Is the safety profile of sirukumab adequate to support approval of sirukumab for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more disease modifying anti-rheumatic drugs (DMARDs)?

6. Do you recommend approval of sirukumab at the proposed dose of 50 mg SC q4w for the proposed indication of the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more DMARDs?

FDA's Advisory Committee Briefing Document

Date	July 6, 2017
From	Sirukumab Review Team
Subject	Advisory Committee Briefing Document
NDA/BLA # Supplement#	761057
Applicant	Janssen Biotech, Inc.
Date of Submission	September 22, 2016
PDUFA Goal Date	September 22, 2017
Proprietary Name / Non-Proprietary Name	PLIVENSIA / Sirukumab
Dosage form(s) / Strength(s)	50 mg/1 mL single dose prefilled syringe or 50 mg/1 mL prefilled SmartJect autoinjector
Applicant Proposed Indication(s)/Population(s)	Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more disease modifying anti-rheumatic drugs (DMARDs)

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1. Background

Janssen Biotech, Inc. (Janssen) submitted biologics license application (BLA) 761057 on September 22, 2016, for the new molecular entity (NME) sirukumab for the treatment of adult patients with moderate to severely active rheumatoid arthritis (RA) who have had an inadequate response or are intolerant to one or more disease modifying anti-rheumatic drugs (DMARDs). The proposed dose is 50 mg once every four weeks. The product is a subcutaneous (SC) injection in 50 mg/1 mL single-dose pre-filled syringes and autoinjectors.

Sirukumab is a human anti-interleukin (IL)-6 immunoglobulin G1 kappa (IgG1k) monoclonal antibody. In contrast, the first approved IL-6 inhibitor, tocilizumab (Actemra®), is a recombinant human IgG1 monoclonal antibody that binds both soluble and membrane-bound IL-6 receptors. Tocilizumab (BLA 125276) was initially approved as an intravenous IL-6 inhibitor for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies on January 8, 2010. This indication was subsequently broadened to the treatment of adult patients with moderate to severely active RA who have had an inadequate response to one or more DMARDs on October 11, 2012. Tocilizumab solution for subcutaneous injection (BLA 125472) was subsequently approved for the same indication as intravenous tocilizumab on October 21, 2013. Sarilumab (Kevzara®, BLA 761037) has the same mechanism of action as tocilizumab and was approved for the same indication on May 22, 2017. The proposed indication for sirukumab is the same as that currently approved for tocilizumab and sarilumab. Therefore, sirukumab would be another choice in the class of IL-6 inhibitor agents for RA.

Rheumatoid arthritis is a chronic, symmetric inflammatory polyarthritis that primarily involves synovial joints. In RA, synovial tissues become inflamed and proliferate, forming pannus that invades bone, cartilage, and ligament and leads to joint damage and deformities. Destruction of synovial joints can lead to severe disability and premature mortality.[1,2]

Rheumatoid arthritis affects approximately 1% of the adult population in North America and Northern Europe.[3] The disease is three times more frequent in women than men. Prevalence rises with age and is highest in women older than 65 years.

While there is heterogeneity in the natural history of RA, it is generally a chronic, progressive disease. Patients can develop joint destruction, severe physical disability and multiple co-morbidities. In contrast to clinical symptoms, structural damage is irreversible and cumulative.[4]

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[1] Scott DL, et al. Long-term outcome of treating rheumatoid arthritis: results after 20 years. *Lancet* 1987;1:1108-11.
[2] Mitchell DM, et al. Survival, prognosis, and causes of death in rheumatoid arthritis. *Arthritis Rheum* 1986;29:706-14.
[3] Gabriel SE, et al. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. *Arthritis Res Ther* 2009;11(3):229.
[4] Scott DL. Radiographic progression in established rheumatoid arthritis. *J Rheumatol Suppl* 2004;69:55-65.

All patients diagnosed with RA are generally treated with disease-modifying antirheumatic drugs (DMARDs). A variety of non-biologic DMARDs are approved for RA, including corticosteroids, various nonsteroidal anti-inflammatory drugs (NSAIDs), sulfasalazine, auranofin, methotrexate (MTX), azathioprine, penicillamine, cyclosporine, and leflunomide. Non-biologic DMARDs, such as MTX, are the first line of therapy for RA.[5] Treatment with a tumor necrosis factor-alpha (TNF-α) antagonist is generally the next line of treatment for patients with ongoing disease activity. Currently approved TNF-α antagonists include etanercept (ENBREL), infliximab (REMICADE), adalimumab (HUMIRA), golimumab (SIMPONI), certolizumab pegol (CIMZIA), golimumab IV (SIMPONI ARIA), infliximab-dyyb (INFLECTRA), etanercept-szzs (ERELZI), infliximab-abda (RENFLEXIS), and adalimumab-atto (AMJEVITA). Between 30% and 40% of patients fail to respond or become intolerant to anti-TNF-α therapy.[6] For patients with ongoing disease activity, the therapeutic strategy usually involves trying another TNF-α antagonist or switching to a medication with a different mechanism of action. Approved alternative therapies include an orally bioavailable Janus kinase (JAK) inhibitor (tofacitinib/XELJANZ OR XELJANZ XR), and biological DMARDs targeting the B-cell antigen CD-20 (rituximab/RITUXAN), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4; abatacept/ORENCIA), and the pro-inflammatory cytokines IL-1 (anakinra/KINERET) and IL-6 (tocilizumab/ACTEMRA and sarilumab/KEVZARA).

Table 1: Small molecule drugs approved for rheumatoid arthritis in the United States

Product Name (Trade Name) [Sponsor]	Mechanism of Action in RA	Year of First Approval for RA
Sulfasalazine (AZULFIDINE) [Pfizer]	Anti-inflammatory and antimicrobial	1950
Methotrexate sodium (METHOTREXATE SODIUM) [Multiple]	Anti-metabolite	1988
Hydroxychloroquine (PLAQUENIL) [Sanofi-Aventis]	Interference with antigen processing	1955
Azathioprine (IMURAN) [Prometheus Labs]	Cytostatic	1968
Penicillamine (CUPRIMINE) [Alton]	Unknown	1970
Auranofin (RIDAURA) [Prometheus Labs]	Unknown	1985
Cyclosporine (NEORAL) (SANDIMMUNE) [Novartis]	T-cell activation inhibitor	1995, 1990
Leflunomide (ARAVA) [Sanofi-Aventis]	Anti-metabolite	1998
Tofacitinib (XELJANZ) [Pfizer]	JAK inhibitor	2012

*Various steroids and NSAIDs are approved for the reduction of signs and symptoms of RA

[5] Katchamart W, et al. Methotrexate monotherapy versus methotrexate combination therapy with non-biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis. *Cochrane Database Syst Rev* 2010;4:CD008495.
[6] Smolen JS, et al. Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. *Nat Rev Rheumatol* 2015;11(5):276-89.

Table 2: Biologics approved for rheumatoid arthritis in the United States

Product Name (Trade Name) [Sponsor] {year}	Presentation and *ROA*	Description and *MOA*
Etanercept (ENBREL) [Immunex/Amgen] {1998}	Vial, prefilled syringe, and SureClick Autoinjector *SC injection*	Fusion protein consisting of TNF-R and human IgG1 Fc *TNF-α inhibitor*
Infliximab (REMICADE) [Centocor] {1999}	Vial *IV infusion*	Chimeric IgG1 k mAb *TNF-α inhibitor*
Anakinra (KINERET) [Amgen] {2001}	Prefilled syringe *SC injection*	Recombinant polypeptide *IL-1 receptor antagonist*
Adalimumab (HUMIRA) [Abbott] {2002}	Vial, prefilled syringe, and Humira Pen *SC injection*	Human IgG1 k mAb *TNF-α inhibitor*
Abatacept (ORENCIA) [Bristol Myers Squibb] {2005}	Lyophilized powder vial *IV infusion*	Fusion protein consisting of CTLA-4 and human IGg1 Fc *T cell activation inhibitor through B7-1 and B7-2*
Rituximab (RITUXAN) [Genentech and Biogen] {2006}	Vial *IV infusion*	Chimeric murine/human IgG1 k mAb *Anti CD20, B cell depletor*
Golimumab (SIMPONI) [Centocor] {2009}	Prefilled syringe, SmartJect Autoinjector *SC injection*	Humanized IgG1 k mAb *TNF-α inhibitor*
Certolizumab Pegol (CIMZIA) [UCB Inc] {2009}	Lyophilized powder, prefilled syringe *SC injection*	Humanized Fab fragment *TNF-α inhibitor*
Tocilizumab (ACTEMRA) [Genentech/Roche] {2010, 2013}	Vial *IV infusion* Prefilled syringe *SC injection*	Humanized IgG1 k mAb *IL-6 receptor inhibitor*
Abatacept (ORENCIA) [Bristol Myers Squibb] {2011}	Prefilled syringe and autoinjector *SC injection*	Fusion protein consisting of CTLA-4 and human IGg1 Fc *T cell activation inhibitor through B7-1 and B7-2*
Golimumab IV (SIMPONI ARIA) [Janssen] {2013}	Vial *IV infusion*	Humanized IgG1 k mAb *TNF-α inhibitor*
Infliximab-dyyb (INFLECTRA) [Celltrion Inc] {2016}	Vial *IV infusion*	Chimeric IgG1 k mAb *TNF-α inhibitor*
Etanercept-szzs (ERELZI) [Sandoz Inc] {2016}	Prefilled syringe and Sensoready Pen Autoinjector *SC injection*	Fusion protein consisting of TNF-R and human IgG1 Fc *TNF-α inhibitor*
Adalimumab-atto (AMJEVITA) [Amgen Inc] {2016}	Prefilled syringe and SureClick Autoinjector	Human IgG1 k mAb *TNF-α inhibitor*
Infliximab-abda (RENFLEXIS) [Samsung] {2017}	Vial *IV infusion*	Chimeric IgG1 k mAb *TNF-α inhibitor*
Sarilumab (KEVZARA) [SANOFI] {2017}	Prefilled syringe *SC injection*	Human recombinant monoclonal IgG1 antibody *IL-6 receptor inhibitor*

Abbreviations: SC=subcutaneous; TNF=tumor necrosis factor; R=receptor; IgG=immunoglobulin; mAb=monoclonal antibody; IV=intravenous; IL=interleukin; ROA=route of administration; MOA=mechanism of action

The long-term goal of treatment is prevention of irreversible joint destruction and functional impairment given the significant impact on patients and public health. The short-term goal of treatment is improvement in signs, symptoms, and functional status.

Key Regulatory Interactions

Key regulatory interactions are listed below by date. Points of discussion or Division recommendations are provided as a bulleted list for each meeting or interaction. The development program for sirukumab occurred under IND 101073.

March 27, 2008 – Pre-IND meeting

- Agreement on CMC and nonclinical data to support initial development

- The design of the proposed two-part phase 2 adaptive design study was discussed. The sponsor was advised that during drug development, they would need to develop evidence to support the choice of a dose.

June 6, 2008 – IND submitted

April 5, 2011 – End of Phase 2 (EOP2) meeting

- Agreement was reached on the proposed patient population, primary and secondary endpoints, and several aspects of the statistical analysis plan. Escape options for patients with ongoing disease activity and the required size of the safety database were discussed.
- FDA expressed concern with the sponsor's proposal to evaluate the 50 mg q12w dosing regimen in phase 3 since this dosing regimen had not been evaluated in phase 2. The importance of adequate dose ranging was emphasized and the sponsor was advised to either do additional dose ranging to evaluate lower doses and/or alternative dosing intervals or choose another dose level for the phase 3 trials that utilizes a dosing regimen evaluated in phase 2 trials. The sponsor acknowledged that if dose selection was not adequately addressed, the phase 3 trials might need to be repeated.
- FDA noted that in order to support a claim for inhibition of structural progression, at least 12 months of data are necessary. Acceptable data could be derived from 6 months of blinded data, followed by an additional 6 months of unblinded data.

October 12, 2012 – Advice/Information Request to submissions dated March 29, 2012 and July 10, 2012

- FDA provided comments on the sponsor's proposed phase 3 study CNTO136ARA3002. FDA noted that prespecified disease activity criteria at Weeks 18 and 40 allowed patients randomized to placebo to be crossed over to active treatment, but that it was possible for patients to be on placebo for 52 weeks. FDA raised ethical concerns regarding withholding treatment from patients with uncontrolled disease activity for extended periods of time. The sponsor was instructed to amend the protocol so that all patients randomized to placebo were switched over to active treatment with sirukumab at an earlier time point.
- With regards to dose selection in studies CNTO136ARA3002 and CNTOARA136ARA3003, the Agency noted that they had reviewed the support for the chosen dosing regimens of sirukumab in the phase 3 studies. It was noted that the selected doses of 100 mg q2 weeks and 50 mg q4 weeks were acceptable and at the sponsor's discretion, but the sponsor was referred to the EOP2 meeting regarding concerns with the adequacy of dose-ranging.

December 3, 2012 – Advice/Information Request to submission dated November 21, 2012

- In follow-up to the sponsor's question regarding whether the rescue mechanisms are adequate for a 52 week placebo control period in the design of study CNTO136ARA3002, FDA responded that the proposal for study CNTO136ARA3002 was generally acceptable. It was noted that the comment conveyed in the October 12, 2012, Information Request regarding the duration of treatment with placebo was intended for the sponsor's consideration given broader, ongoing discussion within and

outside the Agency about the ethics of placebo controls, but the final study design remains at the sponsor's discretion. FDA recommend that the sponsor include the justification for the proposed study design in the BLA application.

July 16, 2013 – Type C meeting (written responses only) and clarification (August 29, 2013)

- Agency outlined the type of data needed to support use of sirukumab as monotherapy. The sponsor proposed an active control trial comparing sirukumab to adalimumab monotherapy.

November 10, 2014 – Advice/Information Request to submission dated August 12, 2013

- Agency noted concerns with use of linear extrapolation to impute Week 52 radiographic scores in patients who escaped to sirukumab or withdrew from the study early. The Agency noted that the planned supportive analysis including post-escape data would be considered important to evaluate the effect of sirukumab on radiographic progression, and recommended that the sponsor conduct additional sensitivity analyses.

July 6, 2015 – Type C meeting (written responses only)

- Agency agreed that data from the monotherapy stratum of the proposed randomized, active-control, superiority study 201645 in addition to positive results from the ongoing study CNTO136ARA3005 should be adequate to support filing an sBLA for superiority of sirukumab as compared to adalimumab monotherapy.
- Discussion of the primary and secondary endpoints and statistical analysis of study 201645.

August 17, 2015 – Type C meeting (written responses only)

- Discussion of the statistical analysis plan for CNTO136ARA3002.
- Agency requested additional safety analyses. The sponsor proposed including the following pooled safety data sets:
    - Placebo controlled set (phase 3 RA studies ARA3002 and ARA3003),
    - Sirukumab controlled analysis set (phase 3 RA studies ARA3001, ARA3002, ARA3003, ARA3005 and data from the long term extension study ARA3004 for patients originally in ARA3002 and ARA3003 when appropriate), and
    - All subjects analysis set (comprised of all the studies in the sirukumab controlled analysis set with data from the phase 1 and 2 RA studies 1001 and C1377T04, the phase 1 and 2 lupus studies C0136T03 and CNTO136LUN2001, and the two phase 1 healthy volunteer studies CNTO136NA1001 and 1003).
- For the assessment of standard adverse events (AEs) and AEs of interest (i.e., targeted events) in the placebo-controlled population, FDA requested the following additional analyses:
    - For the standard AEs and targeted events, the Agency recommended analyses of the data by 0 to 18 weeks, 0 to 6 months, and, for Study ARA3002, 0 to 12 months. In addition to the traditional approach of summarizing by assigned treatment arm, sensitivity analyses should be conducted at Week 18, Week 24, or Week 40, including patients who transitioned from placebo to sirukumab 50

mg q 4 weeks or sirukumab 100 mg q 2 weeks. In other words, patients who escaped or crossed over to sirukumab should be counted in the denominator in both the placebo and sirukumab treatment groups based on their actual on-treatment time. The numerator count will depend on the timing of the event.
    - Additional analyses utilizing Poisson regression were requested.
- For windows of attribution, the sponsor was told that for patients on placebo, it makes sense that attribution stops immediately upon escape, change in therapy, or discontinuation from study. However, for patients on sirukumab, it is more appropriate to include a period of time after treatment has stopped during which time adverse events will be attributed to sirukumab.

May 18, 2016 – pre-BLA meeting

- There was general agreement on the content and format of the planned BLA submission.
- The Integrated Summary of Safety plan remained the same in terms of the placebo controlled and sirukumab controlled analysis sets described above in the August 17, 2015, communication, but the "all subject analysis set" was modified so that it only included data from the sirukumab controlled analysis set and the phase 1 and 2 RA studies (CNTO136ARA1001 and C1377T04). Separate safety analyses that include different patient populations (healthy volunteers (three phase 1 studies CNTO136NAP1001, CNTO136NAP1003, and C0136T01), previously completed lupus studies (phase 1 and 2 studies C0136T03 and CNTO136LUN2001), as well as ongoing studies CNTO136MDD2001 and GCA201677 were proposed to be presented separately since they were generated in populations different from the RA population and evaluated a different formulation and route of administration (intravenous) than proposed for marketing.
- FDA agreed with the sponsor's proposal to integrate studies ARA3001, ARA3002, ARA3003, and ARA3005 into analyses through 52 weeks and long-term.
- FDA requested integrated safety and efficacy analyses from ARA3002, ARA3003, and ARA3005.
- To support the sponsor's proposal to include FACIT-fatigue information in labeling, FDA requested a justification and development information for the use of the FACIT-Fatigue in RA.
- FDA noted that the effect of missing data on the reliability of efficacy results would be a review issue, and recommended tipping point sensitivity analyses for key endpoints.

2. Product Quality

- General product quality considerations

Drug Substance

Sirukumab is a human immunoglobulin G1κ (IgG1κ) monoclonal antibody to interleukin (IL)-6. This interaction prevents the binding of IL-6 to the soluble and membrane-bound IL-6 receptors (sIL-6Rα and mIL-6Rα) and inhibits IL-6 mediated signaling.

Sirukumab is composed of two identical heavy chains (approximately 50 kDa and 449 amino acids each) and two identical light chains (approximately 24 kDa and 213 amino acids each). The chains are linked together via non-covalent heavy-heavy and heavy-light interactions, and also covalent heavy-heavy and heavy-light disulfide bonds.

Drug Product

Sirukumab is a solution for injection with a recommended storage temperature of 2ºC to 8ºC, protected from light. Sirukumab is supplied in a single-use, sterile, ready-to-use 1 mL long prefilled syringe (PFS). One mL of the solution contains 50 mg sirukumab active drug substance, sorbitol, glacial acetic acid, sodium acetate trihydrate, and polysorbate 20 and water for injection at a pH of 5. No preservatives are present. The proposed shelf life is 24 months.

The qualitative and quantitative composition of the 50 mg strength is shown in Table 3.

Table 3: Composition of the 50 mg presentation of sirukumab

Component	Amount per Dose (mg)	Concentration
Sirukumab	53	50 mg/mL
Sorbitol	49	4.6% (w/v)
Glacial acetic acid	0.4	5.6 mM
Sodium acetate trihydrate	0.7	4.9 mM
Polysorbate 20	0.4	0.04% (w/v)
Water for injection	qs to 1.05 mL	NA

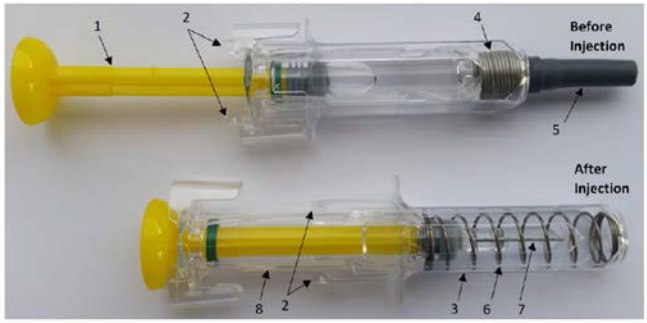
Source: Clinical overview, Table 3, page 17, submitted 9/22/16

Two sirukumab presentations are proposed:

1. A prefilled syringe fitted with UltraSafe Passive™ Delivery System (PFS-U), a single-use, sterile, ready-to-use liquid-filled 1-mL syringe product supplied with a passive safety needle guard for SC administration (Figure 1)
2. A prefilled syringe fitted with SmartJect® Autoinjector (PFS-AI), a single-use, sterile, ready-to-use liquid-filled 1-mL syringe product supplied with a spring-powered, disposable device for SC administration (Figure 2)

UltraSafe is a commercially available needle guard system that is currently utilized with Simponi, Stelara, and Eprex. The proposed autoinjector is the same as that used with Simponi.

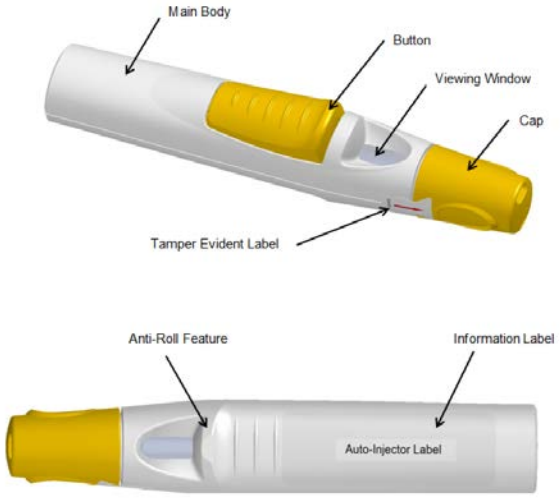
Figure 1: Operational Features of UltraSafe Displaying Before and After Injection Configurations



1 - Plunger Rod; 2 - Trigger Fingers; 3 - Needle Guard; 4 - Coiled Spring; 5 - Needle Shield; 6 - Uncoiled Spring; 7 – Needle; 8 - Body

Source: us-Container Closure System, Module 2.3.P.7, page 6, submitted 9/22/16

Figure 2: Autoinjector Features



Source: ai-Container Closure System, Module 2.3.P.7, page 2, submitted 9/22/16

3. Nonclinical Pharmacology/Toxicology

Pharm-Tox Reviewer: Yu-Mee Kim, PhD; Supervisor/Team Leader: Carol Galvis, PhD

The nonclinical safety program for sirukumab was performed in Cynomolgus monkeys, which were established to be a pharmacologically relevant nonclinical species. Sirukumab neutralizes *in vitro* cell proliferation induced by human IL-6, or Cynomolgus monkey IL-6-containing PBMC supernatant with EC_{50} values of 0.8 ng/mL and 0.3 ng/mL, respectively.

In the repeat-dose toxicity studies in Cynomolgus monkeys, administration of sirukumab for up to 6 months did not identify any dose-limiting toxicity at IV doses up to 50 mg/kg/week or

at a SC dose of 100 mg/kg/week (two weekly doses of 50 mg/kg). Most common effects were a decreased level of globulin and increased levels of albumin and albumin/globulin ratio in the serum. Reduced size and number of germinal centers in the spleen were also observed with minimal to mild severities. Administration of sirukumab diminished IgM or IgG responses following antigen challenge.

Based on species specificity, a rodent carcinogenicity study with sirukumab was not considered feasible. A review of the scientific literature related to the role of IL-6 in cancer was conducted. Published literature generally supports that IL-6 signaling may be involved in pathways that lead to increased tumor growth. However, the literature also supports that the IL-6 pathway can mediate anti-tumor responses by promoting increased immune cell surveillance of the tumor microenvironment. In a non-GLP mechanistic study, anti-mouse IL-6 mAb (a murine surrogate of sirukumab) treatment in mice increased metastasis of murine squamous cell carcinoma cells from the left gastrocnemius muscle (carcinoma cell injection site) to the popliteal lymph node. However, in another study, the surrogate mAb treatment reduced tumor cell colonization in the lungs of the mice intravenously injected with the carcinoma cells. The malignancy risk in humans from an antibody that disrupts IL-6/IL-6R signaling, such as sirukumab, is unknown.

In an enhanced pre and postnatal development study and an embryo/fetal development study in Cynomolgus monkeys, administration of sirukumab increased the incidence of embryofetal loss at IV doses of 10 and 50 mg/kg/week, respectively. Treatment with sirukumab decreased the level of serum globulin in pregnant monkeys and their infants exposed to sirukumab during pregnancy. The serum globulin level returned to normal as sirukumab was cleared from the serum (by 4 to 6 months of age in infants). Immunization of infant monkeys with a neoantigen (KLH), at age 4 to 6 months showed no impairment in the ability of the infants to mount IgM and IgG responses.

Fertility was unaffected in male and female fertility studies conducted in mice treated with anti-mouse IL-6 mAb (murine surrogate of sirukumab) at SC doses up to 100 mg/kg/week.

4. Clinical Pharmacology

Clinical pharmacology reviewers: Dipak Pisal, PhD; Team Leader: Anshu Marathe; Supervisor: Chandrahas Sahajwalla, PhD
Pharmacometrics Reviewer: Chao Liu, PhD; Pharmacometrics Team Leader: Jingyu Yu, PhD

Sirukumab is a human immunoglobulin G1κ (IgG1κ) monoclonal antibody to interleukin (IL)-6. This interaction prevents the binding of IL-6 to the soluble and membrane-bound IL-6 receptors (sIL-6Rα and mIL-6Rα) and inhibits IL-6 mediated signaling.

Sirukumab exhibits linear PK over a dose range of 25 to 100 mg following single or multiple subcutaneous (SC) administrations to healthy subjects or subjects with RA.

Following SC administration, sirukumab was slowly absorbed into the systemic circulation with median time to reach the maximum observed serum concentration (T_{max}) of 3 to 5 days in healthy subjects.

The mean terminal half-life ($T_{1/2}$) of sirukumab ranged from 15 to 19 days following SC administration of sirukumab in healthy subjects and subjects with RA. The mean CL/F of sirukumab appeared to be lower in healthy subjects (6.4-6.8 mL/day/kg) compared to subjects with RA (8.1-16.9 mL/day/kg). The lower CL/F in subjects with RA compared to healthy subjects may be due to elevated levels of IL-6 in subjects under inflammatory conditions.

The mean absolute SC bioavailability of sirukumab ranged from 81% to 95% following a single 50 or 100 mg SC administration of sirukumab by pre-filled syringe (PFS) fitted with UltraSafe Passive™ Delivery System (PFS-U) or PFS fitted with SmartJect® Autoinjector (PFS-AI).

The systemic drug exposure (C_{max} and AUC) of sirukumab was comparable following a single SC administration by PFS-AI or PFS-U in healthy subjects. The median steady-state trough sirukumab concentrations were also comparable before and after switching from PFS-U to PFS-AI in subjects with RA.

Across the Phase 3 studies, following multiple SC dosing of sirukumab at 50 mg once every 4 weeks (q4w) or 100 mg once every 2 weeks (q2w), trough serum sirukumab concentrations reached steady state by approximately Week 12. The median steady-state trough serum sirukumab concentrations at Week 12 ranged from 1.40 to 1.75 μg/mL and 8.30 to 10.13 μg/mL for the 50 mg q4w and 100 mg q2w groups, respectively. Mean accumulation ratios following SC administrations of sirukumab for C_{max} and $AUC_{(t1-t2)}$ were approximately 1.5 to 1.8 for q4w dosing and 2.6 to 3.0 for q2w dosing.

Immunogenicity
In studies ARA3002 and ARA3003, the percentage of patients with antibodies to sirukumab through Week 52 was 3.9% and 1.4% for the sirukumab 50 mg and 100 mg groups, respectively. Of patients who were positive for antibodies to sirukumab through Week 52, five (13%) patients (all in the 50 mg q4w group) were positive for neutralizing antibodies (Nabs) to sirukumab.

The incidence of antibodies to sirukumab through Week 52 appeared to be slightly lower in subjects with MTX use (2.4% [27/1146] overall, 3.5% [20/569] for 50 mg q4w, and 1.2% [7/577] for 100 mg q2w) compared to those without MTX use (3.8% [11/288] overall, 5.6% [8/143] for 50 mg q4w, and 2.1% [3/145] for 100 mg q2w).

In study ARA3005 with sirukumab monotherapy, the incidence of antibodies to sirukumab to sirukumab through Week 24 was 3.2% (11/343), which was similar with that observed in patients without DMARD use at baseline in studies ARA3002 and ARA3003.

There was no clear relationship between the development of ADA and efficacy or safety. Patients with positive antibody status tended to have slightly lower steady-state serum

sirukumab concentrations than those with negative antibody status. However, it should be noted that the number of patients who were positive for antibodies to sirukumab was small, limiting definitive conclusions.

Dose selection and Pharmacodynamics
See Section 8 regarding dose selection and pharmacodynamics considerations.

5. Clinical Microbiology

Not applicable

6. Efficacy

Clinical Primary Reviewer: Mark Borigini, MD; Clinical Team Leader Janet Maynard, MD, MHS
Statistical Reviewer: William Koh, PhD; Statistical Team Leader: Gregory Levin, PhD

6.1 Overview of the clinical program

Results from two phase 3 studies, CTNO136ARA3002 (referred to as ARA3002) and CNTO136ARA3003 (referred to as ARA3003), have been submitted as the primary evidence of efficacy of sirukumab (Table 4). In addition, results from one active control phase 3 study, CNTO136ARA3005 (referred to as ARA3005), were submitted. Table 5 provides a summary of phase 1 studies in RA and phase 1, 2, and 3 studies in other indications.

Table 4: Summary of Phase 2 and 3 Studies in RA Submitted for the BLA

Protocol [study name, ID in label] (Dates)	Overview	Patient Population (Background meds)	Treatment Arms (SC)	N per Arm	Escape provisions/Notable design issues	Primary Endpoints	Duration in wks (duration submitted in study report)
Phase 3 studies							
ARA3002 [SIRROUND D, Study 1] 185 centers Eastern Europe (48%), North America (16%, including 44 US sites), Asia-Pacific (16%, Latin America (13%), and South Africa (6%) (7/12-9/15)	Phase 3, R, DB, PC	DMARD (MTX or SSZ)-IR Active RA with +anti-CCP, +RF or baseline erosion; CRP≥8mg/L (MTX, SSZ, HCQ, CQ, and bucillamine)	SIR 50 mg q4w SIR 100 mg q2w Placebo→re-randomized to SIR at Week 52	557 557 556 N=1670	Subjects in the placebo group who met EE criteria at Week 18 or LE criteria at Week 40 (i.e., had <20% improvement from baseline in both swollen and tender joint counts) were re-randomized to receive blinded SIR 50 mg q4w or SIR 100 mg q2w through Week 104. At Week **28**, subjects in all treatment groups who had <20% improvement from baseline in both swollen and tender joint counts could adjust or initiate DMARDs and/or oral corticosteroids from Week 28 onwards. At Week 52, all remaining subjects in the placebo group were re-randomized to receive one of the two sirukumab dose regimens through Week 104. At Week 52, or any time after, all subjects could adjust or initiate DMARDs and/or oral corticosteroids	ACR20 at wk 16 vdH-S at wk 52 Key secondary: HAQ-DI at wk 24 ACR50 at wk 24 DAS28CRP<2.6 at wk 24 Major clinical response by wk 52	120* (52) 1st DBL: after all subjects complete Week 52 or terminated from study 2nd DBL: after all subjects have either completed their final safety visit (Week 120) or terminated study participation, whichever is later
ARA3003 [SIRROUND T, Study 2] 183 centers North America (53%), Europe (26%), Japan (13%), Latin America (4%), and Asia Pacific (4%) (10/12-10/15)	Phase 3, R, DB, PC	Inadequate response to ≥1 anti-TNF or intolerance to ≥2 anti-TNFs Active RA with +anti-CCP, +RF or baseline erosion; CRP≥8mg/L or ESR≥28mm/hr (MTX, SSZ, HCQ, CQ, and bucillamine)	SIR 50 mg q4w SIR 100 mg q2w Placebo→re-randomized to SIR at Week 24	292 292 294 N=878	Subjects in the placebo group who met EE criteria at Week 18 (i.e., had <20% improvement from baseline in both swollen and tender joint counts) were re-randomized to receive blinded SIR 50 mg q4w or SIR 100 mg q2w. At Week 24, all patients on placebo were re-randomized to SIR 50 mg q4w or SIR 100 mg q2wk. At or any time after Week **24**, subjects in all treatment groups who had <20% improvement from baseline in both swollen and tender joint counts could adjust or initiate DMARDs and/or oral corticosteroids from Week 24 onwards.	ACR20 at wk 16 Key secondary: HAQ-DI at wk 24 ACR50 at wk 24 DAS28CRP<2.6 at wk 24	52 (52)
ARA3005 [SIRROUND H] 102 sites in 16 countries (4/14-10/15)	Phase 3, R, DB, MC	Biologic-naïve and intolerant to MTX, inappropriate for treatment with MTX, or MTX-IR Active RA with CRP≥10mg/L or ESR≥28mm/hr (none)	SIR 50 mg q4w SIR 100 mg q2w Adalimumab 40 q2w	186 187 186 N=559	Escape starting at week 16 (<20% improvement from baseline in both SJC and TJC); subjects on adalimumab 40 q2w would change to q1w dosing, subjects on sirukumab 50 q4w would change to 100 q2w dosing, and subjects on 100 q2w, stayed on this dose. Subjects with <5% improvement from baseline in both SJC and TJC could have discontinued study agent, at the investigator's discretion.	DAS28-ESR at wk 24 ACR50 at wk 24	52 (24)

ARA3001 [SIRROUND M] 21 sites in Japan (10/12-3/15)	Phase 3, R, DB	MTX or SSZ-IR (none)	SIR 50 mg q4w SIR 100 mg q2w	61 61 N=122	At or any time after Week 24, patients who met criteria (<20% improvement from baseline in both swollen and tender joint counts) could initiate DMARDs at the investigator's discretion. At or any time after Week 16, patients who met the same criteria could initiate corticosteroids.	Safety in Japanese patients	52^ (52)
Long term safety study							
ARA3004 [SIRROUND LTE] 246 centers	PG, blinded followed by OL, long-term study Subjects who complete Week 104 of ARA3002 or Week 52 of ARA3003	DMARD or anti-TNF-IR For patients from ARA3002 (after 104 weeks) or ARA3003 (after 52 weeks)	SIR 50 mg q4w SIR 100 mg q2w	N=1697			156 weeks for patients from ARA3002 and 208 weeks for patients from ARA3003
Phase 2							
C1377T04 Part A: Poland, US Part B: Hungary, Japan, Mexico, Poland, Russia, South Korea, US (7/08-3/11)	Phase 2, R, DB, PC No escape	MTX-IR (MTX)	Part A: SIR 100mg q2w Placebo Part B: SIR 100 mg q2w SIR 100 mg q4w SIR 50 mg q4w SIR 25 mg q4w Placebo	 17 19 N=36 30 30 30 31 30 N=151	Part A: After 12 weeks, patients crossed over and received other therapy Part B: Placebo administered through Week 10, followed by SIR beginning at Week 12	Part A: ACR50 at wk 12 Part B: ACR50 at wk 12	Part A: 24 weeks Part B: 24 weeks

Abbreviations: SC=subcutaneous; wks=weeks; US=United States: DMARD=disease modifying antirheumatic drug; MTX=methotrexate; SSZ=sulfasalazine; IR=inadequate response; RA=rheumatoid arthritis: CCP=cyclic citrullinated peptide; RF=rheumatoid factor; CRP=c-reactive protein; HCQ=hydroxychloroquine; CQ=chloroquine; SIR=sirukumab; ACR=American College of Rheumatology; HAQ-DI=health assessment questionnaire –disability index; vdH-S=van der Heijde-modified Sharpe score; DAS28-CRP=disease activity score=28; DBL=database lock; ESR=erythrocyte sedimentation rate; q2w=every 2 weeks; q4w=every 4 weeks; PG=parallel group; OL=open label; R=randomized; DB=double blind; PC=placebo controlled; SJC=swollen joint count; TJC=tender joint count

*Includes 104 weeks of treatment with study agent + 16 weeks of safety follow-up

^Includes 52 weeks of treatment with study agent + 16 weeks of safety follow-up

Table 5: Summary of Phase 1 Studies in RA and Phase 1, 2, and 3 Studies in Other Indications

Protocol (Dates)	Overview	Patient Population	Treatment Arms (SC unless otherwise noted)	N per Arm
Phase 1 studies in RA				
C0136T01	Phase 1, SAD study	Healthy subjects	All doses IV: CNTO136 0.3 mg/kg CNTO136 1 mg/kg CNTO136 3 mg/kg CNTO136 6 mg/kg CNTO136 6 mg/kg (female) CNTO136 10 mg/kg Placebo	 6 6 6 6 6 4 11 N=45
CNTO136NAP1001	PK bridging study in Japanese and Caucasians; single dose administration	Healthy subjects	SIR 25 mg SIR 50 mg SIR 100 mg PBO	16 16 8 13 N=62
CNTO136NAP1003	Bioavailability and PK comparability; single dose administration	Healthy subjects	SIR 100 mg IV SIR 50 mg (PFS) SIR 50 mg (AI) SIR 100 mg (PFS) SIR 100 mg (AI)	19 19 19 44 43 N=144
CNTO136ARA1001	Drug-drug interaction of sirukumab with CYP substrates; single dose administration	RA patients, MTX or SSZ-IR	SIR 300 mg	12
Other indications				
Phase 1				
C0136T03	Safety and PK of multiple ascending doses (Part A 6 weeks; Part B 6 weeks)	CLE (Part A) SLE (Part B)	All doses IV **Part A** CNTO136 1 mg/kg q2w CNTO136 4 mg/kg q2w CNTO136 10 mg/kg q2w Placebo q2w **Part B** CNT0136 10 mg/kg q2w Placebo	 7 8 8 8 10 5 N=46
Phase 2				
CNTO136LUN2001	R, DB, PC, POC study; 24 weeks	Lupus nephritis (class III or IV)	All doses IV CNTO136 10 mg/kg q4w Placebo q4w	 21 4

Abbreviations: SAD=single ascending dose; R=randomized; DB=double blind; PC=placebo controlled; POC=proof of concept; IV=intravenous; SC=subcutaneous; PFS=prefilled syringe; AI=autoinjector; RA=rheumatoid arthritis; MTX=methotrexate; SSZ=sulfasalazine; IR=inadequate response; q2w=every 2 weeks; q4w=every 4 weeks; CLE=cutaneous lupus erythematosus; SLE=systemic lupus erythematosus

Other ongoing or planned studies: GSK201677 (giant cell arteritis); GSK205012 (polymyalgia rheumatic); CNTO136MDD2001 (major depressive disorder)

6.2 Dose selection

Dose selection background

As background, the selection of nominal dose(s) and dosing regimen(s) is a fundamental component of drug product development. The Agency's expectation is that there will be adequate dose-ranging in the clinical development program. This is especially important in RA, where many drug products intended to treat RA have the potential to cause serious dose-related adverse reactions, such as lipid elevations and infections. Further, it is an important

consideration when optimizing the risk/benefit profile in a setting where there are multiple therapeutic options available to patients.

The dose or doses and dosing frequency of drugs for phase 3 studies should be selected based on pharmacokinetic, phamacodynamic, efficacy and safety considerations and from earlier phase dose-ranging studies and should include a wide range of doses and dosing regimens. The endpoint used in dose-ranging studies should be consistent with or known to be predictive of the efficacy endpoint that will be used in phase 3 studies. For studies in rheumatoid arthritis, it is anticipated that the endpoints will focus on signs and symptoms of disease, such as ACR20 or DAS28. Continuous variables may be more sensitive to change in dose-ranging studies. In addition, the dose-ranging studies should evaluate for dose-related safety considerations, such as laboratory changes, which will be incorporated into the benefit-risk assessment for dose selection.

Dose selection in current application

In the current application, the proposed recommended dose is 50 mg q4w. In the phase 3 program, doses of 50 mg q4w and 100 mg q2w were evaluated.

Janssen selected the phase 3 doses of sirukumab based on safety and efficacy data from phase 2 study C1377T04. This study was a multicenter, randomized, double-blind, parallel-group, placebo controlled study in patients with active RA despite MTX therapy. The study was conducted in two parts: Part A (proof-of-concept) and Part B (dose-finding). All patients were to remain on a stable dose of background MTX. Part A consisted of two treatment groups: placebo and sirukumab 100 mg q2w. At the Week 0 visit, patients were randomized into 1 of the 2 treatment groups in a 1:1 ratio. Patients received sirukumab 100 mg or placebo SC injections q2w through Week 10. At Week 12, patients randomized to sirukumab were to receive placebo and patients randomized to placebo were to receive sirukumab 100 mg SC q2w through Week 22. The main endpoint in Part A was the change from baseline in DAS28(CRP) at Week 12. In Part A, a total of 36 patients were randomized to placebo (n=19) or sirukumab (n=17). Based on a sponsor audit at study site 1004, the data integrity of the data at this site was questionable. The data collected at this site was excluded from the efficacy, PK, and PD analyses.

Part B was initiated after safety and efficacy was demonstrated at the Week 12 interim analysis in Part A. Part B consisted of five treatment groups (placebo or sirukumab 25mg q4w, 50mg q4w, 100mg q4w, 100 mg q2w). At Week 12, patients randomized to the placebo group received sirukumab 100 mg SC q2w through Week 24. Patients in the sirukumab treatment arms received treatment through Week 24. A second interim analysis was conducted after approximately 10 patients in each of the 25 mg q4w and 50 mg q4w groups reached Week 2 to assess the degree of serum C-reactive protein suppression. The primary endpoint of the study was the American College of Rheumatology (ACR) 50 response at Week 12 in Part B.

In Part A, there was a significantly greater average improvement (negative change from baseline) in DAS28(CRP) with sirukumab (-2.1) compared to placebo (-0.62) ($P<0.001$).

Similarly, a greater proportion of patients achieved ACR20 response at Week 12 in the sirukumab group (71%) compared with the placebo group (18%) (P<0.05).

In Part B, a total of 151 patients were randomized to placebo (n=30) or sirukumab 25 mg q4w (n=31), 50 mg q4w (n=30), 100 mg q4w (n=30), and sirukumab 100 mg q2w (n=30). A significantly greater average improvement in DAS28(CRP) was observed in each of the sirukumab groups compared with placebo (Table 6). A higher proportion of patients achieved ACR50 responses at Week 12 in each of the 4 sirukumab treatment groups (sirukumab 25 mg q4w, 19%; 50 mg q4w, 27%; 100 mg q4w, 23%; 100 mg q2w, 27%) compared with the placebo group (3%). This difference was statistically significant for the 100 mg q2w and the 50 mg q4w treatment groups.

Table 6: Percentage of patients with ACR20, ACR50, and ACR70 responses at Week 12 in C1377T04 Part B

	Placebo (N=30)	SIR 25 Q4W (N=31)	SIR 50 Q4W (N=30)	SIR 100 Q4W (N=30)	SIR 100 Q2W (N=30)
ACR20, n (%)	9 (30)	19 (61)	17 (57)	18 (60)	19 (63)
p-value	--	0.021	0.067	0.037	0.019
ACR50, n (%)	1 (3)	6 (19)	8 (27)	7 (23)	8 (27)
p-value	--	0.104	0.026	0.052	0.026
ACR70, n (%)	0	1 (3)	2 (7)	1 (3)	5 (17)
p-value	--	1	0.49	1	0.052
ΔDAS28(CRP), mean ± SD	-1.07 ± 0.98	-1.96 ± 0.95	-2.20 ± 0.86	-2.01 ± 0.88	-2.2 ± 1.20
p-value	--	<0.001	<0.001	<0.001	<0.001

Abbreviations: SIR=sirukumab; ACR=American College of Rheumatology; DAS28=disease activity index score 28; CRP=C-reactive protein; SD=standard deviation; q2w=every 2 weeks; q4w=every 4 weeks
Source: C1377t04 study report, Table 10, page 88, submitted 9/22/16

The time-profiles of DAS28(CRP) and Clinical Disease Activity Index (CDAI) are shown in Figure 3. There is no clear dose-response relationships observed for either DAS28(CRP) or the Clinical Disease Activity Index (CDAI)[7] up to Week 12. In contrast, there was some dose separation between the highest dose group (100 mg q2w) and the lower doses (25 mg q4w, 50 mg q4w, and 100 mg q4w) from Weeks 16 to 24. The time-profiles of change from baseline in DAS28(CRP) and Clinical Disease Activity Index (CDAI) are shown in the Appendix (Figure 15). This shows that there was some dose separation between 25 mg q4w and the higher doses (50 mg q4w, 100 mg q4w and 100 mg q2w) from Weeks 16 to 24.

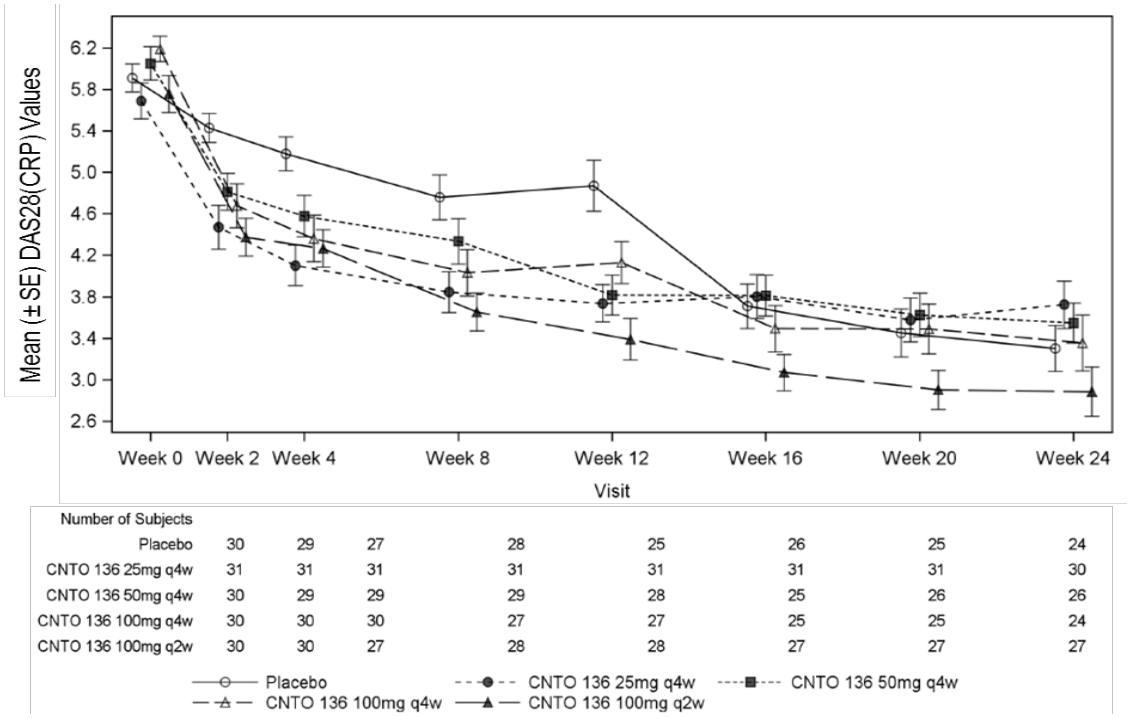
Based on these data, Janssen concluded at least 16 weeks are needed to achieve optimum clinical response and this was the time point most suitable for assessing for dose-response.

Similarly, Janssen compared ACR20, 50, and 70 responses at Weeks 12 and 24 (Figure 4). While efficacy responses were fairly similar at Week 12, there was a suggestion of a slight dose-response for these endpoints at Week 24. Overall, it should be noted that all dose groups showed higher response for all endpoints compared to placebo at Week 12. Similar

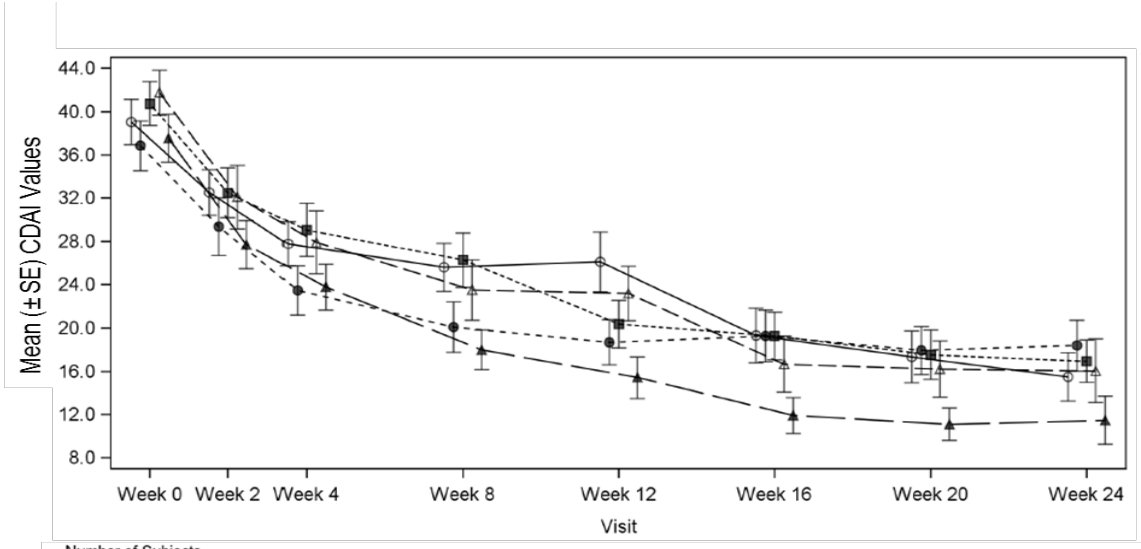
[7] CDAI is a clinical composite index that consists of swollen joint count (out of 28 joints), tender joint count (out of 28 joints), patient global disease activity, and physician global disease activity.

comparison beyond Week 12 was not possible as the placebo group was switched to active treatment after Week 12.

Figure 3: DAS28(CRP) and CDAI Scores by Visit through Week 24 Excluding Data After Treatment Termination in Study C1377T04 Part B



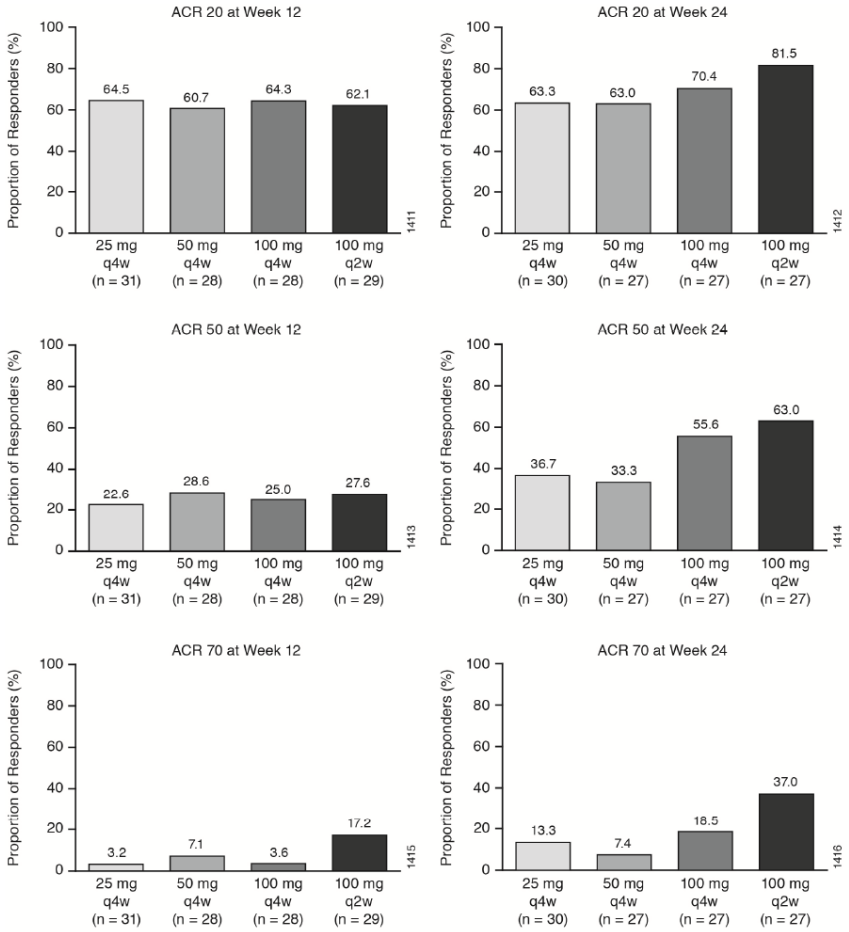
Number of Subjects								
Placebo	30	29	27	28	25	26	25	24
CNTO 136 25mg q4w	31	31	31	31	31	31	31	30
CNTO 136 50mg q4w	30	29	29	29	28	25	26	26
CNTO 136 100mg q4w	30	30	30	27	27	25	25	24
CNTO 136 100mg q2w	30	30	27	28	28	27	27	27



Number of Subjects								
Placebo	30	29	28	28	25	26	25	24
CNTO 136 25mg q4w	31	31	31	31	31	31	31	30
CNTO 136 50mg q4w	30	29	29	29	28	25	26	26
CNTO 136 100mg q4w	30	30	30	27	27	25	25	24
CNTO 136 100mg q2w	30	30	28	28	28	27	27	27

Abbreviations: DAS28 (CRP)=Disease activity index score 28 using C-reactive protein; CDAI=clinical disease activity index; SE= standard error;q2/q2w=every two weeks; q4/q4w=every four weeks
The DAS28 (CRP) values were based on observed data excluding data collected after treatment termination.
The CDAI scores were based on observed data excluding data collected after treatment termination.
Subjects in placebo group crossed over to sirukumab 100 mg q2w group at Week 12.
Source: Response to IR, Figure: GEFDAS01T04A & GEFCDA01T04A, page 17 and 21, submitted 7/6/17

Figure 4: Proportion of Patients Who Achieved ACR20 (Upper Panels), ACR50 (Middle Panels), or ACR70 (Lower Panels) at Weeks 12 and 24 (C1377T04 Part B)



Abbreviations: ACR=American College of Rheumatology; q2/q2w=every two weeks; q4/q4w=every four weeks
Source: Response to Midcycle Communication, Figure 5, page 18, submitted 4/5/17

Various biomarkers were evaluated to support the dose selection. As seen in Table 7, the percent change in CRP at Week 12 was fairly similar for sirukumab 100 mg q2w, 100 mg q4w, and 50 mg q4w, but was less for 25 mg q4w. There is a trend for dose-response for these biomarkers (CRP, SAA, SAP and MMP3). However, all treatment groups showed larger decrease in biomarker levels compared to placebo.

As shown in Table 8, there was no clear dose-ordering in terms of decreases in neutrophil count with increasing doses of sirukumab, however there were greater decreases in neutrophil counts with 100 mg q2w compared to 25 mg q4w. Similarly there was no clear dose response seen between treatment groups in phase 2 study for liver enzymes (ALT/AST), and platelets.

Table 7: Dose-response in Week 12 Changes in CRP and other biomarkers in C1377T04 Part B

Analyte[1]	Placebo	SIR 25 Q4W	SIR 50 Q4W	SIR 100 Q4W	SIR 100 Q2W
CRP	6	-95.4	-98.8	-97.9	-98.4
SAA	-6.7	-87.2	-95.1	-92.7	-92.5
SAP	-16.2	-59.4	-67.3	-68.4	-68.6
MMP3	-11.2	-89.9	-96.1	-96.3	-93.8

Abbreviations: SIR=sirukumab; CRP=C-reactive protein; SAA=serum amyloid A; SAP=Serum amyloid P-component; MMP3=Matrix metalloproteinase-3; q2w=every 2 weeks; q4w=every 4 weeks
1. The % change from baseline to week 12 in serum levels of indicated analyte reported as the geometric mean for the indicated treatment group. Percent changes from baseline were calculated from the LSMean ± standard error for within-subject log2 ratio of week 12/baseline values.
Source: Response to Midcycle Communication, Table 2, page 21, submitted 4/5/17

Table 8: Mean Change from Baseline to Week 12 in Lab Values (C1377T04)

	PBO N=49	SIR 25mg q4w N=31	SIR 50mg q4w N=30	SIR 100 mg q4w N=30	SIR 100 mg q2w N=47
Mean change from baseline at Week 12					
Neutrophil count (x10^3/uL) ± SD, (N)	-0.6 ± 2.2 (N=42)	-2.1 ± 1.7 (N= 29)	-2.6 ± 1.3 (N=24)	-2.3 ± 3.4 (N=26)	-2.8 ± 2.3 (N=43)
Platelet count (x10^3/uL) ± SD, (N)	-4.4 ± 67.8 (N=43)	-106.4 ± 51.3 (N=30)	-102.3 ± 38.0 (N=27)	-109.1 ± 81.7 (N=26)	-115.3 ± 67.0 (N=44)
Hemoglobin (g/dL) ± SD, (N)	-0.2 ± 0.7 (N= 44)	0.5 ± 0.8 (N=30)	0.8 ± 0.8 (N=27)	1.2 ± 1.8 (N=27)	0.9 ± 1.0 (N=44)
Leukocyte Count (x10^3/uL) ± SD, (N)	-0.2 ± 2.3 (N= 44)	-1.9 ± 1.7 (N=30)	-2.9 ± 1.5 (N=27)	-2.1 ± 3.9 (N=27)	-2.8 ± 2.3 (N=44)
AST (IU/L) ± SD, (N)	-0.3 ± 11.8 (N=44)	13.2 ± 29.0 (N=30)	6.0 ± 15.4 (N=28)	4.8 ± 19.3 (N=27)	5.3 ± 16.5 (N=44)
ALT (IU/L) ± SD, (N)	-4.0 ± 16.0 (N=44)	16.9 ± 16.8 (N=30)	14.3 ± 30.0 (N=28)	10.6 ± 24.6 (N=27)	13.5 ± 30.8 (N=44)

Abbreviations: AST=aspartate aminotransferase; ALT=alanine aminotransferase; PBO=placebo; SIR=sirukumab, SD= Standard deviation, N= Number of subjects; q2w=every 2 weeks; q4w=every 4 weeks
Source: IR Response, Tables 31 to 37, page 115 to 118, submitted 5/26/17

A discussion point for this Advisory Committee meeting is whether Janssen's selection of 50 mg q4w and 100 mg q2w for evaluation in phase 3 was reasonable in light of the safety profile observed in the phase 3 studies.

6.3 Phase 3 trial designs

The primary evidence of efficacy is from trials ARA3002 and ARA3003. Both were double-blind, placebo-controlled studies in patients with moderately to severely active RA.

Both studies enrolled adults with active RA. Patients in ARA3002 had an inadequate response to DMARD therapy (that included MTX or SSZ), while patients in ARA3003 had an inadequate response to 1 or more anti-TNF agents or intolerance to 2 or more anti-TNF agents. In ARA3002, patients had at least 6 tender and 6 swollen joints, compared to at least 4 tender and 4 swollen joints in ARA3003. In both studies, patients had a CRP ≥8mg/L at screening and at baseline. Study drug was administered in a pre-filled syringe in both studies.

In ARA3002, the co-primary endpoints were ACR20 response rate at Week 16 and change from baseline in vdH-S score at Week 52. In ARA3003, the primary efficacy endpoint was the

ACR20 response rate at Week 16. The length of placebo control was different in the two studies (52 weeks for ARA3002 and 24 weeks for ARA3003). In addition, radiographs were assessed in ARA3002 and not assessed in ARA3003.

ARA3002 Design

ARA3002 was a randomized, double-blind, parallel-group, placebo-controlled trial to assess the efficacy and safety of sirukumab, in patients with moderately to severely active RA. The study included a 52-week placebo-controlled period, followed by a 52-week uncontrolled period. Patients were randomly assigned to receive either placebo, sirukumab 100 mg q2w, or sirukumab 50 mg q4w in a ratio of 1:1:1. Randomization was stratified by MTX use at baseline (0, >0-12.5mg/week, ≥12.5mg/week). Patients could continue stable concomitant DMARDs, including MTX, SSZ, HCQ, CQ, or bucillamine.

The enrolled patients were adults with RA and an inadequate response to DMARD therapy that included MTX or SSZ. Patients were excluded if they had a history of intolerance to at least two or inadequate response to at least one anti-TNFα agent after 3 months of therapy. In addition, patients were excluded if they had a history of intolerance or inadequate response to tocilizumab. Patients had at least 6 (of 68) tender joints and 6 (of 66) swollen joints at screening and at baseline, a CRP ≥8 mg/L, and must have met one of the following three criteria: (a) anti-cyclic citrullinated peptide (CCP) antibody-positive at screening, (b) rheumatoid factor (RF)-positive at screening, or (c) documented history of radiographic evidence of erosive RA in hands or feet.

The trial was placebo-controlled for 52 weeks, with opportunities for subjects in the placebo group to be re-randomized in a 1:1 ratio to sirukumab 100 mg q2w or sirukumab 50 mg q4w starting from Week 18 if the subjects met early escape (EE) criteria (i.e., had <20% improvement from baseline in both swollen and tender joint counts at Week 18) or starting from Week 40 if the subjects met late escape (LE) criteria (i.e., did not meet EE criteria at Week 18 and had <20% improvement from baseline in both swollen and tender joint counts at Week 40). At Week 28, subjects in all treatment groups who had <20% improvement from baseline in both swollen and tender joint counts were considered as meeting criteria for adjusting or initiating DMARDs and/or oral corticosteroids from Week 28 onwards. At Week 52, all remaining subjects on placebo crossed over and were re-randomized in a 1:1 ratio to sirukumab 100 mg q2w or sirukumab 50 mg q4w from Week 52 through Week 104. At Week 52, or any time after Week 52, all subjects could adjust or initiate DMARDs and/or oral corticosteroids.

The co-primary endpoints were ACR20 response rate at Week 16 and change from baseline in vdH-S score at Week 52. The major secondary endpoints were change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 24, the proportion of patients who achieved an ACR50 response at Week 24, the proportion of patients who achieved a DAS28(CRP)<2.6 at Week 24, and major clinical response by Week 52.

Radiographic assessments were made at baseline, Week 18 (if patients met EE criteria) or Week 24 (if patients did not meet EE criteria), and Week 52. Patients who discontinued

treatment had a radiographic assessment within four weeks following discontinuation provided a radiographic assessment had not been made in the six weeks prior to treatment discontinuation.

Considerations related to 12-month placebo-controlled period of study ARA3002

An issue discussed during the review cycle for this application was the appropriateness of a 12-month placebo-controlled study. The goal of treatment of RA is early and aggressive treatment of disease targeting low disease activity or remission.[8] Given the desire to target low disease activity, the appropriate length of placebo control has been discussed by various stakeholders. In 2010, the American College of Rheumatology organized a conference regarding RA clinical trials. The conference summary recommended that placebo exposure should be kept to a minimum and early rescue therapy should be provided (in most cases at the 12-16 week time point or sooner).[9] Subsequently, the FDA updated the Guidance for Developing Products for the Treatment of RA[10] in 2013 to state that studies longer than 12 weeks should include an active comparator as the control or provisions for escape therapy to rescue treatment for patients with active disease.

Given these considerations, the Division asked Janssen to justify that the patients who remained on placebo for 52 weeks in the study were provided treatment appropriate and consistent with the severity of their disease and acceptable at the time the study was done. Janssen cited the availability of formal rescue treatment opportunities and the option to withdraw and receive alternative treatment outside of the study. Similarly, Janssen noted that the study design was acceptable to health authorities, including FDA and other National Health Authorities, institutional review boards, and ethics committees.

We ask the AC panel to discuss optimal study design for assessment of radiographic progression in rheumatoid arthritis.

ARA3003 Design

ARA3003 was a randomized, double-blind, parallel-group, placebo-controlled trial to assess the efficacy and safety of sirukumab, administered with concomitant MTX, in patients with moderately to severely active RA. The study included a 24-week placebo-controlled period, followed by a 28-week uncontrolled period and a 16-week safety follow-up period. Janssen submitted the 52-week study report. Patients were randomly assigned to receive either placebo, sirukumab 100 mg q2w, or sirukumab 50 mg q4w in a ratio of 1:1:1. Randomization was stratified by MTX use at baseline (0, >0-12.5mg/week, ≥12.5mg/week).

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[8] Singh JA, et al. 2012 Update of the 2008 American College of Rheumatology (ACR) Recommendations for the use of Disease-Modifying Anti-Rheumatic Drugs and Biologics in the treatment of Rheumatoid Arthritis (RA). *Arthritis Care Res (Hoboken).* 2012;64(5):625-639.

[9] Conference Summary: American College of Rheumatology Clinical Trials Priorities and Design Conference, July 22-23, 2010. *Arthritis Rheum.* 2011;63(8): 2151-6.

[10] Draft Guidance for Industry Rheumatoid Arthritis: Developing Drug Products for Treatment, https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm354468.pdf, accessed 6/16/17

The enrolled patients were adults with RA and an inadequate response to one or more anti-TNF agents or intolerance to two or more anti-TNF agents. Patients had at least four (of 68) tender joints and four (of 66) swollen joints and a CRP ≥8mg/L at screening and at baseline, and met one of the following three criteria: (a) anti-CCP antibody positive at screening, (b) RF positive at screening, or c) documented history of radiographic evidence of erosive RA in hands or feet prior to the first administration of study agent. Study drug was administered in a pre-filled syringe.

The trial was placebo-controlled for 24 weeks. Patients in the placebo group who met EE criteria at Week 18 (i.e., had <20% improvement from baseline in both swollen and tender joint counts) were re-randomized to receive blinded sirukumab 50 mg q4w or sirukumab 100 mg q2w. At Week 24, all patients on placebo were re-randomized to sirukumab 50 mg q4w or sirukumab 100 mg q2w. At or any time after Week 24, patients in all treatment groups who had <20% improvement from baseline in both swollen and tender joint counts could adjust or initiate DMARDs and/or oral corticosteroids.

The primary efficacy endpoint was the ACR20 response rate at Week 16. The major secondary endpoints were change from baseline in HAQ-DI score at Week 24, ACR50 response at Week 24, and DAS28(CRP) <2.6 at Week 24.

ARA3005 Design

Additional supportive evidence of efficacy and safety were provided from trial CNTO136ARA3005 (ARA3005), in which sirukumab was compared to an active comparator. ARA3005 was a randomized, double-blind, parallel-group, active-controlled trial. All patients were on monotherapy. The planned duration is 52 weeks, and 24 weeks of data were submitted in the BLA. There were 559 patients randomized to adalimumab 40 mg SC q2w, sirukumab 100 mg q2w, or sirukumab 50 mg q4w. Randomization was stratified by two groups based on the reason for which subjects failed MTX, either for efficacy alone or for any safety/tolerability reason. At Week 16, subjects in all treatment groups who had <20% improvement from baseline in both swollen and tender joint counts qualified for EE. When escape criteria was met, patients on adalimumab 40 mg q2w up-titrated to qw dosing, patients on sirukumab 50 mg q4w were switched to 100 mg q2w dosing, and patients already on 100 mg q2w remained on the same regimen. The co-primary endpoints were change from baseline in DAS28(ESR) at Week 24 and the proportion of patients with an ACR50 response at Week 24. Major secondary endpoints were the proportion of patients with DAS28(ESR)<2.6 at Week 24 and the proportion of patients with an ACR20 response at Week 24.

To be eligible for this trial, patients had to be at least 18 years of age, have moderately to severely active RA with at least eight of 68 tender joints and six of 66 swollen joints at screening and at baseline, a CRP ≥10.00 mg/L or ESR ≥28mm/hr at screening, and be considered intolerant to MTX, inappropriate for treatment with MTX (including MTX-naïve subjects for whom it is inappropriate to administer MTX), and/or inadequate responders to MTX. Patients with inadequate response to MTX must have had at least 12 weeks of MTX treatment. Additionally, it was recommended that patients should have been exposed to a dose of MTX of at least 15 mg per week to be considered inadequate responders.

Brief Description of Efficacy Endpoints

- *ACR Response Rates*

In 1995, the American College of Rheumatology (ACR) published a definition of improvement for clinical trials in RA, which has since been used in drug development trials to demonstrate evidence of efficacy for signs and symptoms of RA.[11] The ACR20 response is calculated as a >20% improvement in:

- tender joint count (of 68 joints) and
- swollen joint count (of 66 joints) and
- 3 of the 5 remaining ACR core set measures
    - Patient Global Assessment of Arthritis on a 0 – 10 unit visual analog scale (VAS)
    - Physician Global Assessment of Arthritis on a 0 – 10 unit VAS
    - Patient Assessment of Pain on a 0 – 10 unit VAS
    - Patient Assessment of Physical Function (e.g. Health Assessment Questionnaire)
    - Acute Phase Reactant (ESR or CRP)

Fifty percent and 70 percent improvement (ACR50 and ACR70) are similarly calculated using these higher levels of improvement.

- *Health Assessment Questionnaire-Disability Index (HAQ-DI)*

The Agency has historically recognized a distinct claim in RA for "improvement in physical function" based on outcome measures such as the HAQ-DI.[12] This instrument assesses a patient's level of functional ability and includes questions pertaining to fine movements of the upper extremity, locomotor activities of the lower extremities, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning which represent a comprehensive set of functional activities: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. Patients respond on a four-level difficulty scale ranging from zero (no difficulty) to three (unable to do). The eight category scores are

[11] Felson DT, et al. *Arthritis Rheum.* 1995. June, 38(6):727-735.
[12] Bruce B and Fries JF. The Health Assessment Questionnaire (HAQ). *Clin Exp Rheumatol.* 2005; 23 (Suppl 39):S14-S18.

averaged into an overall HAQ-DI score on a scale from zero (no disability) to three (completely disabled). Some investigators have suggested that the minimal clinically important difference in the HAQ-DI score is 0.22 units.[13]

- *Disease Activity Score (DAS)-28*

The DAS28 is a composite index of RA disease activity which incorporates the number of tender and swollen joints (out of 28 possible), a patient global assessment of disease activity (0-100 mm visual analog scale), and ESR results.[14] An alternative equation is available for use with CRP results. These variables are summed and weighted mathematically into a single numerical value ranging from 0 to 10. Comparing the DAS28 and the ACR response criteria, beyond the differences in number of maximum tender or swollen joints counted (e.g. DAS28 does not include the joints of the feet), additional variables of physician global assessment, patient pain, and HAQ-DI score are incorporated into the ACR response criteria. The DAS28 has additional utility in measuring the level of disease activity at a given time point, whereas the ACR response criteria are calculated as improvement in the variables over a set period of time. A DAS28 score >5.1 is indicative of high disease activity, and <3.2 of low disease activity. A score of <2.6 has been used to describe an even lower threshold of disease activity.

- *Radiographic Outcome: van der Heijde modified Sharp Score (vdH-S)*

The van der Heijde-modified Sharp radiographic scoring method grades the presence of erosions in the joints of the hands and feet, and the presence of joint space narrowing (JSN) in the hands, wrists, and feet.[15] The scores for each feature for the individual joints are summed. Erosions are assessed at 16 locations in each hand and wrists and 12 locations in each foot, using a 6-point scale from 0 to 5. Scores are derived based on the number and size of discrete erosions in each location, but are summed to a maximum of 5. Thus, the maximum erosion score for the hands/wrists is 160, and the maximum erosion score for the feet is 120, for a maximum total erosion score of 280. JSN scores are based on 15 locations in each hand and wrist and 6 locations in each foot, scored using a 5-point scale from 0 to 4: 0 = normal; 1 = focal or minimal and generalized narrowing; 2 = generalized narrowing <50%; 3 = generalized narrowing >50% or subluxation; and 4 = ankylosis or complete dislocation. The maximum total JSN for the hands/wrists is 120, and the maximum total JSN for the feet is 48, for a maximum total JSN score of 168. Therefore, the theoretical maximum van der Heijde-modified Sharp Score (vdH-S) is 448, although the actual clinical range in RA drug development trials is typically much lower because a given individual typically only has a fraction of his or her joints affected by radiographically evident damage.

- *Major clinical response*

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[13] Bruce B and Fries JF, *The Stanford Health Assessment Questionnaire: Dimensions and Practical Applications.* Health Qual Life Outcomes. 2003;1:20.

[14] Fransen J and van Riel PLCM. The Disease Activity Score and the EULAR Response Criteria. *Clin Exp Rheumatol.* 2005; 23 (Suppl 39): S93-S99.

[15] van der Heijde DM, et al. Biannual radiographic assessments of hands and feet in a three-year prospective follow-up of patients with early rheumatoid arthritis. *Arthritis Rheum.* 1992;35(1):26-34.

A major clinical response is defined as the event of maintaining an improvement as assessed by the ACR70 at all visits over at least 24 consecutive weeks during a 52-week period.

- *SF-36*

The medical outcome short form health survey (SF-36) is an instrument used to measure health-related quality of life or general health status. It consists of eight subscales that are scored individually: physical functioning (10 items), role-physical (four items), bodily pain (two items), general health (five items), vitality (four items), social functioning (two items), role-emotional (three items), and mental health (five items). Two summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS), also can be computed.

Statistical considerations

Studies ARA3002, ARA3003, and ARA3005 were designed as superiority studies with control of the overall Type 1 error probability at the two-sided 5% level. The multiplicity procedures to control the overall Type 1 error probability across the multiple dose and endpoint comparisons in each study are shown in the Appendix in Figure 16, Figure 17, and Figure 18. In Studies ARA3002 and ARA3003, sirukumab 50 mg q4w and sirukumab 100 mg q2w were each compared to the placebo arm. In Study ARA3005, the sirukumab arms were compared to adalimumab 40 mg q2w. Statistical methodologies used for Studies ARA3002, ARA3003, and ARA3005 were generally similar.

The primary analysis of ACR20 at Week 16 was based on a Cochran-Mantel-Haenszel (CMH) test stratified by the randomized stratification factor and carried out in all randomized subjects who received at least one dose of study treatment. Patients were defined to have met treatment failure criteria if they: (1) initiated treatment with DMARDs, systemic immunosuppressives, and/or biologics for RA; (2) initiated treatment with oral corticosteroids for RA, increased the dose of oral corticosteroids for RA above the baseline dose, or received intravenous or intramuscular administration of corticosteroids for RA; or (3) discontinued study treatment agent administration for any reason. Patients who met these criteria or who discontinued the study were considered non-responders. Other binary endpoints were similarly analyzed. For binary endpoints assessed after escape, patients who met escape criteria were considered non-responders.

In Study ARA3002, the co-primary endpoint change in vdH-S score at Week 52 was analyzed using linear regression on van der Waerden normal scores, adjusting for categorical MTX use. Linear extrapolation based on all observed data collected (typically, at baseline and Week 18) was used to impute a Week 52 score in placebo patients who early escaped and in patients from all arms with missing Week 52 data. The baseline score was carried forward to Week 52 if no post-baseline radiographic data were collected. Scoring of all radiographs was done by two separate central blinded assessors, and these scores were averaged in analyses.

Because of concerns with the reliability of the linear extrapolation approach (which were conveyed during IND development), we considered several supportive analyses of radiographic progression to be important. In particular, we find merit in the following analyses: (1) linear regression analysis of Week 52 change according to randomized treatment group based on all observed data, regardless of escape or treatment discontinuation; (2) linear regression analysis of Week 18/24 change according to randomized treatment group based on all observed data, regardless of escape or treatment discontinuation; and (3) mixed effects model analysis of rate of change over 52 weeks according to randomized treatment group, excluding data collected after escape on the placebo arm. See the Appendix for additional discussion about statistical considerations in the evaluation of radiographic progression.

The analysis of continuous non-radiographic endpoints was based on a linear regression, adjusting for baseline value of the endpoint and the randomization stratification factor. In the applicant's analyses, last observation carried forward (LOCF) was used to impute missing values and values after a patient met escape criteria. Because of concerns about this approach, we carried out and considered important additional analyses evaluating treatment effects at Week 16, prior to the first time point of escape. Results at Week 16 are presented in this briefing document.

To evaluate the potential effect of violations in missing data assumptions on the conclusions, tipping point sensitivity analyses were conducted for key efficacy endpoints. In these analyses, assumptions about the missing outcomes on the treatment arms were systematically varied to identify and discuss the plausibility of those assumptions under which there was no longer evidence of efficacy.

6.4 Patient disposition, demographic, and baseline characteristics

ARA3002

In ARA3002, a total of 1,670 patients were randomized (556 in the placebo group, 557 in the sirukumab 50 mg q4w group, and 557 in the sirukumab 100 mg q2w group). Approximately 84% of patients completed the 52-week study on randomized or escape treatment (Table 9). The proportion of patients who discontinued prior to Week 52 was slightly higher in the placebo group (17%) than the sirukumab 100 mg group (16%) and the sirukumab 50 mg group (14%).

At Week 18, 34% of patients on placebo met EE criteria. At Week 40, an additional 4% of patients randomized to placebo met LE criteria. Of the 556 patients originally randomized to placebo, 49% (n=273) remained on placebo until Week 52. This was notably lower than the proportions of patients randomized to sirukumab 50 mg (86%) and sirukumab 100 mg (84%) who remained on their originally randomized treatment until Week 52.

Baseline demographics and disease characteristics were well balanced among the treatment groups. The majority of patients were female (80%) and white (72%), with a mean age of 53 years and a mean weight of 72 kg. The mean duration of RA was 8.6 years. The patients had

moderately to severely active RA. The mean number of swollen joints was 15.2 and the mean number of tender joints was 24.9. The mean CRP was 2.4 mg/dL. Of the enrolled patients, 81% were positive for rheumatoid factor, and 86% were positive for anti-CCP antibody. The mean baseline DAS28-CRP was 5.9. Nearly all patients (98.5%) had a history of methotrexate use. A total of 35% had previous exposure to biological therapies for RA. At baseline, 92% of patients were taking a DMARD and 88% were taking methotrexate.

Table 9: Patient Disposition in Study ARA3002 During the 52-week Placebo-controlled Period

	Placebo N = 556	SIR 50 q4w N = 557	SIR 100 q2w N = 557
Completed randomized treatment up to Week 16	513 (92%)	530 (95%)	518 (93%)
Qualified for EE[a] at Week 18	187 (34%)	81 (15%)	57 (10%)
Met criteria for adjustment or initiation of DMARDs and/or oral steroids at Week 28	47 (8%)	26 (5%)	33 (6%)
Qualified for LE[b] at Week 40	24 (4%)	18 (3%)	21 (4%)
Completed randomized treatment up to Week 52	273 (49%)	481 (86%)	470 (84%)
Completed randomized or escape treatment up to Week 52	459 (82%)	481 (86%)	470 (84%)
Discontinued[c] prior to Week 52	97 (17%)	76 (14%)	87 (16%)

Cell contents are frequency (percentage of total randomized)
Abbreviations: SIR=sirukumab; EE=early escape; LE=late escape; DMARDs=disease modifying anti-rheumatoid drugs; q2w=every 2 weeks; q4w=every 4 weeks; N=total randomized
[a] Patients on placebo meeting early escape criteria were re-randomized to sirukumab 50 mg or 100 mg, patients on the sirukumab arms remained on their originally assigned treatment
[b] Patients on placebo, who had not met early escape criteria at Week 18, meeting late escape criteria were re-randomized to sirukumab 50 mg or 100 mg, patients on the sirukumab arms remained on their originally assigned treatment
[c] Limited assessments were made in some of these patients who discontinued study treatment (randomized or escape treatment) in the 16 weeks after discontinuation
Source: Statistical Reviewer

ARA3003

In trial ARA3003, a total of 878 patients were randomized (294 in the placebo group, 292 in the sirukumab 50 mg q4w group, and 292 in the sirukumab 100 mg q2w group). Approximately 90% of patients completed the 24-week placebo-controlled period on randomized or escape therapy (Table 10). The proportion of patients who discontinued prior to Week 24 was fairly balanced between groups (14% placebo; 19% sirukumab 50 mg q4w, and 16% sirukumab 100 mg q2w). The proportions of patients discontinuing prior to Week 52 were similar on to the sirukumab 50 mg q4w (30%) and 100 mg q2w (27%) arms.

At Week 18, 184 subjects met EE criteria. The highest proportion of EE was in the placebo group (32%); this was compared with 16% in the sirukumab 50 mg and 15% in the sirukumab 100 mg groups. Approximately 56% of patients in the placebo group remained on originally assigned treatment through Week 24, as compared to 81% and 83% of patients in the sirukumab 50 mg and 100 mg groups, respectively.

Baseline demographics and disease characteristics were well balanced among the treatment groups. The majority of patients were female (81%) and white (75%), with mean age of 55

years and a mean weight of 76 kg. The mean duration of RA was 12 years. The patients had moderately to severely active RA. The mean number of swollen joints was 16.4 and the mean number of tender joints was 28. The mean CRP was 21.5 mg/L. Of the enrolled patients, 77% were positive for rheumatoid factor, and 81% were positive for anti-CCP antibody. The mean baseline DAS28-CRP was 5.88. All patients had previously been treated with anti-TNF therapy and had inadequate response or intolerance. Of all patients, 72% were taking MTX at baseline.

Table 10: Patient Disposition in ARA3003 During the 24-week Placebo-controlled Period

	Placebo N = 294	SIR 50 q4w N = 292	SIR 100 q2w N = 292
Completed randomized treatment up to Week 16	261 (89%)	249 (85%)	252 (86%)
Qualified for EE[a] at Week 18	94 (32%)	46 (16%)	44 (15%)
Completed randomized treatment up to Week 24	166 (56%)	237 (81%)	245 (83%)
Completed randomized or escape treatment up to Week 24	252 (86%)	237 (81%)	245 (83%)
Discontinued[b] prior to Week 24	42 (14%)	55 (19%)	47 (17%)

Cell contents are frequency (percentage of total randomized)
Abbreviations: SIR=sirukumab; EE=early escape; q2w=every 2 weeks; q4w=every 4 weeks; N=total randomized
[a] Patients on placebo meeting early escape criteria were re-randomized to sirukumab 50 mg or 100 mg, patients on the sirukumab arms remained on their originally assigned treatment
[b] Limited assessments were made in some of these patients who discontinued study treatment (randomized or escape treatment) in the 16 weeks after discontinuation
Source: Statistical Reviewer

ARA3005

In ARA3005, a total of 559 patients were randomized (186 in the adalimumab group, 186 in the sirukumab 50 mg q4w group, and 187 in the sirukumab 100 mg q2w group). Approximately 87% of patients completed the 24-week study on randomized or escape treatment (Table 11). The proportion of patients who discontinued prior to Week 24 was lower for adalimumab (10%) than the sirukumab 50 mg and 100 mg arms (16% and 13%, respectively). At Week 16, slightly more patients qualified for early escape on the sirukumab 50 mg arm (9%) compared to the adalimumab arm (7%).

Baseline demographics and disease characteristics were well balanced among the treatment groups. The majority of patients were female (84%) and white (92%), with mean age of 52 years and a mean weight of 75 kg. The patients had moderately to severely active RA. The mean number of swollen joints was 19 and the mean number of tender joints was 32. The mean CRP was 2.0 mg/dL. Of the enrolled patients, 72% were positive for rheumatoid factor, and 76% were positive for anti-CCP antibody. The mean baseline DAS28-CRP was 6.9. All patients were considered intolerant to MTX, and/or inappropriate for treatment with MTX, (including MTX-naïve subjects for whom it is inappropriate to administer MTX) and/or inadequate responders to MTX. Subjects with inadequate response to MTX must have had at least 12 weeks of MTX treatment. Additionally, it was recommended that subjects should have been exposed to a dose of MTX of at least 15 mg per week to be considered inadequate responders. Patients did not receive methotrexate during the trial.

Table 11: Patient Disposition in ARA3005 up to Week 24

	Adalimumab 40 mg q2w N = 186	SIR 50 q4w N = 186	SIR 100 q2w N = 187
Completed randomized treatment up to Week 16	172 (92%)	165 (89%)	168 (90%)
Qualified for EE[a] at Week 16	13 (7%)	17 (9%)	7 (4%)
Completed randomized treatment up to Week 24	155 (83%)	142 (76%)	163 (87%)
Completed randomized or escape treatment up to Week 24	167 (90%)	156 (84%)	163 (87%)
Discontinued study agent prior to Week 24[b]	19 (10%)	30 (16%)	24 (13%)

Cell contents are frequency (percentage of total randomized)
Abbreviations: SIR=sirukumab; EE=early escape; q2w=every 2 weeks; q4w=every 4 weeks; N=total randomized
[a] Patients on adalimumab 40 mg q2w meeting early escape criteria received adalimumab 40 mg qw, patients on the sirukumab 50 mg q4w arm received sirukumab 100 mg q2w, and patients on the sirukumab 100 mg q2w arm remained on their originally assigned treatment
[b] Some of these patients who discontinued study treatment remained in the study up to the Week 24 visit
Source: Statistical Reviewer

6.5 Efficacy findings

The focus of the efficacy review is on the results of the two placebo-controlled phase 3 studies: ARA3002 and ARA3003. Additional discussion of ARA3005 is provided at the end of the efficacy review.

ACR Response Rates

The primary endpoint in both trials was the ACR20 response at Week 16. As shown in Table 12, sirukumab treatment was associated with a higher proportion of ACR responders in both trials at both the 50 mg q4w and 100 mg q2w doses, and the difference was statistically significant compared to placebo. The estimated absolute increases in ACR20 response on sirukumab 50 mg q4w, as compared to placebo, were 28% and 16% in the two studies.

Both the sirukumab 50 mg and 100 mg groups showed greater improvements in each ACR component compared to placebo, with no single component driving the efficacy in terms of ACR20 response (Appendix Table 64 and Table 65). In ARA3002, the two doses of sirukumab had a similar proportion of ACR20 responders, while in ARA3003, the proportion of ACR20 responders was slightly higher for the 100 mg q2w group (45%) compared to the 50 mg q4w group (40%).

In the primary analysis, patients who met treatment failure criteria, discontinued treatment, or were missing data were considered non-responders. The amount of missing data at Week 16 was generally small, ranging from 5–8% and 12–14% across the arms in Studies ARA3002 and ARA3003, respectively. Tipping point sensitivity analyses including all observed data regardless of use of concomitant medications or treatment discontinuation and varying assumptions about the missing data indicated that the findings were convincing

notwithstanding the missing data (see results for the 50 mg dose in Appendix Figure 19 and Figure 20).

Table 12: ACR20 Response Probabilities at Week 16 in ARA3002 and ARA3003

Treatment Group	# Responders (%)	Comparison to Placebo[a]		
		Difference[b]	95% CI[b]	p-value
ARA3002				
Placebo (N=556)	147 (26)	--	--	--
SIR 50 mg q4w (N=557)	305 (55)	28.3	22.8, 33.8	<0.0001
SIR 100 mg q2w (N=557)	298 (54)	27.1	21.6, 32.6	<0.0001
ARA3003				
Placebo (N=294)	71 (24)	--	--	--
SIR 50 mg q4w (N=292)	117 (40)	15.9	8.5, 23.2	<0.0001
SIR 100 mg q2w (N=292)	132 (45)	21.0	13.6, 28.5	<0.0001

Patients who met treatment failure criteria, discontinued treatment, or were missing data were considered non-responders
Abbreviations: ACR=American College of Rheumatology; CI=confidence interval; SIR=sirukumab; q2w=every 2 weeks; q4w=every 4 weeks; N=total randomized
[a] Comparison to placebo based on Cochran-Mantel-Haenszel test, stratified by baseline categorical methotrexate use
[b] Estimated absolute difference in percentage points
Source: Statistical Reviewer

Consistent with the primary endpoint results, the proportions of patients experiencing ACR50 and ACR70 levels of improvement were higher in both sirukumab groups compared to the placebo group (Table 13 and Table 14). In ARA3002, the proportion of patients achieving an ACR50 response at Week 16 was slightly higher for sirukumab 50 mg q4w compared to 100 mg q4w, and ACR50 responses were similar between the two doses in ARA3003. In ARA3002, the proportion of patients achieving an ACR70 response at Week 16 was the same for the two sirukumab dose groups. In ARA3003, the proportion of patients achieving an ACR70 response at Week 16 was slightly higher for sirukumab 100 mg q2w compared to 50 mg q4w.

Table 13: ACR50 Response Probabilities at Week 16 in ARA3002 and ARA3003

Treatment Group	# Responders (%)	Comparison to Placebo[a]		
		Difference[b]	95% CI[b]	p-value
ARA3002				
Placebo (N=556)	60 (11)	--	--	--
SIR 50 mg q4w (N=557)	167 (30)	19.2	14.6, 23.8	<0.0001
SIR 100 mg q2w (N=557)	146 (26)	15.4	11.0, 19.9	<0.0001
ARA3003				
Placebo (N=294)	27 (9)	--	--	--
SIR 50 mg q4w (N=292)	60 (21)	11.4	5.7, 17.0	<0.0001
SIR 100 mg q2w (N=292)	63 (22)	12.4	6.7, 18.1	<0.0001

Patients who met treatment failure criteria, discontinued treatment, or were missing data were considered non-responders
Abbreviations: ACR=American College of Rheumatology; CI=confidence interval; SIR=sirukumab; q2w=every 2 weeks; q4w=every 4 weeks; N=total randomized
[a] Comparison to placebo based on Cochran-Mantel-Haenszel test, stratified by baseline categorical methotrexate use
[b] Estimated absolute difference in percentage points
Source: Statistical Reviewer

Table 14: ACR70 Response Probabilities at Week 16 in ARA3002 and ARA3003

Treatment Group	# Responders (%)	Comparison to Placebo[a]		
		Difference[b]	95% CI[b]	p-value
ARA3002				
Placebo (N=556)	22 (4)	--	--	--
SIR 50 mg q4w (N=557)	75 (13)	9.5	6.3, 12.8	<0.0001
SIR 100 mg q2w (N=557)	75 (13)	9.5	6.3, 12.8	<0.0001
ARA3003				
Placebo (N=294)	9 (3)	--	--	--
SIR 50 mg q4w (N=292)	18 (6)	3.1	-0.3, 6.5	0.07
SIR 100 mg q2w (N=292)	29 (10)	6.9	2.9, 10.8	0.0007

Patients who met treatment failure criteria, discontinued treatment, or were missing data were considered non-responders
Abbreviations: ACR=American College of Rheumatology; CI=confidence interval; SIR=sirukumab; q2w=every 2 weeks; q4w=every 4 weeks; N=total randomized
[a] Comparison to placebo based on Cochran-Mantel-Haenszel test, stratified by baseline categorical methotrexate use
[b] Estimated absolute difference in percentage points
Source: Statistical Reviewer

Health Assessment Questionnaire-Disability Index (HAQ-DI)

Both phase 3 trials assessed the treatment effect of sirukumab on HAQ-DI. Sirukumab was associated with statistically significant improvement (greater decrease) with respect to the mean change from baseline at Week 16 in HAQ-DI over placebo in both trials (Table 15). In both trials, slightly greater improvement was observed for the 100 mg dose group.

Table 15: Mean Change from Baseline in HAQ-DI Score at Week 16 in ARA3002 and ARA3003

Treatment Group	Mean (SD)	Comparison to Placebo[a]		
		Mean Difference	95% CI	p-value
ARA3002				
Placebo (N=556)	-0.22 (0.54)	--	--	--
SIR 50 mg q4w (N=557)	-0.42 (0.58)	-0.21	-0.27, -0.15	<0.0001
SIR 100 mg q2w (N=557)	-0.45 (0.55)	-0.24	-0.30, -0.18	<0.0001
ARA3003				
Placebo (N=294)	-0.16 (0.45)	--	--	--
SIR 50 mg q4w (N=292)	-0.28 (0.54)	-0.11	-0.19, -0.02	0.013
SIR 100 mg q2w (N=292)	-0.35 (0.52)	-0.18	-0.26, -0.09	<0.001

Abbreviations: SIR=sirukumab; HAQ-DI=Health Assessment Questionnaire-Disability Index; SD=standard deviation; CI=confidence interval; q2w=every 2 weeks; q4w=every 4 weeks; N=total randomized
[a] Comparison to placebo based on linear regression, adjusting for baseline value and baseline categorical methotrexate use
Source: Statistical Reviewer

The applicant's results for mean change in HAQ-DI at Week 24 were generally similar (data not shown). In a supportive analysis conducted by the applicant, HAQ-DI response was defined as a change of <-0.22 from baseline in HAQ-DI score. In ARA3002, at Week 24, a HAQ-DI score of <-0.22 was achieved by 63% of patients in the sirukumab 50 mg group and 65% of patients in the sirukumab 100 mg group compared with 47% of patients in the placebo group. In ARA3003, at Week 24, the proportion of HAQ-DI responders was 52% in the sirukumab 50 mg group and 55% in the sirukumab 100 mg group compared to 37% in the placebo group.

Major clinical response by Week 52

Major clinical response (MCR) was defined as the event of achieving and maintaining an ACR70 response at all visits over six continuous months by Week 52. This endpoint was only assessed in ARA3002 since ARA3003 had a placebo-controlled duration of only six months. A statistically significantly larger proportion of patients in the sirukumab dose groups achieved major clinical response compared to the placebo group (Table 16). There were was a slightly higher proportion of responders in the 100 mg group compared to the 50 mg group.

Table 16: Major Clinical Response by Week 52 in ARA3002[a]

Treatment Group	# Responders (%)	Comparison to Placebo[b]		
		Difference[c]	95% CI[c]	p-value
Placebo (N=556)	10 (2)	--	--	--
SIR 50 mg q4w (N=557)	28 (5)	3.2	1.1, 5.4	0.003
SIR 100 mg q2w (N=557)	48 (9)	6.8	4.2, 9.4	<0.0001

Major clinical response = achieve ACR70 response at all visits over at least 24 consecutive weeks during the 52-week period
Patients who met treatment failure criteria, discontinued treatment, or were missing data were considered non-responders
Abbreviations: SIR=sirukumab; CI=confidence interval; q2w=every 2 weeks; q4w=every 4 weeks; N=total randomized
[a] Differs slightly from applicant's analysis as some patients did not meet the protocol-defined criteria for major clinical response: two patients from SIR 50mg and two from SIR 100 mg who had missing visits during the 24-week period with an ACR70 response were considered non-responders
[b] Comparison to placebo based on Cochran-Mantel-Haenszel test, stratified by baseline categorical methotrexate use
[c] Absolute difference, in percentage points
Source: Statistical Reviewer

DAS28(CRP)<2.6

The proportion of patients who achieved a DAS28(CRP)<2.6 and remained on randomized treatment at Week 24 in patients treated with sirukumab was statistically significantly greater compared to patients treated with placebo in both studies (Table 17). The proportions of patients with DAS28(CRP)<2.6 were numerically similar for the two doses in ARA3002 and ARA3003.

Table 17: DAS28(CRP)<2.6 Response Probabilities at Week 24 in ARA3002 and ARA3003

Treatment Group	# Responders (%)	Comparison to Placebo[a]		
		Difference[b]	95% CI[b]	p-value
ARA3002				
Placebo (N=556)	31 (6)	--	--	--
SIR 50 mg q4w (N=557)	145 (26)	20.5	16.4, 24.6	<0.0001
SIR 100 mg q2w (N=557)	142 (26)	19.9	15.8, 24.0	<0.0001
ARA3003				
Placebo (N=294)	24 (8)	--	--	--
SIR 50 mg q4w (N=292)	56 (19)	11.0	5.5, 16.5	0.0001
SIR 100 mg q2w (N=292)	63 (22)	13.4	7.8, 19.1	<0.0001

Patients who met escape criteria, met treatment failure criteria, discontinued treatment, or were missing data were considered non-responders
Abbreviations: SIR=sirukumab; DAS28=Disease Activity Index Score 28; CI=confidence interval; q2w=every 2 weeks; q4w=every 4 weeks; N=total randomized
[a] Comparison to placebo based on Cochran-Mantel-Haenszel test, stratified by baseline categorical methotrexate use
[b] Absolute difference, in percentage points
Source: Statistical Reviewer

While the results from analyses of DAS28(CRP)<2.6 support the efficacy of sirukumab for RA, it is important to note that of patients achieving a DAS28(CRP)<2.6 on sirukumab 50 mg, 65% (94/145) and 63% (35/56) had at least one active joint in ARA3002 and ARA3003, respectively. Of the patients treated with sirukumab 50 mg who achieved a DAS28-CRP<2.6, 24% (35/145) and 23% (13/56) had three or more active joints in ARA3002 and ARA3003, respectively. Thus, many of the patients achieving a DAS28-CRP<2.6 on sirukumab still had disease activity.

Change from baseline in SF-36

The mean changes in the SF-36 physical component and mental component summary scores at Week 16 in patients treated with sirukumab were statistically significantly greater compared to patients treated with placebo in both trials (Table 18). When comparing the two doses, the mean changes were similar in ARA3002 and slightly greater for the 100 mg dose in ARA3003. In ARA3003, both doses of sirukumab demonstrated statistically significantly greater improvements from baseline compared with placebo in all eight domains of the SF-36 (bodily pain, general health, physical function, role-physical, mental health, role-emotional, social function, and vitality) at Week 16. In ARA3003, results for all eight domains were either statistically significant or trended toward benefit for sirukumab. The applicant's results at Week 24 were generally similar (data not shown).

Table 18: Change from Baseline in SF-36 Physical and Mental Component Summary Scores at Week 16 in ARA3002 and ARA3003

Treatment Group	n	Mean Change (SD)	Comparison to Placebo[a]		
			Mean Difference	95% CI	p-value
ARA3002					
SF-36 PCS					
Placebo (N=556)	514	2.6 (6.5)	--	--	--
SIR 50 mg q4w (N=557)	527	5.5 (7.2)	2.9	2.1, 3.7	<0.0001
SIR 100 mg q2w (N=557)	516	5.8 (6.8)	3.2	2.4, 4.0	<0.0001
SF-36 MCS					
Placebo (N=556)	514	2.7 (9.6)	--	--	--
SIR 50 mg q4w (N=557)	527	4.8 (9.3)	2.1	1.0, 3.3	0.0001
SIR 100 mg q2w (N=557)	516	4.8 (9.6)	2.1	1.0, 3.3	0.0001
ARA3003					
SF-36 PCS					
Placebo (N=294)	261	2.0 (6.8)	--	--	--
SIR 50 mg q4w (N=291)	251	5.3 (6.7)	2.7	1.5, 3.9	<0.0001
SIR 100 mg q2w (N=292)	255	4.7 (7.0)	3.2	2.0, 4.4	<0.0001
SF-36 MCS					
Placebo (N=294)	261	1.6 (9.1)	--	--	--
SIR 50 mg q4w (N=291)	251	3.4 (11.4)	1.8	0.1, 3.5	0.04
SIR 100 mg q2w (N=292)	255	4.4 (8.9)	2.8	1.1, 4.5	0.001

Abbreviations: SIR=sirukumab; SF-36=short form 36 item health survey; PCS=physical component score; MCS=mental component score; SD=standard deviation; CI=confidence interval; N=total randomized; n=number of observed values; q2w=every 2 weeks; q4w=every 4 weeks
[a] Comparison to placebo based on linear regression, adjusting for baseline value and baseline categorical methotrexate use used
Source: Statistical Reviewer

Change from baseline in vdH-S

The primary radiographic endpoint in ARA3002 was assessed at Week 52. Approximately 49% of placebo patients were still on placebo at Week 52. There was also an assessment of radiographs at Week 24. Approximately 58% of placebo patients were still on placebo at Week 24.

As shown in Table 19, in the primary analysis using linear extrapolation, the mean change in vdH-S at Week 52 in patients treated with the sirukumab dosing regimens was statistically significantly less compared to patients treated with placebo. Similar analyses at Week 24, when there was less escape and less missing data, also provided evidence of a treatment effect (Table 19). As anticipated, the treatment effect was smaller at Week 24 than Week 52. Results were generally consistent across the components of vdH-S, the erosion and joint space narrowing scores.

Given concerns with the linear extrapolation approach, we considered several additional supportive analyses to be important. These analyses supported the findings of the pre-specified analysis based on linear extrapolation. In particular, analyses based on all observed data, regardless of escape or treatment discontinuation, also showed persuasive evidence of an effect of sirukumab on radiographic progression for both doses at both Week 52 and Week 18/24 (Table 20). Analyses evaluating the rate of change in vdH-S in the absence of escape also supported an effect of sirukumab (Table 21). Finally, tipping point sensitivity analyses

including all observed data, regardless of use of escape or treatment discontinuation, and varying assumptions about the missing data indicated that the findings were convincing notwithstanding the missing data (see results for the 50 mg dose in Appendix Figure 21).

Results in Table 22 show that more patients had no radiographic progression in the sirukumab 50 mg and 100 mg dose groups compared to placebo. In addition, there was a slightly higher proportion of patients without radiographic progression in the 100 mg versus the 50 mg dose group. Results were supportive using all observed data regardless of escape or treatment discontinuation (non-progression proportions of 56% and 62% on 50 and 100 mg, respectively, compared to 41% on placebo). Furthermore, empirical distribution plots of change from baseline in vdH-S at Week 52 show separation between both sirukumab groups and the placebo group and no separation between the two sirukumab groups (Figure 5).

In summary, the totality of the data supports a treatment effect of sirukumab on structural damage progression. The amount of estimated radiographic inhibition was similar for the two doses of sirukumab. Although there was only a single trial assessing radiographic progression, the evidence is sufficient due to the highly statistically significant results (p-values<0.0001) and the consistency of results across the two doses and in supportive and sensitivity analyses.

Table 19: Change from Baseline in the van der Heijde-modified Sharp Score, and the Erosion and Joint Space Narrowing Component Scores, at Week 52 and Week 24 using Linear Extrapolation for Missing Data and for Post-escape Data on Placebo in ARA3002

Treatment Group	n	Mean Change (SD)	Comparison to Placebo		
			Mean Difference[a]	95% CI[a]	p-value[b]
Week 52: vdH-S					
Placebo (N=556)	550	3.7 (9.3)	--	--	--
SIR 50 mg q4w (N=557)	553	0.5 (3.0)	-3.2	-3.9, -2.5	<0.0001
SIR 100 mg q2w (N=557)	551	0.5 (3.3)	-3.2	-3.9, -2.5	<0.0001
Week 52: Erosion					
Placebo (N=556)	550	2.2 (5.9)	--	--	--
SIR 50 mg q4w (N=557)	553	0.1 (1.8)	-2.1	-2.6, -1.7	<0.0001
SIR 100 mg q2w (N=557)	551	0.1 (2.0)	-2.1	-2.6, -1.7	<0.0001
Week 52: JSN					
Placebo (N=556)	550	1.5 (4.3)	--	--	--
SIR 50 mg q4w (N=557)	553	0.4 (1.8)	-1.1	-1.4, -0.7	<0.0001
SIR 100 mg q2w (N=557)	551	0.4 (2.2)	-1.1	-1.4, -0.7	<0.0001
Week 24: vdH-S					
Placebo (N=556)	550	2.0 (5.4)	--	--	--
SIR 50 mg q4w (N=557)	553	0.4 (2.2)	-1.6	-2.0, -1.2	<0.0001
SIR 100 mg q2w (N=557)	551	0.3 (2.2)	-1.7	-2.1, -1.3	<0.0001
Week 24: Erosion					
Placebo (N=556)	550	1.2 (3.4)	--	--	--
SIR 50 mg q4w (N=557)	553	0.1 (1.3)	-1.1	-1.4, -0.8	<0.0001
SIR 100 mg q2w (N=557)	551	0.1 (1.3)	-1.1	-1.4, -0.7	<0.0001
Week 24: JSN					
Placebo (N=556)	550	0.8 (2.5)	--	--	--
SIR 50 mg q4w (N=557)	553	0.2 (1.4)	-0.5	-0.7, -0.3	<0.0001
SIR 100 mg q2w (N=557)	551	0.2 (1.5)	-0.5	-0.8, -0.3	<0.0001

Based on linear extrapolation for subjects with missing data on all treatment arms who had at least one post-baseline measurement, linear extrapolation for placebo patients who early-escaped, and baseline observation forward for subjects on all treatment arms missing post-baseline radiographs

Abbreviations: SIR=sirukumab; SD=standard deviation; vdH-S=van der Heijde-modified Sharp score; JSN=joint space narrowing; CI=confidence interval; N=total randomized; n=number of values used (observed or imputed) in analysis; q2w=every 2 weeks; q4w=every 4 weeks

[a] Estimated difference relative to placebo and 95% CI were based on a post-hoc FDA analysis using linear regression, adjusting for baseline score and baseline categorical methotrexate use

[b] p-value for comparison relative to placebo obtained from applicant's prespecified rank-based ANOVA analysis using van der Waerden normal scores

Source: Statistical Reviewer

Table 20: Change from Baseline in vdH-S at Week 52 and Week 18/24 using all Observed Data Regardless of Escape or Treatment Discontinuation in ARA3002

Treatment Group	n	Mean Change (SD)	Comparison to Placebo[a]		
			Mean Difference	95% CI	p-value
Week 52					
Placebo (N=556)	440	3.0 (8.0)	--	--	--
SIR 50 mg q4w (N=557)	459	0.6 (2.9)	-2.4	-3.2, -1.6	<0.0001
SIR 100 mg q2w (N=557)	460	0.4 (2.7)	-2.7	-3.4, -1.9	<0.0001
Week 18/24					
Placebo (N=556)	473	2.0 (5.3)	--	--	--
SIR 50 mg q4w (N=557)	488	0.4 (2.2)	-1.6	-2.1, -1.1	<0.0001
SIR 100 mg q2w (N=557)	467	0.3 (2.1)	-1.7	-2.2, -1.2	<0.0001

Based on linear regression using all observed data regardless of early escape, late escape, or treatment discontinuation; Data used within Week 52±28 days for Week 52 analysis and within Week 18-14 days to Week 24+14 days for Week 18/24 analyses
Abbreviations: SIR=sirukumab; SD=standard deviation; vdH-S=van der Heijde-modified Sharp score; CI=confidence interval; N=total randomized; n=number of observed values; q2w=every 2 weeks; q4w=every 4 weeks
[a] Comparison to placebo based on linear regression, adjusting for baseline score and baseline categorical methotrexate use
Source: Statistical Reviewer

Table 21: Rate of Change in vdH-S over 52 weeks in ARA3002

Treatment Group	n	Estimated mean rate	Comparison to Placebo		
			Difference in mean rate	95% CI	p-value
Placebo (N=556)	520	4.1	--	--	--
SIR 50 mg q4w (N=557)	537	0.6	-3.5	-4.3, -2.8	<0.0001
SIR 100 mg q2w (N=557)	523	0.5	-3.6	-4.3, -2.9	<0.0001

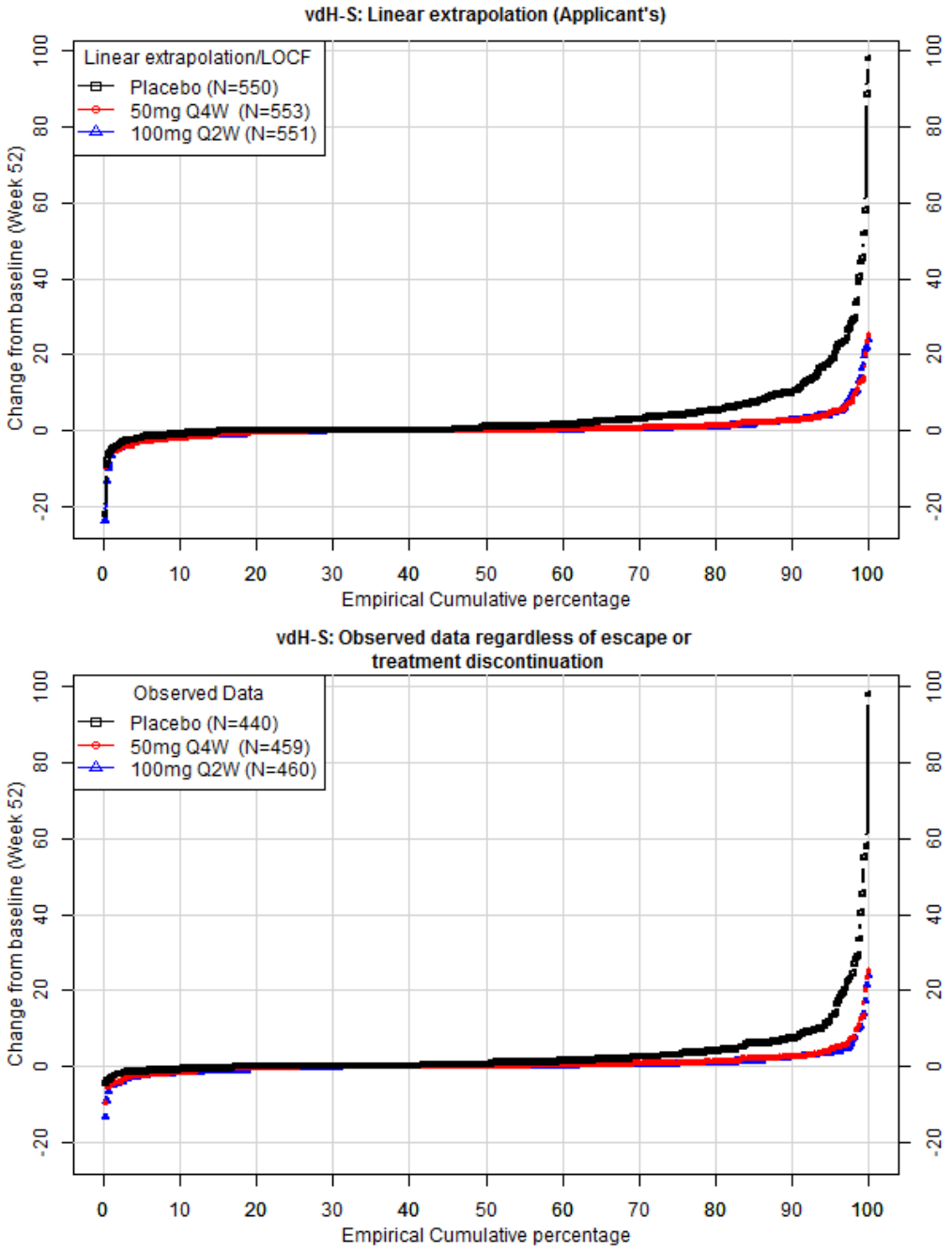
Based on linear mixed effects model, adjusting for scheduled visit week and treatment-by-week interaction only, excluding data after early escape in placebo patients
Abbreviations: SIR=sirukumab; SD=standard deviation; vdH-S=van der Heijde-modified Sharp score; CI=confidence interval; N=total randomized; n=number of patients with at least one observed change from baseline value; q2w=every 2 weeks; q4w=every 4 weeks
Source: Statistical Reviewer

Table 22: Proportion of Patients with no Radiographic Progression (Change of ≤0 from Baseline in vdH-S) at Week 52 in ARA3002

Treatment Group	No Progression n/n* (%)	Comparison to Placebo		
		Difference[a]	95% CI[a]	p-value
Placebo (N=556)	250/550 (45)	--	--	--
SIR 50 mg q4w (N=556)	326/553 (59)	13.5	7.7, 19.4	<0.0001
SIR 100 mg q2w (N=557)	344/551 (62)	17.0	11.2, 22.8	<0.0001

Based on linear extrapolation for post-escape data on the placebo arm, considers patients without post-baseline x-rays as non-progressors
Abbreviations: SIR=sirukumab; vdHS=van der Heijde-modified Sharp Score; CI=confidence interval; N=total randomized; n=number of patients with no progression; n*=number of patients randomized with a baseline x-ray; q2w=every 2 weeks; q4w=every 4 weeks
[a] Absolute difference, in percentage points
Source: Statistical Reviewer

Figure 5: Probability Plots of Change from Baseline in vdH-S at Week 52 in ARA3002



Source: Statistical Reviewer

Subgroup analyses, including in patients not receiving DMARDs at baseline

Subgroup analyses evaluating ACR20 response by demographic and baseline characteristics generally showed consistent trends toward benefit for the sirukumab doses in the two phase 3 studies (data not shown). Of note, subgroup analyses were carried out in patients not receiving

DMARDs at baseline (Table 23). These analyses are exploratory in nature and limited by the small sizes of the subgroups, but trends were generally consistent with the findings in the overall population. Furthermore, there is some additional support for the effectiveness of sirukumab as a monotherapy from the active-controlled study ARA3005 (results described in next section).

Table 23: ACR20 Response Probabilities at Week 16 in the Subgroup of Patients not Using DMARDs at Baseline in ARA3002 and ARA3003

Treatment Group	# Responders (%)	Comparison to Placebo[a]	
		Difference[b]	95% CI[b]
ARA3002			
Placebo (N=48)	7 (15)	--	--
SIR 50 mg q4w (N=39)	18 (46)	31.6	10.7, 52.5
SIR 100 mg q2w (N=46)	24 (52)	37.6	17.9, 57.3
ARA3003			
Placebo (N=51)	7 (14)	--	--
SIR 50 mg q4w (N=58)	15 (26)	12.1	-4.4, 28.7
SIR 100 mg q2w (N=57)	22 (39)	24.9	7.2, 42.5

Patients who met treatment failure criteria, discontinued treatment, or were missing data were considered non-responders
Abbreviations: SIR=sirukumab; ACR=American College of Rheumatology; CI=confidence interval; N=number of randomized patients in the subgroup; q2w=every 2 weeks; q4w=every 4 weeks
[a] Comparison to placebo based on Cochran-Mantel-Haenszel test, stratified by baseline categorical methotrexate use, restricted to the subgroup
[b] Absolute difference, in percentage points
Source: Statistical Reviewer

Comparison to Adalimumab

Trial ARA3005 compared sirukumab to an active comparator adalimumab. The two co-primary endpoints in this trial were change from baseline in DAS28(ESR) at Week 24 and proportion of patients with an ACR50 response at Week 24. Both doses of sirukumab led to significantly larger decreases in DAS28(ESR) at Week 24 than adalimumab (Table 24). However, ACR50 response rates at Week 24 were not statistically different between either sirukumab group and adalimumab (Table 25). Furthermore, while analyses of the ACR and DAS28 components suggested that sirukumab has greater effects than adalimumab on the acute phase reactants CRP and ESR, effects on symptoms and function were largely similar between the products (Appendix Table 66). Thus, the trial did not show superiority of sirukumab compared to adalimumab. However, the relatively similar improvements observed on sirukumab and the approved, effective active control adalimumab provide additional support for the effectiveness of sirukumab.

Table 24: Change from Baseline in DAS28(ESR) at Week 24 in ARA3005

Treatment Group	Mean (SD)	Comparison to Adalimumab[a]		
		Mean Difference	95% CI	p-value
Adalimumab (N=186)	-2.19 (1.4)	--	--	--
SIR 50 mg q4w (N=186)	-2.58 (1.5)	-0.39	-0.69, 0.08	0.013
SIR 100 mg q2w (N=187)	-2.96 (1.6)	-0.76	-1.07, -0.46	<0.001

Abbreviations: SIR=sirukumab; DAS28(ESR)=disease activity score-28 (erythrocyte sedimentation rate); SD=standard deviation; CI=confidence interval; q2w=every 2 weeks; q4w=every 4 weeks; N=total randomized
[a] Comparison to adalimumab based on linear regression, adjusting for baseline score and baseline reason for methotrexate failure; missing Week 24 values imputed as no change
Source: Statistical Reviewer

Table 25: ACR50 Response Probabilities at Week 24 in ARA3005

Treatment Group	# Responders (%)	Comparison to Adalimumab[a]		
		Difference (%)[b]	95% CI	p-value
Adalimumab (N=186)	59 (32)[c]	--	--	--
SIR 50 mg q4w (N=186)	50 (27)	-4.8	-14.1, 4.4	0.306
SIR 100 mg q2w (N=187)	66 (35)	3.6	-6.0, 13.1	0.464

Patients who met treatment failure criteria, discontinued treatment, escaped, or were missing data were considered non-responders
Abbreviations: SIR=sirukumab; ACR=American College of Rheumatology; CI=confidence interval; q2w=every 2 weeks; q4w=every 4 weeks; ; N=total randomized
[a] Comparison to adalimumab based on Cochran-Mantel-Haenszel test, stratified by baseline reason for methotrexate failure
[b] Absolute difference, in percentage points
[c] When all observed data were evaluated (i.e., patients who escaped from adalimumab q2w to adalimumab weekly were *not* considered non-responders; their Week 24 data, if observed, was used instead), the ACR50 response probability on adalimumab remained 32%
Source: Statistical Reviewer

7. Safety

7.1 Studies contributing to integrated safety analyses and the Applicant's pooling and attribution strategies

A summary of the studies contributing to the safety analyses may be found in Table 4 and Table 5. The primary source of safety data is from the two phase 3 trials (ARA3002 and ARA3003) and their long term extension study (ARA3004). Additional data are available from an adalimumab active control trial (ARA3005), an uncontrolled study of sirukumab in Japanese patients (ARA3001), a phase 2 study in RA (C1377T04), and a phase 1 drug-drug interaction study (ARA1001). In addition to the proposed RA indication, sirukumab has been studied in lupus nephritis and healthy volunteers, but those safety data were not pooled with the safety data from RA as there are important differences between the populations, such as background medications.

As noted in Table 4, placebo-controlled periods were limited to 12 to 24 weeks for all of the studies, except for ARA3002, which was placebo-controlled for 52 weeks with the option for rescue starting at Week 18. See Section 8 for a discussion of considerations related to the 52-week placebo-controlled period of ARA3002. For ARA3003, the placebo-controlled period

was 24 weeks, with the option for rescue starting at Week 18. ARA3005 was active controlled with adalimumab with the option of escape beginning at Week 16. ARA3001 was uncontrolled and the remainder of the studies (C1377T04 and ARA1001) were placebo-controlled for the entire study, without the option for rescue given the fairly limited study duration.

In ARA3002, patients in the placebo group who met early escape (EE) criteria at Week 18 or late escape (LE) criteria at Week 40 (i.e., had <20% improvement from baseline in both swollen and tender joint counts) were re-randomized to receive blinded sirukumab 50 mg q4w or sirukumab 100 mg q2w through Week 104. At Week 28, subjects in all treatment groups who had <20% improvement from baseline in both swollen and tender joint counts could adjust or initiate DMARDs and/or oral corticosteroids from Week 28 onwards. At Week 52, all remaining subjects in the placebo group were re-randomized to receive 1 of the 2 sirukumab dose regimens through Week 104. At Week 52, or any time after, all subjects could adjust or initiate DMARDs and/or oral corticosteroids.

In ARA3003, the same EE criteria and procedure was used as in trial ARA3002. Unlike ARA3002, trial ARA3003 was only placebo-controlled for 24 weeks and all patients in the placebo group crossed over (CO) at Week 24 to receive sirukumab (randomized to either 50 mg or 100 mg) until week 52. Another difference between trial ARA3003 and ARA3002 is when patients could adjust or initiate DMARDs and/or oral corticosteroids (if a patient had <20% improvement from baseline in both swollen and tender joint counts). This occurred from Week 28 onwards in ARA3002 and from Week 24 onwards in ARA3003.

Patients in ARA3002 and ARA3003 were able to enroll into an open-label uncontrolled extension study (ARA3004). Patients could enter ARA3004 during the Week 104 visit in ARA3002 or the Week 52 visit in ARA3003, and therefore those visits correspond to the Week 0 visit in ARA3004. The study duration for ARA3004 is a minimum of one year for subjects from ARA3002 or a minimum of two years for subjects from ARA3003. The maximum duration of the study is 208 weeks, followed by approximately 16 weeks of safety and efficacy follow-up.

The analysis of safety data from the clinical studies in patients with RA is complicated by differences in study duration, duration of placebo-controlled periods, time of rescue, and comparator and background therapy. Given the complexities of the study design, Janssen performed a variety of different analyses, including analyses based on Poisson regression to compare incidence rates between treatment arms and to quantify the uncertainty around comparisons. Kaplan Meier plots and Cox proportional hazards regression analyses were also used for selected endpoints. Additional details on the specific statistical methods are provided when results are presented (e.g., in table captions).

Table 26 provides the Agency's key pooling and analysis strategies. The initial focus of the Agency's safety review was the placebo-controlled phase 3 studies (ARA2002 and ARA2003) (referred to by Janssen as the exposure time controlled analysis set) through 18 weeks, through 52 weeks of exposure, and through the Summary of Clinical Safety (SCS) data cutoff (February 2, 2016). These analyses include safety data from the phase 3 studies that included

a placebo group. For analyses through 52 weeks of exposure, exposure data from trial ARA3003 were included after the placebo-controlled period ended, e.g., from 24 to 52 weeks, and then continuously in study ARA3004 from Week 0 to Week 24 for patients who were originally randomized to placebo in ARA3003. Data from ARA3004 for patients who early escaped (EE) or crossed over from placebo in ARA3003 were included in the analyses of the exposure time controlled analysis dataset, e.g. through 52 weeks of exposure dataset, and in the analyses through the Summary of Clinical Safety (SCS) cut-off date.

Janssen displayed safety data from sirukumab arms based on whether patients were originally randomized to sirukumab or whether patients were originally randomized to placebo, but crossed over or escaped to sirukumab. Data that is displayed for patients originally randomized to sirukumab are referred to as **sirukumab start arms**. Data that is displayed for patients who were originally randomized to sirukumab or were originally randomized to placebo, but crossed over or escaped to sirukumab are referred to as **combined sirukumab arms**.

We focused primarily on comparisons between the sirukumab 50 mg start and sirukumab 100 mg start arms and placebo, given that these represented on-treatment comparisons based on the originally randomized treatment arms. The analyses through 52 weeks of exposure are limited by the escape/cross-over of many placebo patients prior to 52 weeks. We also present results for the sirukumab 50 mg combined and 100 mg combined arms. These combined arms include patients originally randomized to the particular sirukumab dose, as well as patients who crossed over or escaped from placebo to that sirukumab dose. For patients crossing over or escaping to sirukumab included in the sirukumab combined arms, exposure time began at the time of cross-over/escape. The analyses of the sirukumab combined arms capture additional events, increasing precision in comparisons, but may be subject to additional bias, given that inadequate responders to placebo who escaped to the sirukumab arms and who may not be representative of those randomized to sirukumab are included in the sirukumab combined arms. We also present results through the SCS cutoff date for the combined sirukumab 50 mg and sirukumab 100 mg groups.

The active comparator study (ARA3005) was not included in these analyses because it does not have a placebo group. However, data from this study was included in a larger dataset (sirukumab controlled analysis set) from studies ARA3001, ARA3002, ARA3003, ARA3004, and ARA3005 through 52 weeks and through SCS cutoff date to compare the two sirukumab doses (which were included in all these studies) and evaluate for rare events or events with longer latency.

Table 26: Summary of Agency's Key Data Presentations for the Sirukumab Rheumatoid Arthritis Program

Presentation	Studies Included	Analysis Period (analysis set)	Notes
Safety of sirukumab 50 mg, 100 mg start and combined groups vs placebo group; Comparison of sirukumab doses	ARA3002, ARA3003 (Data from ARA3004 are included for analyses through 52 and SCS cutoff)	• Through 18 weeks of exposure • Through 52 weeks of exposure • Through SCS cutoff (exposure time controlled analysis set)	Through 18 weeks of exposure • Compares safety of patients originally randomized to placebo, sirukumab 50 mg, or sirukumab 100 mg through 18 weeks of exposure Through 52 weeks of exposure • Compares safety of patients originally randomized to placebo, sirukumab 50 mg, or sirukumab 100 mg • Also includes comparisons to the combined sirukumab groups which includes data from patients originally randomized to placebo who EE/LE/CO to sirukumab. • Placebo summaries beyond 18 weeks must be interpreted recognizing that placebo exposure is reduced once patients could EE/LE/CO; placebo patients with longer term follow-up may not be representative of the originally randomized group Through SCS cutoff • Compares the safety of the two sirukumab doses through SCS cutoff. Includes data for patients initially randomized to placebo who EE/LE/CO to sirukumab.
Safety of sirukumab 50 mg, 100 mg vs adalimumab	ARA3005	• Through 24 weeks (adalimumab controlled analysis set)	• ARA3005 is the only study with an active control and sirukumab administered as monotherapy
Comparison of sirukumab 50 mg vs sirukumab 100 mg (long-term dose response)	ARA3001, ARA3002, ARA3003, ARA3004, ARA3005	• Data through SCS data cutoff (sirukumab controlled analysis set)	• Includes all phase 3 sirukumab data for dose comparisons; does not include placebo data

Abbreviations: EE=early escape; LE=late escape; CO=crossover
SCS cutoff date: February 2, 2016

a. Includes safety observations from first dose extending to 16 weeks (at least 5 half-lives) after last dose of study treatment, provided that these observations did not exceed the end of the analysis period or data cutoff
b. "Start" excludes exposure to sirukumab that occurred after switching treatment by study design (due to escape or crossover) from placebo

Source: Reviewer and Summary of Clinical Safety, Table 5, page 39, submitted 9/22/16

Table 27 describes the attribution window of time on placebo and sirukumab based upon a patient's exposure to placebo and sirukumab and the period of analysis (through 18 and 52 weeks of exposure).

Table 27: Attribution Windows through 18 Weeks of Exposure (A) and through 52 Weeks of Exposure (B) for the Exposure time Controlled Analyses

A

Cohort	Placebo	Sirukumab 50mg q4w		Sirukumab 100 mg q2w	
		Sirukumab 50 mg start	Sirukumab 50 mg switch	Sirukumab 100 mg start	Sirukumab 100 mg switch
Placebo → EE 50 mg	W0 – W18		W18 – W36		
Placebo → EE 100 mg	W0 – W18				W18 – W36
Placebo → LE 50 mg	W0 – W18		W40 – W58		
Placebo → LE 100 mg	W0 – W18				W40 – W58
Placebo → CO 50 mg	W0 – W18		W52 – W70 (ARA3002) W24 – W42 (ARA3003)		
Placebo → CO 100 mg	W0 – W18				W52 – W70 (ARA3002) W24 – W42 (ARA3003)
Sirukumab 50 mg		W0 – W18			
Sirukumab 100 mg				W0 – W18	

B

Cohort	Placebo[1]	Sirukumab 50mg q4w		Sirukumab 100 mg q2w	
		Sirukumab 50 mg start	Sirukumab 50 mg switch	Sirukumab 100 mg start	Sirukumab 100 mg switch
Placebo → EE 50 mg	W0 – W18		W18 – W70		
Placebo → EE 100 mg	W0 – W18				W18 – W70
Placebo → LE 50 mg	W0 – W40		W40 – W92		
Placebo → LE 100 mg	W0 – W40				W40 – W92
Placebo → CO 50 mg	W0 – W52		W52 – W104		
Placebo → CO 100 mg	W0 – W52				W52 – W104
Sirukumab 50 mg		W0 – W52			
Sirukumab 100 mg				W0 – W52	

The length of the attribution window defines the duration of exposure.
After the date of the last dose of study agent, safety data were collected for up to 16 weeks ± 2 weeks.
Source: IR Response, pages 5-6, submitted 4/28/17

Given the complexity of the study design with escape and cross over from placebo to sirukumab, Janssen's windows of attribution classified adverse events considering the study drug received during a particular time window.

7.2 Adjudication

In the sirukumab clinical program, three types of events were adjudicated: major adverse cardiovascular events (MACE), gastrointestinal perforation (GIP), and hepatobiliary events. In a submission dated June 5, 2017, Janssen stated that in the process of review and preparation for the Advisory Committee meeting and while preparing data in the response to an Information Request (IR) from May 02, 2017, they realized that not all events in the Summary of Clinical Safety/Integrated Summary of Safety (SCS/ISS) and 120-day safety update that required adjudication were actually adjudicated.

For MACE, safety events requiring adjudication were adjudicated through three months prior to the SCS database lock, i.e., not up through the database lock. For GIP, safety events were

to be adjudicated prior to individual phase 3 study database locks for the study period in which the events occurred. For some GIP cases, adjudication occurred after the individual phase 3 study database locks for the study period in which the events occurred (but before the SCS database lock). These gaps between the last adjudication and the SCS database lock resulted in SCS datasets that lacked completed adjudications of all possible MACE and possible GIP events, but did not affect hepatobiliary events because no additional events occurred in this timeframe. The sponsor further clarified during a June 9, 2017, teleconference that there were additional discrepancies based on human error in the course of the medical monitor carrying out the flagging of events as adjudicated MACE and GI perforation after these events were sent for adjudication. Not all of these events were appropriately classified following completion of the adjudication.

Recognition of the issue triggered a review and validation of all data related to the adjudicated events, recreation of affected Tables, Listings, and Figures and review of the corrected data by Janssen and the Agency. In addition, the Agency reviewed a sample of the original MACE adjudication case report forms and confirmed the accuracy of the revised datasets. Of note, many of the updated results were submitted late in the review cycle and every attempt has been made to reflect the accurate results, but there were challenges with updating the background materials late in the review cycle.

7.3 Adequacy of the drug exposure experience (i.e., the safety database)

In the placebo-controlled analysis set (studies ARA3002 and ARA3003), 848 patients received sirukumab 50 mg q4w, 850 patients received sirukumab 100 mg q2w, and 850 patients received placebo. In the sirukumab controlled analysis set (studies ARA3001, ARA3002, ARA3003, ARA3004, and ARA3005), a total of 2,926 patients received sirukumab (1,461 patients: sirukumab 50 mg q4w and 1,465 patients: sirukumab 100 mg q2w). In this dataset, 2,082 patients received sirukumab treatment for 52 weeks or longer (1,041 patients on each dose) (Table 28). At escape or cross over from placebo to sirukumab, patients were re-randomized to the two dose options. Thus, the exposure for the two evaluated doses is similar. The initial regulatory submission is based on all data available through the SCS cutoff date of February 2, 2016.

The size and scope of the safety database were reasonable and consistent with the safety database of other biologic products approved for RA.

Table 28: Number of Patients with Duration of Exposure by Category (Studies ARA3001, ARA3002, ARA3003, ARA3004, and ARA3005)

	Sirukumab		
	50 mg	100 mg	Combined
Number of patients exposed	1461	1465	2926
Duration of exposure			
≥24 weeks	1363 (93%)	1372 (94%)	2735 (94%)
≥52 weeks	1041 (71%)	1041 (71%)	2082 (71%)
≥104 weeks	392 (27%)	406 (28%)	798 (27%)
≥156 weeks	23 (2%)	22 (2%)	45 (2%)

Source: Summary of Clinical Safety, Table 5, page 39, submitted 9/22/16

7.4 Key safety results, including deaths, serious adverse events (SAEs), discontinuations due to AEs, other AEs, and results of laboratory tests

Death

As of February 2, 2016, there were a total of 35 deaths reported in the RA clinical development program. Of the 35 deaths, 34 occurred in sirukumab-treated patients. Numbers and incidence rates of death in Studies ARA3002, ARA3003, and ARA3004 are shown in Table 29. In the placebo-controlled period (through 18 weeks of exposure), one patient each in the placebo (acute respiratory distress syndrome), sirukumab 50 mg (sudden cardiac death), and sirukumab 100 mg (myocardial infarction, hypertension) groups died. The patient treated with sirukumab 100 mg was hospitalized with uncontrolled hypertension and a myocardial infarction (adjudicated as non-MACE) and had thrombocytopenia (platelet count of 61,000) and a GI bleed. The exposure adjusted mortality rate was 0.34 per 100 patient-years (PYs) of exposure in each of the treatment arms. In pooled placebo-controlled studies through 52 weeks of exposure, the incidence rate of death (per 100 PYs) was 0.2, 0.5, and 0.8 for patients in the placebo, sirukumab 50 mg q4w, and sirukumab 100 mg q2 week treatment arms, respectively. Compared to the incidence rate of death for patients who were initially randomized to sirukumab, the incidence rate of death was higher for the combined sirukumab 50 mg and 100 mg groups (0.9 and 1.1, respectively). As previously noted, there are limitations in comparing the placebo group to the combined sirukumab groups through 52 weeks of exposure given that the combined groups include patients who escaped from placebo sirukumab and only patients with greater disease activity could escape. Thus, these comparisons are not balanced by randomization. However, an imbalance in deaths is seen in the through-52-weeks-of exposure analyses regardless of whether data after crossover and escape are included in the analyses. Through the SCS cutoff, the incidence rate of death remained fairly similar to what was seen through 52 weeks of exposure (0.8 and 0.7 for sirukumab 50 mg combined and 100 mg combined, respectively).

To further assess the safety related to death, Janssen performed Poisson regression analyses adjusting for exposure duration and study. There was a numerical imbalance between both the sirukumab 50 mg start and sirukumab 100 mg start arms, as compared to placebo, and the confidence intervals for the differences in incidence rates with respect to the placebo group highlight the uncertainty surrounding the estimates (Table 30). Figure 6 shows the cumulative

incidence of death over time through 52 weeks of exposure by treatment arm in the placebo-controlled studies.

Janssen also carried out additional Poisson regression analyses comparing placebo with the combined sirukumab arms, and analyses adjusting for additional baseline risk factors and disease burden covariates in the models. These additional analyses and results will not be presented in this document. There are limitations in these analyses, e.g., due to the inclusion of post-escape data and due to their post hoc nature (i.e., after identification of a numerical imbalance). Furthermore, the results were generally qualitatively similar to the results presented here. In particular, mortality rates were greater on the sirukumab arms than placebo, but the total number of deaths was small, with wide confidence intervals for comparisons indicating that the imbalance could be due to chance but also that relatively large increases in mortality on sirukumab cannot be ruled out based on the data alone.

The Agency compared the observed mortality rate with the mortality rate in the published literature. The estimated incidence rate of death (per 100 PYs) in a study of 3,080 patients with RA randomized to tocilizumab (n=1538) or etanercept (n=1542) was 1.31 in both the etanercept and tocilizumab treatment arms.[16] Of note, this study enrolled patients at least 50 years of age with at least one cardiovascular disease risk factor. In the tocilizumab clinical program, the incidence rate of deaths per 100 patient-years was 0.6 for the all exposure population, but varied depending on the specific treatment group evaluated. It is important to note that there are differences in study design and analysis methods that limit cross study comparisons.

[16] Giles JT, et al. Comparative Cardiovascular Safety of Tocilizumab Vs Etanercept in Rheumatoid Arthritis: Results of a Randomized, Parallel-Group, Multicenter, Noninferioirty, Phase 4 Clinical Trial [abstract]. *Arthritis Rheumatol.* 2016; 68 (suppl 10). http://acrabstracts.org/abstract/comparative-cardiovascular-safety-of-tocilizumab-vs-etanercept-in-rheumatoid-arthritis-results-of-a-randomized-parallel-group-multicenter-noninferiority-phase-4-clinical-trial/. Accessed June 15, 2017. Estimated incidence rate of 1.31 deaths per 100 PYs based on information in publication and the following calculation: 1.31=64 deaths/~4900 PY x 100, with PY of follow-up for MACE used as approximation of PY of follow-up for death

Table 29: Overview of Deaths for Different Safety Pools and Follow-up Times

	ARA3002 and ARA3003 Through 18 weeks of exposure			ARA3002 and ARA3003[1] Through 52 weeks of exposure					ARA3002 and ARA3003[1] Through SCS cutoff	
	PBO N=850	SIR 50 mg[2] N=848	SIR 100 mg[3] N=850	PBO N=850	SIR 50 mg[2] N=848	SIR 100 mg[3] N=850	SIR Combined[4] 50 mg N=1214	SIR Combined[5] 100 mg N=1217	SIR Combined[4] 50 mg N=1214	SIR Combined[5] 100 mg N=1217
Total patient-years of exposure[6]	292	292	294	520	787	784	1109	1111	1964	1975
Death, N (%[7]), IR	1 (0.1), 0.3	1 (0.1), 0.3	1 (0.1), 0.3	1, 0.2	4, 0.5	6, 0.8	10, 0.9	12, 1.1	15, 0.8	13, 0.7

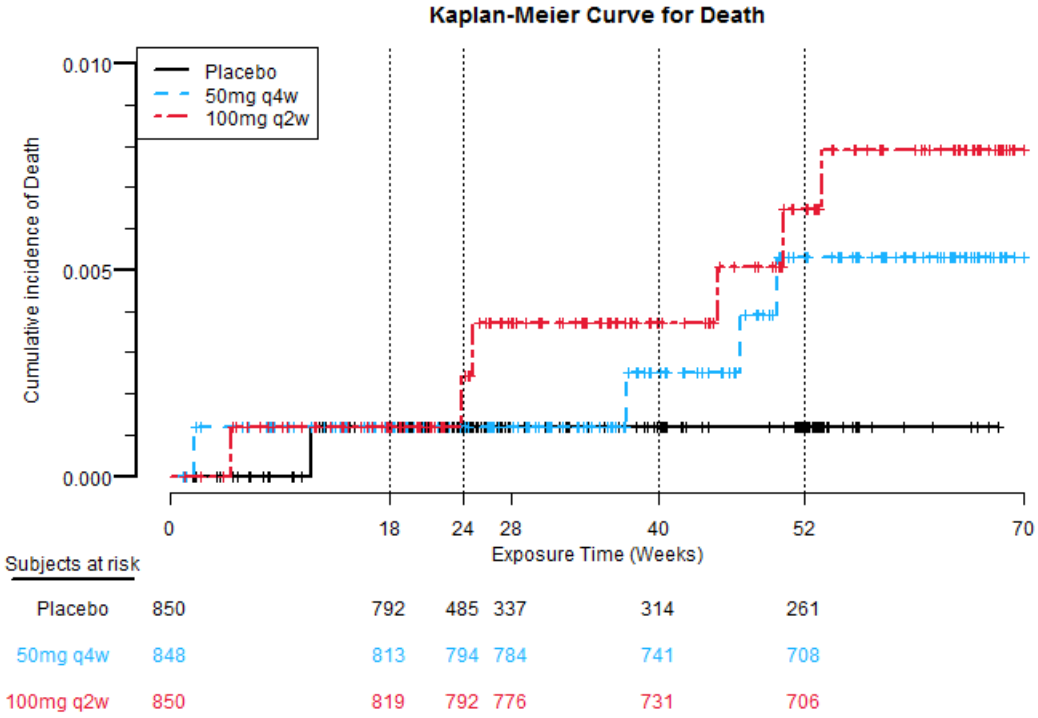
1 Includes data from ARA3004
2 Only includes patients randomized to sirukumab 50 mg q4w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w
3 Only includes patients randomized to sirukumab 100 mg q2w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w.
4 All patients who received at least one dose of sirukumab 50 mg q4w through the noted exposure time. This includes patients who were initially randomized to sirukumab 50mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w.
5 All patients who received at least one dose of sirukumab 100 mg q2w through the noted exposure time. This includes patients who were initially randomized to sirukumab 100 mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w.
6 Total patient-years of exposure is calculated as the total amount of safety follow-up in the given window with censoring due to lost to follow-up, completion of planned follow-up, or window cutoff
7 Cumulative incidence percentages are only shown through 18 weeks and no other time periods given differences in exposure between sirukumab and placebo after 18 weeks.
Abbreviations: PBO=placebo; SIR=sirukumab; EE=early escape; LE=late escape; CO=cross over; SCS=Summary of Clinical Safety; IR=incidence rate per 100 person years; q2w=every 2 weeks; q4w=every 4 weeks
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: IR response, page 128, submitted 5/26/17

Table 30: Poisson Regression Analyses for Deaths Through 52 Weeks of Exposure (Studies ARA3002 and ARA3003)

	PBO	SIR start 50 mg q4w[1]	SIR start 100 mg q2w[2]
Treated patients	850	848	850
Number of patients who died	1	4	6
Total subject years of exposure	520	787	784
Crude incidence rate per 100 patient-years	0.19	0.51	0.77
Ratio of incidence rates (95% CI) versus placebo group	--	2.8 (0.3, 25.0)	4.2 (0.5, 35.0)
Difference of incidence rates (95% CI) versus placebo group, per 100 patient-years	--	0.27 (-0.25, 0.79)	0.48 (-0.14, 1.11)

Based on Poisson regression, with an offset for follow-up time, adjusting for study; difference in incidence rates calculated based on the delta method
1 Only includes patients randomized to sirukumab 50 mg q4w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w
2 Only includes patients randomized to sirukumab 100 mg q2w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w
Abbreviations: PBO=placebo; SIR=sirukumab; q2w=every 2 weeks; q4w=every 4 weeks; CI=confidence interval
Source: Statistical Reviewer

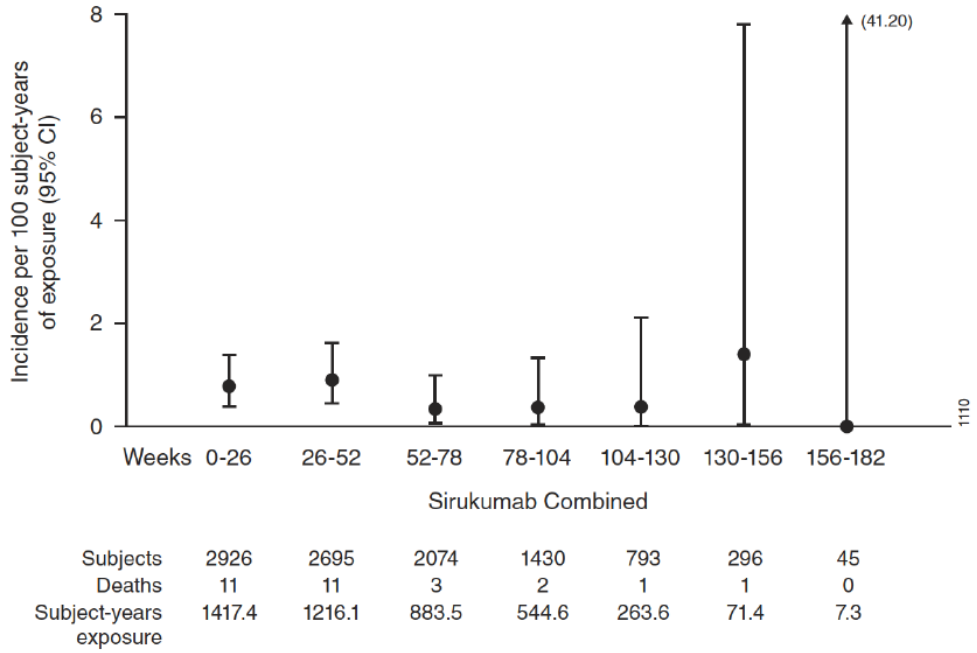
Figure 6: Kaplan-Meier Analysis of Time to Death Through 52 Weeks of Exposure in Studies ARA3002 and ARA3003



Based on all subjects who started off on placebo, sirukumab 50 mg q4w, or sirukumab 100 mg q2w. At-risk time for placebo patients extended up to the time at which placebo patients early escaped, late escaped, or crossed over to sirukumab. Patients who discontinued from the study were also censored. Cross-hairs represent the time at which patients were censored.
Abbreviations: 100mg q2w=sirukumab 100 mg every 2 weeks; 50mg q4w=sirukumab 50 mg every 4 weeks
Source: Statistical Reviewer

To evaluate whether rates of death increased over time with longer exposure to sirukumab, Janssen evaluated incidence rates of death by 6-month intervals of death. These results did not show an increase in incidence rates of death over time, but the confidence intervals do widen over time (Figure 7).

Figure 7: Incidence Rate (patient based per 100 patient years of follow-up) of deaths in 6-month incremental periods with sirukumab treatment exposure time aligned to Week 0 for EE, LE, and CO patients (all phase 3 studies)



Source: Summary of Clinical Safety, Figure 3, page 56, submitted 9/22/16

Most of the deaths occurred in trial ARA3002 (Table 31). Of the 35 deaths that occurred in the sirukumab RA program, 31 deaths occurred within 16 weeks of last dose of study agent. Deaths that occurred more than 16 weeks after the patient's last dose of study drug where not included in the exposure adjusted analyses, but are listed in Table 34. The causes of death in the sirukumab-treated patients were suggestive of immunosuppressive effects in patients with RA. The main causes of death were cardiovascular events (n=13), serious infections (n=8), malignancies (n=6), and other causes (n=9) (Table 32). Cardiovascular events, serious infection, and malignancy are discussed in further detail in this safety review. The remaining 9 deaths were due to other causes that would not be unusual in RA clinical studies. An overview of the system organ classes (SOC) and preferred terms (PT) for patients who died is provided in Table 33. Additional details regarding the causes of death in studies ARA3002 and ARA3003 are provided in Table 34. Note that in these tables, patients could have more than one cause of death attributed by the investigator. The main causes of death were related to cardiovascular events (myocardial infarction, cerebrovascular events, and sudden cardiac death), malignancies (lung, breast, bladder, and renal cancers and acute myeloid leukemia), and a variety of serious infections (pneumonia, sepsis, cellulitis, and peritonitis).

Table 31: Deaths in the Sirukumab RA Program by Study

Study	Total (# of deaths that occurred ≤16 weeks of last dose of study agent)
C1377T04	1 (1)
ARA3001	0 (0)
ARA3002	22 (20[a])
ARA3002 during LTE (ARA3004)	3 (3)
ARA3003	6 (5)
ARA3003 during LTE (ARA3004)	1 (1)
ARA3005	2 (1)
Total	35[a] (31[a])

a One death occurred in a placebo-treated patient
Data through SCS cutoff of February 2, 2016
Source: Summary of Clinical Safety, Table 12, page 51, submitted 9/22/16

Table 32: Incidence Rate (Subject Based Per 100 Patient-Years of Follow-up) of Death Overall and by Cause in the Sirukumab RA Development Program (All Subject Analysis Set)

	Sirukumab (n=3,120)	
Study	**Number of deaths**	**Incidence per 100 PY, 95% CI**
All cause of death (as assessed by the investigator)	34[a,b]	0.75 (0.52, 1.04)
MACE	13	0.29 (0.15, 0.49)
Malignancy	6	0.13 (0.05, 0.29)
Serious infection	8	0.18 (0.08, 0.35)
Other causes	9	0.20 (0.09, 0.38)

a The deaths listed in this study are only for patients exposed to sirukumab and this table does not include the one death on placebo
b Patients could have more than one cause of death as attributed by the investigator
Abbreviations: MACE=major adverse cardiovascular event; RA=rheumatoid arthritis; PY=patient years; CI=confidence interval
Source: Summary of Clinical Safety—Correction Report, Table 15, page 9, received 6/12/17

Table 33: Causes of Death through 52 Weeks of Exposure (Studies ARA3002 and ARA3003)

System organ class (n[3]) Preferred term (n[4])	PBO N=850	Combined[1] SIR 50 mg N=1214	Combined[2] SIR 100 mg N=1217
Patients who died	1	10	12
Infections and infestations	0	3	4
Pneumonia	0	0	2
Sepsis	0	1	1
Arthritis bacterial	0	1	0
Bacterial sepsis	0	0	1
Cellulitis staphylococcal	0	1	0
Peritonitis	0	1	0
Septic shock	0	1	0
Vascular disorders	0	0	3
Aortic dissection	0	0	2
Hypertension	0	0	1
General disorders and administration site conditions	0	2	2
Death	0	1	1
Sudden death	0	0	1
Sudden cardiac death	0	1	0
Nervous system disorders	0	2	2
Cerebral hemorrhage, cerebral infarction	0	0	2
Cerebrovascular accident	0	2	0
Cardiac disorders	0	1	2
Myocardial infarction	0	1	2
Neoplasms benign, malignant and unspecified	0	0	2
Lung cancer metastatic and lung neoplasm malignant	0	0	1
Lung neoplasm malignant	0	0	1
Respiratory, thoracic, and mediastinal disorders	1	0	2
Acute respiratory distress syndrome	1	0	1
Pleural effusion	0	0	1
Blood and lymphatic system disorders	0	1	0
Anemia	0	1	0
Injury, poisoning, and procedural complications	0	1	0
Road traffic accident	0	1	0

1 All patients who received at least one dose of sirukumab 50 mg q4w. This includes patients who were initially randomized to sirukumab 50mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w.
2 All patients who received at least one dose of sirukumab 100 mg q2w. This includes patients who were initially randomized to sirukumab 100 mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w.
3 n=number of deaths attributed to adverse event of each system organ class; patients could have more than one adverse event system organ cause of death attributed by the investigator
4 n=number of deaths attributed to adverse event of each preferred term; patients could have more than adverse event preferred term cause of death attributed by the investigator
Abbreviations: PBO=placebo; SIR=sirukumab; EE=early escape; LE=late escape; CO=cross over
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: Summary of Clinical Safety, TSFAE663, pages 1146-7

Table 34: Summary of Deaths in the Sirukumab RA development program: All subject Analysis Set

Study-Subject ID	Treatment group (EE/LE/CO or NA)	Age, Sex, Race	Study date of: Last dose before death/Death	Cause of death (as assessed by investigator)
Before W18				
ARA3002-21971	PBO (NA)	62, F, W	71/81	Acute respiratory distress syndrome
ARA3002-20993	SIR 50 mg q4w (NA)	66, M, W	1/14	Sudden cardiac death
ARA3002-20002	SIR 100 mg q2w (NA)	81, F, W	17/35	Myocardial infarction (adjudicated as non-MACE), hypertension
After W18, Before W52				
ARA3002-20065	PBO→SIR 50 mg (EE)	60, M, A	284/286	Road traffic accident
ARA3002-20813	PBO→SIR 50 mg (LE)	70, M, A	349/351	Myocardial infarction
ARA3002-21125	PBO→SIR 50 mg (EE)	71, F, W	197/233	Cerebrovascular accident
ARA3003-30335	PBO→SIR 50 mg (CO)	78, F, B/AA	197/211	Cerebrovascular accident
C1377T04-40225	PBO→SIR 100 mg (EE)	58, F, W	171/217	Intracranial aneurysm
ARA3003-30039	PBO→SIR 100 mg (EE)	46, F, W	141/248	Myocardial infarction (adjudicated as non-MACE)
ARA3002-21254	SIR 50 mg (NA)	63, F, Other	338/348	Death
ARA3002-21018	SIR 50 mg (NA)	73, M, W	225/327	Peritonitis
ARA3002-22472	SIR 50 mg (NA)	60, F, Other	203/262	Septic shock
ARA3005-50118	SIR 50 mg (NA)	82, M, W	114/247	Adenocarcinoma
ARA3002-21129	SIR 100 mg (NA)	79, F, W	139/167	Acute respiratory distress, bacterial sepsis
ARA3002-21473	SIR 100 mg (NA)	61, F, W	339/374	Cerebral infarction
ARA3002-22412	SIR 100 mg (NA)	76, F, M	253/314	Lung cancer metastatic
ARA3003-31225	SIR 100 mg (NA)	63, M, W	337/352	Pneumonia
ARA3003-31299	SIR 100 mg (NA)	61, F, W	155/174	Sudden death
ARA3005-50259	SIR 100 mg (NA)	67, F, W	182/190	Hemorrhagic stroke
After W52				
ARA3002-20488	PBO→SIR 50 mg (CO)	46, M, W	631/637	Cellulitis staphylococcal, arthritis bacterial
ARA3002/3004-21203	PBO→SIR 50 mg (CO)	55, F, W	786/791	Cardiopulmonary arrest
ARA3003-30457	PBO→SIR 50 mg (CO)	59, M, W	351/399	Anemia (adjudicated as MACE)
ARA3002-20504	PBO→SIR 100 mg (EE)	71, M, Other	574/587	Myocardial infarction
ARA3002-21104	PBO→SIR 100 mg (CO)	81, M, Other	518/536	Death
ARA3002-21811	PBO→SIR 100 mg (EE)	62, M, W	340/439	Lung neoplasm malignant
ARA3002-21880	PBO→SIR 100 mg (CO)	65, F, A	664/704	Aortic dissection
ARA3002-22316	PBO→SIR 100 mg (CO)	76, F, W	393/404	Pneumonia
ARA3003/3004-30660	PBO→SIR 100 mg (CO)	76, F, W	377/402	Aortic dissection, cerebral hemorrhage, pleural effusion, sepsis
ARA3002-20106	SIR 50 mg (NA)	73, M, W	519/549	Acute myeloid leukemia, necrotizing fasciitis, sepsis, urinary tract infection
ARA3002/3004-20316	SIR 50 mg (NA)	75, F, W	902/913	Intestinal ischemia
ARA3002/3004-20406	SIR 50 mg (NA)	63, F, W	841/860	Atlantoaxial instability, cerebral infarction
ARA3002-20426	SIR 50 mg (NA)	63, M, A	344/896	Malignant neoplasm of renal pelvis
ARA3002-20892	SIR 50 mg (NA)	68, F, W, H	519/562	Respiratory failure
ARA3003-31280	SIR 100 mg (NA)	39, F, W	198/475	Breast cancer metastatic
ARA3002-21985	SIR 100 mg (NA)	57, M, W	127/385	Bladder cancer

Abbreviations: A=Asian; M=male; F=female; M=male; W=white; H=Hispanic; B/AA=black/African American; CO=crossover; EE=early escape; LE=late escape; NA=not applicable; PBO=placebo; SIR=sirukumab
Sirukumab dosing is 50 mg every 4 weeks and 100 mg every 2 week
Source: Summary of Clinical Safety Correction Report, Table 16, pages 12-17, submitted 6/09/17

Serious Adverse Events (SAE)

As discussed in the section above, in the placebo-controlled period (through 18 weeks of exposure), one patient each in the placebo, sirukumab 50 mg, and sirukumab 100 mg groups

died. The exposure adjusted mortality rate was 0.34 per 100 PYs of exposure in each of the treatment arms. In the pooled placebo-controlled studies through 52 weeks of exposure, there was an imbalance in deaths. Specifically, through 52 weeks of exposure, the incidence rate of death (per 100 PYs) was 0.2, 0.5, and 0.8 for patients in the placebo, sirukumab 50 mg q4w, and sirukumab 100 mg q2 week treatment arms, respectively. The main categories of death were MACE, infection, and malignancy.

As shown in Table 35, through 18 weeks of exposure, the incidence rate (per 100 PYs) of serious adverse events was higher in each of the sirukumab treatment groups (14.4 and 16.1 for 50 mg and 100 mg, respectively) compared to placebo (9.4). Infections and Infestations were the system organ class (SOC) in which SAEs were most frequently reported; these were reported in 0.7%, 1.9%, and 1.8% of patients on placebo, sirukumab 50 mg, and 100 mg groups, respectively (Table 36). Pneumonia and cellulitis were the most commonly reported SAEs in this SOC. Through 52 weeks of exposure, Infections and Infestations remained the SOC in which SAEs were most frequently reported. These adverse events of special interest will be discussed in more detail in sections to follow.

Through 52 weeks of exposure and through the SCS cutoff, the incidence rate of SAEs remained fairly constant and were similar between sirukumab 50 mg and 100 mg (Table 35).

Table 35: Overview of SAEs for Different Safety Pools and Follow-up Times

	ARA3002 and ARA3003			ARA3002 and ARA3003[1]					ARA3002 and ARA3003[1]	
	Through 18 weeks of exposure			Through 52 weeks of exposure					Through SCS cutoff	
	PBO N=850	50 mg[2] N=848	100 mg[3] N=850	PBO N=850	50 mg[2] N=848	100 mg[3] N=850	Combined[4] 50 mg N=1214	Combined[5] 100 mg N=1217	Combined[4] 50 mg N=1214	Combined[5] 100 mg N=1217
Total patient-years of exposure[6]	292	292	294	520	787	784	1109	1111	1964	1975
Subjects with ≥1 event, N (%[6]), IR:										
SAE (according to CFR definition)	27 (3.2) 9.4	41 (4.8) 14.4	46 (5.4) 16.1	56, 11.1	112, 15.1	95, 12.7	151, 14.3	152, 14.4	237, 13.5	246, 14.0

1 Includes data from ARA3004
2 Only includes patients randomized to sirukumab 50 mg q4w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w
3 Only includes patients randomized to sirukumab 100 mg q2w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w.
4 All patients who received at least one dose of sirukumab 50 mg q4w through the noted exposure time. This includes patients who were initially randomized to sirukumab 50mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w.
5 All patients who received at least one dose of sirukumab 100 mg q2w through the noted exposure time. This includes patients who were initially randomized to sirukumab 100 mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w.
6 Total patient-years of exposure is calculated as the total amount of safety follow-up in the given window with censoring due to lost to follow-up, completion of planned follow-up, window cutoff, or death
7 Cumulative incidence percentages are only shown through 18 weeks and no other time periods given differences in exposure between sirukumab and placebo after 18 weeks.
Abbreviations: PBO=placebo; SIR=sirukumab; EE=early escape; LE=late escape; CO=cross over; SCS=Summary of Clinical Safety; IR=incidence rate per 100 person years; q2w=every 2 weeks; q4w=every 4 weeks
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: IR response, page 128, submitted 5/26/17

Table 36: SAEs Through 18 Weeks of Exposure by MedDRA SOC (ARA3002 and ARA3003)

	Randomized Treatment Groups in ARA3002 and ARA3003 Through 18 weeks of exposure		
	PBO N=850	50 mg N=848	100 mg N=850
Subjects with ≥1 event, N (%)			
SAE	27 (3.2)	41 (4.8)	46 (5.4)
MedDRA SOC			
Infections and infestations	6 (0.7)	16 (1.9)	15 (1.8)
Investigations	2 (0.2)	2 (0.2)	5 (0.6)
Musculoskeletal and connective tissue disorders	6 (0.7)	8 (0.9)	6 (0.7)
Injury, poisoning, procedural complications	3 (0.4)	4 (0.5)	6 (0.7)
Gastrointestinal disorders	3 (0.4)	3 (0.4)	5 (0.6)
Respiratory, thoracic and mediastinal disorders	2 (0.2)	0	2 (0.2)
Hepatobiliary disorders	0	0	3 (0.4)
Cardiac disorders	4 (0.5)	3 (0.4)	2 (0.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.1)	0	2 (0.2)
Nervous system disorders	1 (0.1)	1 (0.1)	2 (0.2)
Skin and subcutaneous tissue disorders	1 (0.1)	0	3 (0.4)
Vascular disorders	1 (0.1)	0	3 (0.4)
Blood and lymphatic system	1 (0.1)	1 (0.1)	2 (0.2)
Eye disorders	0	1 (0.1)	1 (0.1)
General disorders and administration site conditions	1 (0.1)	4 (0.5)	2 (0.2)
Metabolism and nutrition disorders	0	0	1 (0.1)
Renal and urinary disorders	1 (0.1)	0	1 (0.1)
Pregnancy, puerperium and perinatal conditions	0	0	1 (0.1)
Psychiatric disorders	1 (0.1)	1 (0.1)	0
Reproductive system and breast disorders	1 (0.1)	0	0

Abbreviations: SAE=Serious Adverse Event; SOC=system organ class
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: Summary of Clinical Safety, Table 17, page 71, submitted 9/22/16

Discontinuations due to Adverse Events

Through 18 weeks of exposure, the proportion of patients discontinuing study agent administration due to one or more AE in trials ARA3002 and ARA3003 was higher in the two sirukumab groups compared to placebo (Table 37). The proportions of patients with AEs leading to discontinuation were 2.6%, 4.0%, and 5.3%, for the placebo, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups, respectively. A similar trend was seen through 52 weeks of exposure as the incidence rate of discontinuations due to AEs was higher in the two sirukumab groups compared to the placebo group. When comparing the two doses of sirukumab, there were more discontinuations due to AEs in the 100 mg q2w group compared to the 50 mg q4w group.

Through 18 weeks of exposure, the SOC with the most frequently reported AEs leading to discontinuation was Investigations. Across the three treatment groups, most events in this

SOC were events related to increases in hepatic enzymes. Through the SCS cutoff, Infections and Infestations was the SOC in which AEs leading to discontinuation were more frequently reported.

Table 37: Overview of Adverse Events Leading to Discontinuation for Different Safety Pools and Follow-up Times

	ARA3002 and ARA3003			ARA3002 and ARA3003[1]					ARA3002 and ARA3003[1]	
	Through 18 weeks of exposure			Through 52 weeks of exposure					Through SCS cutoff	
	PBO N=850	50 mg[2] N=848	100 mg[3] N=850	PBO N=850	50 mg[2] N=848	100 mg[3] N=850	Combined[4] 50 mg N=1214	Combined[5] 100 mg N=1217	Combined[4] 50 mg N=1214	Combined[5] 100 mg N=1217
Total patient-years of exposure[6]	292	292	294	520	787	784	1109	1111	1964	1975
Subjects with ≥1 event, N (%[7]), IR:										
AE leading to discontinuation	22 (2.6), 7.63	34 (4.0), 11.93	45 (5.3), 15.81	31, 6.05	76, 9.94	80, 10.48	100, 9.26	123, 11.41	142, 7.39	172, 8.93

1 Includes data from ARA3004
2 Only includes patients randomized to sirukumab 50 mg q4w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w
3 Only includes patients randomized to sirukumab 100 mg q2w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w.
4 All patients who received at least 1 dose of sirukumab 50 mg q4w through the noted exposure time. This includes patients who were initially randomized to sirukumab 50mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w.
5 All patients who received at least 1 dose of sirukumab 100 mg q2w through the noted exposure time. This includes patients who were initially randomized to sirukumab 100 mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w.
6 Total patient-years of exposure is calculated as the total amount of safety follow-up in the given window with censoring due to lost to follow-up, completion of planned follow-up, window cutoff, or death
7 Cumulative incidence percentages are only shown through 18 weeks and no other time periods given differences in exposure between sirukumab and placebo after 18 weeks.
Abbreviations: PBO=placebo; SIR=sirukumab; EE=early escape; LE=late escape; CO=cross over; SCS=Summary of Clinical Safety; IR=incidence rate per 100 person years; q2w=every 2 weeks; q4w=every 4 weeks
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: IR response, page 128, submitted 5/26/17

Common adverse events

Table 38 presents the common treatment-emergent adverse events (TEAEs) by SOC/PT through 18 weeks of exposure for events that occurred in ≥5% of patients. During the first 18 weeks of exposure in ARA3002 and ARA3003, more patients in the sirukumab arms experienced any TEAE as compared to subjects in the placebo arm (52% placebo arm, 61% sirukumab 50 mg q4w, and 65% sirukumab 100 mg q2w). Adverse events in the Infections and Infestations SOC were the most common adverse event. The most common infections were upper respiratory tract infection, urinary tract infection, and nasopharyngitis. Investigations were next most common, with ALT and AST increased being the most common preferred term (PT). The most common TEAEs (by PT) were increased ALT, increased AST, and injection site erythema. All of these TEAEs occurred more frequently in patients on sirukumab. When comparing the two doses, the overall proportion of patients with AEs was greater for the 100 mg than the 50 mg dose group. Similar trends were seen for three of the four SOCs seen in Table 38. In contrast, the proportion of patients with Infections and infestations was greater in the 50 mg than the 100 mg group. During longer duration of exposure, similar trends were noted. Infections and infestations remained the SOC in which AEs were the most frequently reported.

Table 38: Number of patients with ≥1 TEAE(s) by MedDRA SOC through 18 weeks of exposure in ≥5% of patients by PT (any treatment group)

	Randomized Treatment Groups in ARA3002 and ARA3003 Through 18 weeks of exposure		
	PBO N=850	SIR 50 mg N=848	SIR 100 mg N=850
Total patient-years of exposure	292	292	294
Subjects with ≥1 AE, N (%), IR	444 (52.2), 227.34	515 (60.7), 293.59	548 (64.5), 333.70
MedDRA SOC/PT			
Infections and infestations	220 (25.9)	219 (25.8)	200 (23.5)
Upper respiratory tract infection	56 (6.6)	38 (4.5)	35 (4.1)
Nasopharyngitis	46 (5.4)	46 (5.4)	30 (3.5)
Investigations	43 (5.1)	159 (18.8)	165 (19.4)
ALT increased	16 (1.9)	82 (9.7)	95 (11.2)
AST increased	9 (1.1)	53 (6.3)	66 (7.8)
General disorders and administration site conditions	51 (6)	92 (10.8)	161 (18.9)
Injection site erythema	11 (1.3)	48 (5.7)	88 (10.4)
Injection site pruritus	2 (0.2)	10 (1.2)	48 (5.6)
Musculoskeletal and connective tissue disorders	110 (12.9)	68 (8.0)	81 (9.5)
RA	49 (5.8)	20 (2.4)	19 (2.2)

Abbreviations: PBO=placebo; SIR=sirukumab; SOC=system organ class; PT=preferred term; ALT=alanine aminotransferase; AST=aspartate transferase; RA=rheumatoid arthritis
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: Summary of Clinical Safety, Table 10, page 47, submitted 9/22/16 and IR response, page 128, submitted 5/26/17

Laboratory Abnormalities

Sirukumab was associated with changes in certain hematologic, hepatobiliary, and lipid parameters. For ARA3002 and ARA3003, the protocols incorporated pre-specified criteria for permanent discontinuation due to laboratory abnormalities as follows:

- Two confirmed absolute neutrophil counts (ANC) of $<0.5x10^3/\mu L$
- Two confirmed consecutive platelet counts < 50,000/μL
- Drug induced liver injury including any one of the following:
  - ALT or AST ≥5x upper limit of normal (ULN), but <8x ULN and cannot be monitored weekly for ≥2 weeks
  - ALT or AST ≥8x ULN
  - ALT or AST ≥5x ULN for 2 or more weeks
  - ALT or AST ≥3x ULN and total bilirubin ≥2x ULN (>35% direct bilirubin or ALT or AST ≥3x ULN and INR>1.5, if INR measured)
  - ALT or AST ≥3x ULN accompanied by clinical symptoms believed to be related to hepatitis or hypersensitivity such as new or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash.

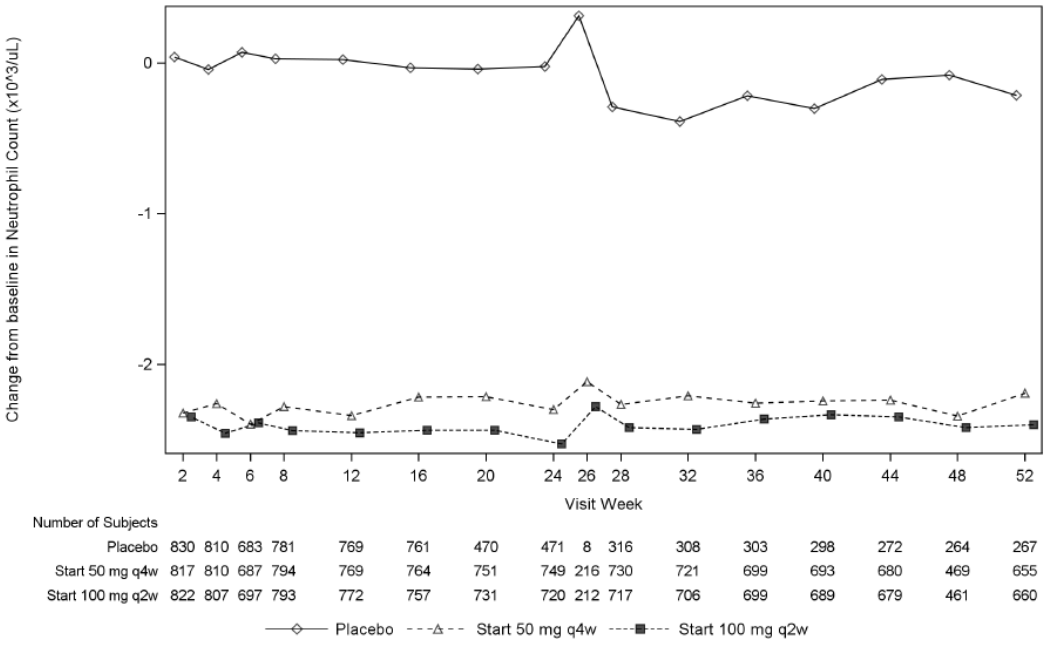
In addition, there were protocol-specified criteria for interruption of study agent administration for the following laboratory criteria:

- ALT or AST ≥3x ULN
- Neutrophil count 0.5 to $\leq 1x10^3/\mu L$ of $<0.5x10^3/\mu L$
- Platelet count 50,000 to ≤100,000/μL or <50,000/μL

White blood cells/Neutrophils

Decreases in ANCs have been associated with IL-6 inhibition and were also observed in the sirukumab studies. Figure 8 displays the mean change in neutrophil count across visits through 52 weeks of exposure in trials ARA3002 and ARA3003. The decrease in neutrophil was evident two weeks after initiation of therapy, which was the first time point measured, and was fairly stable after the initial decrease. At week 16, the mean decrease in neutrophil count was 0.03, 2.2, and 2.4x10^3/µL for the placebo, sirukumab 50 mg q4w, and the sirukumab 100 mg q2 week groups, respectively. Although a decrease was observed, the majority of patients had neutrophil counts within the normal range. Table 39 displays the number of patients with post-baseline values by maximum toxicity grade. More patients treated with sirukumab than placebo had grade 1, 2, and 3 decreases in neutrophil counts.

Figure 8: Mean Change from Baseline in Neutrophil Count (x10^3/uL) by Visit Through 52 Weeks of Exposure (Studies ARA3002 and ARA3003)



Week 26 from ARA3003 only; Week 48 from ARA3002 only.
Source: IR Response, page 12, submitted 5/26/17

Table 39: Number of Patients with Post-Baseline Values by Maximum Toxicity Grade for Neutrophils through 18 Weeks of Exposure (ARA3002 and ARA3003)

	Randomized Treatment Groups in ARA3002 and ARA3003		
	Through 18 weeks of exposure		
	PBO N=850	SIR 50 mg N=848	SIR 100 mg N=850
Patients with post-baseline maximum:			
Toxicity grade 0 (≥LLN)	816 (96.9)	576 (68.3)	568 (67.1)
Toxicity grade 1 (<LLN-1,5000/mm^3)	19 (2.3)	149 (17.7)	167 (19.7)
Toxicity grade 2 (<1,500-1,000/mm^3)	5 (0.6)	97 (11.5)	94 (11.1)
Toxicity grade 3 (<1,000-500/mm^3)	1 (0.1)	21 (2.5)	16 (1.9)
Toxicity grade 4 (<500/mm^3)	1 (0.1)	0	1 (0.1)

Abbreviations: LLN=lower limit of normal; PBO=placebo; SIR=sirukumab
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: Clinical Summary of Safety, Table 36, page 114, submitted 9/22/16

Across the phase 3 studies through SCS cutoff, the majority of cases of grade 4 decreases in neutrophils were not associated with infections. Serious infection was reported in two cases (UTI and peritonsillar abscess) within 3 weeks of the occurrence of neutropenia.

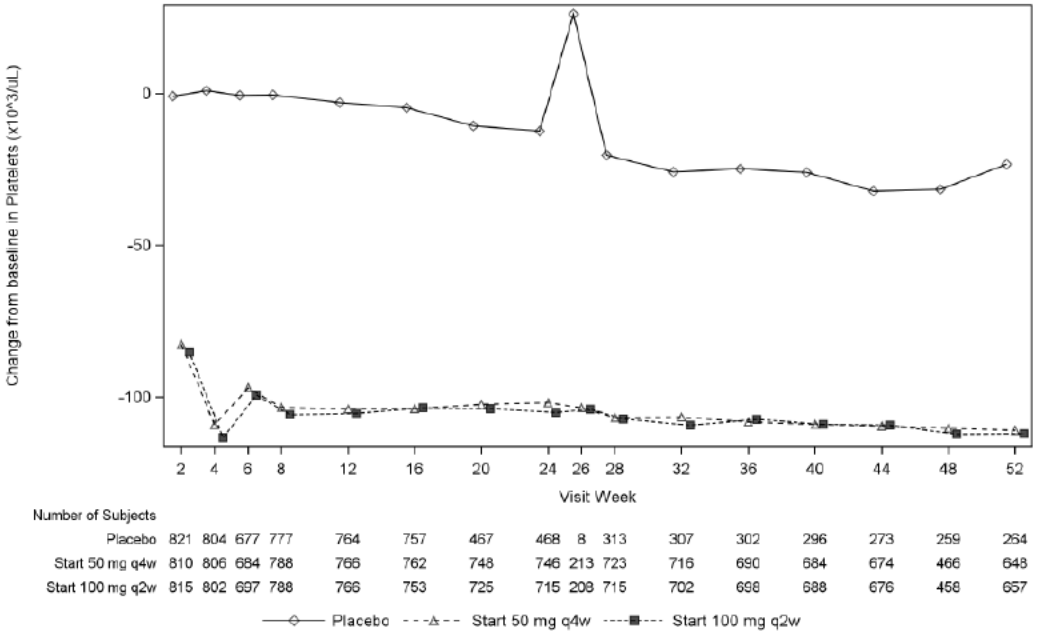
Based on the trajectory of decreases in neutrophil counts, Janssen proposes prescribers monitor neutrophil counts four to eight weeks after start of therapy and then according to routine clinical practice.

Sirukumab is associated with an overall decrease in WBC (leukocyte count). The WBC count decrease associated with sirukumab is primarily due to a decrease in neutrophils.

Platelet count

During the double-blind treatment period, there was a clear trend toward a decline in platelets in patients on sirukumab. Figure 9 displays the mean platelet counts over time through 52 weeks of exposure in trials ARA3002 and ARA3003. After the initial decrease (at week 2, the first time it was measured), mean platelet counts stabilized throughout the remainder of treatment. At Week 16, the mean platelet decrease was 104, 104, and $5x10^3/\mu L$, for sirukumab 50 mg q4w, sirukumab 100mg q2w, and placebo, respectively. Despite the decreases in platelet counts, the majority of patients had platelet counts within normal limits. Through 18 weeks of exposure, there were more grade 1 and grade 2 platelet count decreases in the sirukumab groups compared to the placebo group (Table 40). Across the phase 3 studies through the SCS cutoff date, one patient (20002) had grade 3 thrombocytopenia, an MI, cardiac arrest, and GI hemorrhage. The patient died due to these medical events.

Figure 9: Change from Baseline in Platelets (x10^3/µL) by Visit through 52 Weeks (ARA3002 and ARA3003)



Week 26 from ARA3003 only. Week 48 from ARA3002 only.

Source: IR Response, page 10, submitted 5/26/17

Table 40: Number of Patients with Post-Baseline Values by Maximum Toxicity Grade for Platelets through 18 Weeks of Exposure (ARA3002 and ARA3003)

	ARA3002 and ARA3003		
	Through 18 weeks of exposure		
	PBO N=850	SIR 50 mg N=848	SIR 100 mg N=850
Patients with post-baseline maximum:			
Toxicity grade 0 (≥LLN)	836 (99.4)	768 (91.1)	759 (89.8)
Toxicity grade 1 (<LLN-75,000/mm^3)	5 (0.6)	74 (8.8)	81 (9.6)
Toxicity grade 2 (<75,000-50,000/mm^3)	0	1 (0.1)	5 (0.6)
Toxicity grade 3 (<50,000-25,000/mm^3)	0	0	0
Toxicity grade 4 (<25,000/mm^3)	0	0	0

Abbreviations: LLN=lower limit of normal; PBO=placebo; SIR=sirukumab
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: Clinical Summary of Safety, Table 36, page 114, submitted 9/22/16

Hepatic enzyme abnormalities

There were increases in mean AST, ALT, and bilirubin values with sirukumab compared to placebo (Table 41). Compared with patients who were not treated with DMARDs at baseline, patients treated with DMARDs at baseline were more likely to have elevations in AST and ALT.

Liver function test abnormalities were relatively common in the RA clinical development program (Table 43). Through 18 weeks of exposure, the proportion of patients with increases in ALT >ULN was 21%, 58%, and 57%, for the placebo, sirukumab 50 mg, and sirukumab

100 mg groups, respectively. The majority of patients with increases in ALT had grade 1 abnormalities. Through 18 weeks of exposure, the proportion of patients with increases in AST >ULN was 16%, 45%, and 45%, for the placebo, sirukumab 50 mg, and sirukumab 100 mg groups, respectively. The majority of patients with increases in AST had grade 1 abnormalities.

Hepatobiliary events were adjudicated if a patient met one of the following criteria:

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

Ten cases were adjudicated: three patients in the placebo group, one patient in the sirukumab 50 mg q4w group, and six patients in the 100 mg q2w group. Of the 10 cases, five cases were considered possibly or probably related to treatment: two in the placebo group (both for grade 4 ALT/AST toxicity) and three in the sirukumab 100 mg group (two meeting Hy's law laboratory criteria for ALT/AST ≥3×ULN and bilirubin ≥2×ULN, and one for grade 4 ALT/AST toxicity and HEV IgM+). No evidence for drug-induced liver injury was observed for the sirukumab 50 mg dose. The two cases that met laboratory criteria for Hy's law[17] were confounded by the presence of preexisting hepatic steatosis and concomitant hepatotoxic drugs. Thus, Janssen felt the clinical criteria were not met and there was not clear evidence of hepatotoxic effects of sirukumab.

[17] Reuben A. Hy's law. Hepatology. 2004;39(2):574-8.

Table 41: Mean Changes from Baseline in AST, ALT, and Bilirubin Laboratory Values (ARA3002 and ARA3003)

	ARA3002 and ARA3003 Through 18 weeks of exposure			ARA3002 and ARA3003 Through 52 weeks of exposure		
	PBO N=850	SIR 50 mg N=848	SIR 100 mg N=850	PBO N=850	SIR 50 mg[1] N=848	SIR 100 mg[2] N=850
ALT (IU/L), mean change	-0.2	12.0	13.0	-1.1	11.1	11.6
AST (IU/L), mean change	0.04	6.3	7.5	-0.5	6.4	6.7
Total bilirubin (mg/dL), mean change	-0.01	0.3	0.3	0.02	0.3	0.3

1 Only includes patients randomized to sirukumab 50 mg q4w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w
2 Only includes patients randomized to sirukumab 100 mg q2w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w
Abbreviations: PBO=placebo; SIR=sirukumab; EE=early escape; LE=late escape; CO=cross over; q2w=every 2 weeks; q4w=every 4 weeks
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: IR Response, page 132, submitted 5/26/17

Table 42: AST, ALT, and Bilirubin Laboratory Changes by Multiples of the Upper Limit of Normal through 18 Weeks of Exposure (ARA3002 and ARA3003)

	ARA3002 and ARA3003 Through 18 weeks of exposure		
	PBO N=850	SIR 50 mg N=848	SIR 100 mg N=850
Patients with any event of ALT >ULN, %	21.2	58.3	57.1
Patients with any event of ALT≥3x ULN, %	1.3	6.3	8.2
Patients with any event of ALT≥5x ULN, %	0.6	1.7	2.1
Patients with any event of ALT≥8xULN, %	0.2	0.5	0.8
Patients with any event of AST >ULN, %	16.2	44.6	44.7
Patients with any event of AST≥3x ULN, %	0.7	2.4	3.4
Patients with any event of AST≥5x ULN, %	0.4	0.2	0.7
Patients with any event of AST≥8xULN, %	0.2	0	0.1
Patients with any event of total bilirubin >ULN, %	1.2	9.4	11.8

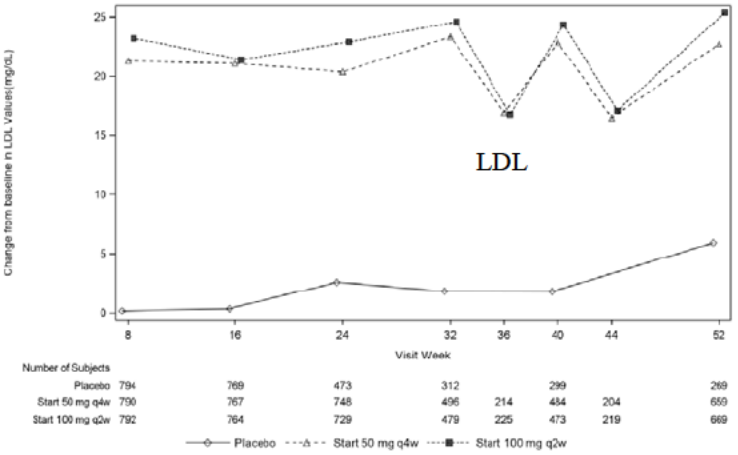
Abbreviations: PBO=placebo; SIR=sirukumab; EE=early escape; LE=late escape; CO=cross over; q2w=every 2 weeks; q4w=every 4 weeks
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: IR Response, page 132, submitted 5/26/17

Elevation in lipids

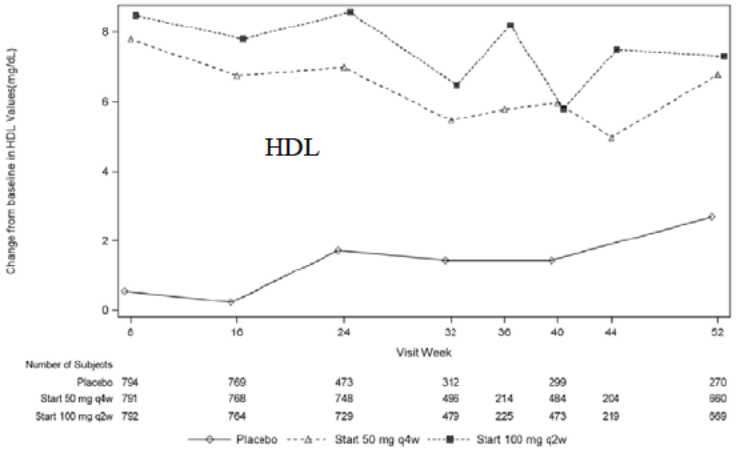
The mean changes from baseline in LDL, HDL, and triglycerides over time in studies ARA3002 and ARA3003 are displayed in Figure 10. Compared to placebo, a mean increase from baseline in LDL, HDL, and triglycerides was observed in the sirukumab treatment groups. The change from baseline was very similar for the two sirukumab doses (Table 43). At Week 16, the mean increase on sirukumab 50 mg in LDL was ~21 mg/dL, the mean increase in triglycerides was ~37 mg/dL, and the mean increase in HDL was ~7 mg/dL. Recognizing the limitations in cross study comparisons, the lipid increases seen with sirukumab were slightly greater than what was seen with another IL-6 inhibitor, sarilumab, but similar to those seen with another IL-6 inhibitor, tocilizumab (Table 44).

In the sirukumab program, after the initial elevation, the lipid elevations remained relatively stable. Internal consultation from the Division of Metabolic and Endocrine Products (DMEP) was obtained regarding the implications of these lipid parameter changes. DMEP consultants were of the opinion that it is difficult to predict the net effect of sirukumab on cardiovascular risk in patients with RA. It was noted that there is a complex interplay of inflammation with lipid levels and CV risk in patients with RA. Additional discussion of cardiovascular outcomes is provided below.

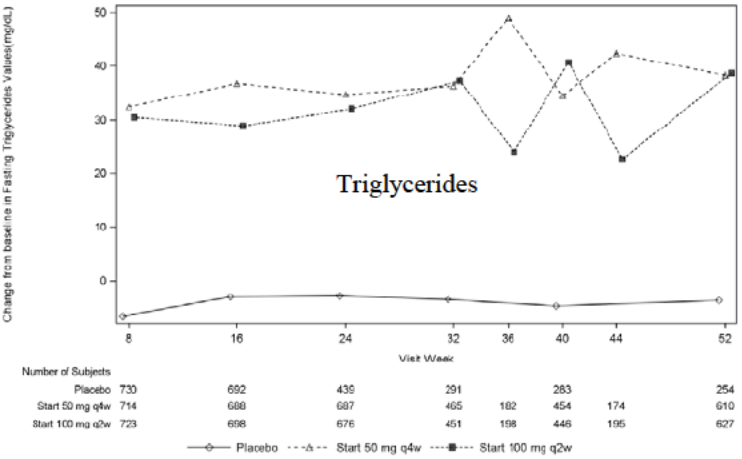
Figure 10: Mean Changes from Baseline in LDL, HDL, and Triglyceride (mg/dL) (ARA3002 and ARA3003)



Weeks 32, 40 from ARA3002 only; Weeks 36, 44 from ARA 3003 only.



Weeks 32, 40 from ARA3002 only; Weeks 36, 44 from ARA 3003 only.



Weeks 32, 40 from ARA3002 only; Weeks 36, 44 from ARA 3003 only.

Source: IR Response, pages 5 (LDL), 6 (HDL), and 8 (triglycerides), submitted 5/26/17

Table 43: Mean Changes from Baseline in LDL, HDL, Total Cholesterol, and Triglyceride Values (ARA3002 and ARA3003)

	PBO N=850	SIR 50 mg q4w N=848	SIR 100 mg q2w N=850
Mean change from baseline at Week 16 (mg/dL)			
HDL	0.23	6.76	7.81
LDL	0.37	21.08	21.38
Total cholesterol	0.03	34.73	35.11
Triglycerides	-3.03	36.74	28.93

Abbreviations: PBO=placebo; SIR=sirukumab; HDL=high density lipoprotein; LDL=low density lipoprotein
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: IR Response, pages 31-38, submitted 5/26/17

Table 44: Comparison of Approximated Mean Change from Baseline in LDL, HDL, and Triglyceride Values with Different IL-6 Inhibitors

Product	Sarilumab*		Tocilizumab^		Sirukumab	
Time point of assessment	Week 4		Week 24		Week 16	
Dose	150mg q2w SC	200mg q2w SC	4mg/kg IV	8mg/kg IV	50mg q4w SC	100mg q2w SC
Mean change from baseline (mg/dL)						
HDL	3	3	3	5	7	8
LDL	12	16	20	25	21	21
Triglycerides	20	27	~30-40#		37	29

*Sarilumab prescribing information
^Tocilizumab prescribing information
#Estimated from clinical review: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125276s000MedR.pdf (accessed 6/2/17)
Abbreviations: PBO=placebo; SIR=sirukumab; HDL=high density lipoprotein; LDL=low density lipoprotein

No patients developed severe triglyceridemia and pancreatitis. There were a total of five cases (three serious, two non-serious) of pancreatitis reported through the data cutoff date for the SCS. None of the subjects had increases in triglycerides >500 mg/dL at any time. With the exception of one subject with one isolated value of 304 mg/dL (over five months prior to the event), all subjects had triglycerides less than 300 mg/dL throughout their treatment with sirukumab.

Through 18 weeks of exposure in ARA3002 and ARA3003, a higher proportion of patients in the sirukumab 50 mg and 100 mg groups had post-baseline total cholesterol values greater than the upper limit of normal compared with the placebo group (Table 45). The majority of patients with increased cholesterol had grade 1 (>ULN-300 mg/dL) or grade 2 (>300-400 mg/dL) increases. Through 18 weeks of exposure, a higher proportion of patients treated with sirukumab initiated statins compared to patients treated with placebo (Table 46).

Table 45: Number of Patients with Post-Baseline Values for Total Cholesterol by Maximum Toxicity Grade Through 18 Weeks of Exposure

	ARA3002 and ARA3003 Through 18 weeks of exposure		
	PBO N=850	SIR 50 mg N=848	SIR 100 mg N=850
Patients with post-baseline maximum:			
Toxicity grade 0 (≤ULN)	783 (94.5%)	667 (80.7%)	662 (79.4%)
Toxicity grade 1 (>ULN-300 mg/dL)	17 (2.1%)	51 (6.2%)	58 (7.0%)
Toxicity grade 2 (>300-400 mg/dL)	29 (3.5%)	101 (12.2%)	110 (13.2%)
Toxicity grade 3 (>400-500 mg/dL)	0	7 (0.8%)	3 (0.4%)
Toxicity grade 4 (>500 mg/dL)	0	1 (0.1%)	1 (0.1%)

Abbreviations: PBO=placebo; SIR=sirukumab; q2w=every 2 weeks; q4w=every 4 weeks
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: Summary of Clinical Safety, Table 45, page 123, submitted 9/22/16

Table 46: Number of Patients who Initiated Statins (Studies ARA 3002 and ARA3003)

	ARA3002 and ARA3003 Through 18 weeks of exposure		
	PBO N=850	SIR 50 mg N=848	SIR 100 mg N=850
Patients who initiated statins, n (%)	9 (1.1%)	25 (2.9%)	15 (1.8%)

Abbreviations: PBO=placebo; SIR=sirukumab; q2w=every 2 weeks; q4w=every 4 weeks
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: IR Response, page 8, submitted 6/16/17

7.5 Additional adverse events of special interest

Infections

Infections

Through 18 weeks of exposure, the incidence of infection was similar between the placebo and sirukumab 50 mg groups (Table 47). The incidence of infection was lower for the sirukumab 100 mg group compared to the sirukumab 50 mg group. Similar trends were noted through 52 weeks of exposure and through SCS cutoff. The most frequently reported infections included upper respiratory tract infection, nasopharyngitis, and urinary tract infection.

Serious infections

The incidence of serious infections was higher for both sirukumab groups than placebo through 18 and 52 weeks of exposure (Table 47). Through 52 weeks of exposure, the incidence rate of serious infections (per 100 PYs) was 2.7, 5.3, and 4.7 in the placebo, sirukumab 50 mg, and sirukumab 100 mg treatment arms, respectively. Through SCS cutoff, the rate of serious infections was similar in the sirukumab dose groups.

Through 18 weeks of exposure, the most commonly reported serious infections were pneumonia and cellulitis. The pattern of serious infections and deaths related to infections is

consistent with the conclusion that sirukumab is associated with significant immunosuppression.

Opportunistic infections, herpes zoster, and tuberculosis

Through 18 weeks of exposure, there were no opportunistic infections. Through 52 weeks of exposure, there was one opportunistic infection in the sirukumab 50 mg (combined) group (incidence rate 0.09/100 PY) and two opportunistic infections in the sirukumab 100 mg (combined) group (incidence rate 0.18/100 PY). The incidence rate of opportunistic infections was similar through SCS cutoff (Table 47). Through the SCS cutoff, the opportunistic infections were two cases of herpes ophthalmic and two cases of esophageal candidiasis. There were no serious opportunistic infections through the SCS cutoff date. Three additional cases were identified after the SCS cutoff date: retro-orbital *Aspergillus* infection, Cytomegalovirus (CMV) colitis, and cystitis secondary to *Candida glabrata.*

Through 18 weeks of exposure, the incidence rate (per 100 PYs) of herpes zoster was higher in both sirukumab groups than placebo. Similar trends were noted through 52 weeks of exposure and through SCS cutoff.

Through SCS cutoff for studies ARA3002, ARA3003, and ARA3004, there was one case of tuberculosis in the 100 mg (combined) group.

Conclusions regarding infections

The number and pattern of serious infections, fatal infections, and opportunistic infections observed with sirukumab treatment suggests significant immunosuppression that is apparent with both doses. The proposed prescribing information includes a boxed warning regarding the risk of serious infections leading to hospitalization or death.

Table 47: Overview of Infections for Different Safety Pools and Follow-up Times

	ARA3002 and ARA3003			ARA3002 and ARA3003[1]					ARA3002 and ARA3003[1]	
	Through 18 weeks of exposure			Through 52 weeks of exposure					Through SCS cutoff	
	PBO N=850	SIR 50 mg[2] N=848	SIR 100 mg[3] N=850	PBO N=850	SIR 50 mg[2] N=848	SIR 100 mg[3] N=850	Combined[4] SIR 50 mg N=1214	Combined[5] SIR 100 mg N=1217	Combined[4] SIR 50 mg N=1214	Combined[5] SIR 100 mg N=1217
Total patient-years of exposure[6]	292 3	292.3	293.5	519.5	786.9	784.4	1109.4	1111.1	1963.8	1974.6
Subjects with ≥1 event, N (%[7]), IR:										
Infection										
Infection	205 (24 1), 80.9	209 (24.6), 81.9	186 (21.9), 71.8	280, 67.96	391, 68.73	365, 63.08	529, 65.24	517, 62.77	636, 52.31	623, 50.76
AE preferred term										
Upper respiratory tract infection	52 (6.1)	36 (4.2)	35 (4.1)	---	---	---	---	---	---	---
Nasopharyngitis	45 (5.3)	46 (5.4)	27 (3.2)	---	---	---	---	---	---	---
SAE of infection	7 (0.8), 2.4	16 (1.9), 5.5	14 (1.6), 4.8	14, 2.7	41, 5.3	36, 4.7	54, 4 9	54, 4.9	89, 4.7	95, 5.0
SAE preferred term										
Pneumonia	1 (0.1)	5 (0.6)	4 (0.5)	---	---	---	---	---	---	---
Cellulitis	1 (0.1)	3 (0.4)	0	---	---	---	---	---	---	---
Abdominal abscess	0	0	1 (0.1)	---	---	---	---	---	---	---
All opportunistic infections	0	0	0	0	0	1, 0.13	1, 0.09	2, 0.18	1, 0.05	3, 0.15
Herpes zoster[8]	4 (0.5), 1 37	9 (1.1), 3.09	6 (0.7), 2.05	8, 1.55	22, 2.83	14, 1.80	27, 2.46	18, 1.63	34, 1.77	27, 1.38
Tuberculosis	0	0	0	0	0	1, 0.13	0	1, 0.09	0	1, 0.05

1 Includes data from ARA3004
2 Only includes patients randomized to sirukumab 50 mg q4w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w
3 Only includes patients randomized to sirukumab 100 mg q2w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w.
4 All patients who received at least 1 dose of sirukumab 50 mg q4w through the noted exposure time. This includes patients who were initially randomized to sirukumab 50mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w.
5 All patients who received at least 1 dose of sirukumab 100 mg q2w through the noted exposure time. This includes patients who were initially randomized to sirukumab 100 mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w.
6 Total patient-years of exposure is calculated as the total amount of safety follow-up in the given window with censoring due to lost to follow-up, completion of planned follow-up, window cutoff, or death
7 Cumulative incidence percentages are only shown through 18 weeks and no other time periods given differences in exposure between sirukumab and placebo after 18 weeks.
8 Defined as AE preferred terms: herpes zoster, ophthalmic herpes zoster, varicella zoster virus infection, herpes zoster oticus
Abbreviations: PBO=placebo; SIR=sirukumab; EE=early escape; LE=late escape; CO=cross over SCS=Summary of Clinical Safety; IR=incidence rate per 100 person years; q2w=every 2 weeks; q4w=every 4 weeks; SAE=serious adverse event; AE=adverse event
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: IR response, page 130, submitted 5/26/17

GI perforations

Events of GI perforation have been reported in clinical trials of other IL-6 inhibitors in patients with RA, primarily as complications of diverticulitis. Patients with acute diverticulitis requiring antibiotic treatment or history of GI perforation were excluded from the clinical trials.

For the GI perforation adjudication process, a Standard MedDRA Query (SMQ) and specific MedDRA preferred terms (diverticulitis intestinal hemorrhagic, diverticular fistula, diverticular perforation, and diverticulitis) were reviewed and agreed with the Adjudicator as a search strategy and were utilized to identify potential cases of GI perforation. This SMQ, with additional PTs, served as a trigger list to query the clinical database for serious cases that represented potential GI perforation events. Based upon results from the trigger list, all serious cases were medically reviewed by Janssen. If the case represented, or was suspected to represent an event of GI perforation, diverticulitis, intra-abdominal abscess, or peritonitis, the case was provided to the Adjudicator for review. Adverse events of possible GI perforation were adjudicated by a single, independent gastroenterology expert to confirm the diagnosis. The Adjudicator reviewed each potential GI perforation event based on pre-specified definitions and prepared an adjudication form which was returned to the Medical Monitor.

During the review, Janssen noted issues with the adjudication process. See the discussion of the adjudication issues in Section 7.2. As discussed above, Janssen submitted corrected data during the review, and these analyses were based on the revised data.

Through 18 weeks of exposure, there were four patients with GI perforations (one on 50 mg and three on 100 mg sirukumab; IR 0.34 and 1.02/100 PYs) (Table 48). There were no events in the placebo group. Through 52 weeks of exposure the IR/100 PYs of GI perforation were 0.19, 0.25, and 0.51 for the placebo, sirukumab 50 mg (start), and sirukumab 100 mg (start) groups, respectively. Thus, the incidence rate of GI perforation was higher in the sirukumab groups compared to placebo. Rates were slightly greater on sirukumab when including post-escape data (i.e., in the sirukumab combined arms). When evaluating the dataset from studies ARA3001, ARA3002, ARA3003, ARA3004, and ARA3005, there were more cases of GI perforation, but the incidence rates remained similar to what was seen in studies ARA3002 and ARA3003 (Table 49). When comparing the incidence rate between the sirukumab doses in the larger dataset of five studies, the rate was slightly higher in the 100 mg group compared to the 50 mg group.

The majority of events of GI perforation were lower GI perforations related to diverticulitis or diverticular perforation. There were also events of intestinal ischemia, large intestine perforation, perforated appendicitis, gastric ulcer perforation, and duodenal ulcer perforation. The proposed prescribing information includes a Warning for GI perforations.

Table 48: Overview of GI Perforations for Different Safety Pools and Follow-up Times

	ARA3002 and ARA3003			ARA3002 and ARA3003[1]					ARA3002 and ARA3003[1]	
	Through 18 weeks of exposure			Through 52 weeks of exposure					Through SCS cutoff	
	PBO N=850	SIR 50 mg[2] N=848	SIR 100 mg[3] N=850	PBO N=850	SIR 50 mg[2] N=848	SIR 100 mg[3] N=850	Combined[4] SIR 50 mg N=1214	Combined[5] SIR 100 mg N=1217	Combined[4] SIR 50 mg N=1214	Combined[5] SIR 100 mg N=1217
Total patient-years of exposure[6]	292	292	293	519	786	783	1108	1109	1961	1972
Subjects with ≥1 event, N, IR[7]:										
Adjudicated GI perforation	0	1, 0.34	3, 1.02	1, 0.19	2, 0.25	4, 0.51	3, 0.27	6, 0.54	6, 0.31	8, 0.41

1 Includes data from ARA3004
2 Only includes patients randomized to sirukumab 50 mg q4w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w
3 Only includes patients randomized to sirukumab 100 mg q2w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w.
4 All patients who received at least one dose of sirukumab 50 mg q4w through the noted exposure time. This includes patients who were initially randomized to sirukumab 50mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w.
5 All patients who received at least one dose of sirukumab 100 mg q2w through the noted exposure time. This includes patients who were initially randomized to sirukumab 100 mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w.
6 Total patient-years of exposure is calculated as the total amount of safety follow-up in the given window with censoring due to lost to follow-up, completion of planned follow-up, window cutoff, or death
7 Exposure adjusted incidence rate
Abbreviations: PBO=placebo; SIR=sirukumab; EE=early escape; LE=late escape; CO=cross over; SCS=Summary of Clinical Safety; IR=incidence rate per 100 person years; GI=gastrointestinal; q2w=every 2 weeks; q4w=every 4 weeks
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: IR response, pages 3-4, submitted 6/12/17 and IR response, 7/6/17, page 8

Table 49: GI Perforation from Studies ARA3001, ARA3002, ARA3003, ARA3004, and ARA3005

GI Perforation	Combined[1] SIR 50 mg	Combined[2] SIR 100mg
	Through SCS cutoff	
Total patient-years of exposure	2192	2208
Patients with ≥1 event, N, IR		
Adjudicated GI perforation	7, 0.32	8, 0.36

1 All patients who received at least one dose of sirukumab 50 mg q4w through the noted exposure time. This includes patients who were initially randomized to sirukumab 50 mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w.
2 All patients who received at least one dose of sirukumab 100 mg q2w through the noted exposure time. This includes patients who were initially randomized to sirukumab 100 mg q2w, patients randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w, and patients initially randomized to sirukumab 50 mg q2w who escape to 100 mg q4w.
Abbreviations: SIR=sirukumab; EE=early escape; LE=late escape; CO=cross over; SCS=Summary of Clinical Safety; IR=incidence rate per 100 person years; GI=gastrointestinal; q2w=every 2 weeks; q4w=every 4 weeks
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: IR response, page 3-4, submitted 6/12/17

Major Adverse Cardiovascular Events

An independent Clinical Events Committee (CEC) at the Cleveland Clinic was established for the phase 3 clinical program to review case information on serious cardiovascular events. The CEC reviewed and adjudicated all deaths and serious CV AEs in a blinded fashion. Events for adjudication were identified once monthly by comparing SAEs to a list of MedDRA preferred terms on a trigger list. The trigger list was a list of pre-defined MedRA Preferred Terms to identify possible MACE cases for CEC adjudication. In addition, the Medical Monitor also could identify a case for adjudication. The members of the CEC adjudicated each potential event based on pre-specified definitions, and rendered an assessment as to whether the case

represented a confirmed event, a non-event, or lacked sufficient documentation for confirmation of an event.

Janssen defined MACE ("broad") as non-fatal MI, non-fatal stroke, cardiovascular death, hospitalization for unstable angina, and hospitalization for TIA. The Agency requested additional analyses for MACE ("narrow") defined as non-fatal MI, non-fatal stroke, and cardiovascular death.

In studies ARA3002 and ARA3003, cardiovascular risk factors were balanced across the treatment groups. In study ARA3002, the mean age was 53 years old. The frequency of CV risk factors in the study population included: hypertension (36%), hyperlipidemia (15%), diabetes mellitus (7%), past or current cigarette smoking (25%), family history of coronary artery disease (2%), and previous MI (1%). In study ARA3003, the mean age was 55 years old. The frequency of CV risk factors in the study population included: hypertension (45%), hyperlipidemia (24%), diabetes mellitus (13%), past or current cigarette smoking (38%), family history of coronary artery disease (8%), and previous MI (3%).

During the review, Janssen noted issues in the adjudication process for MACE data. See the discussion of the adjudication issues at the beginning of this section. Table 50 provides an overview of the number of patients with an adjudication performed and the number of patients with events adjudicated as MACE. As discussed above, the Agency reviewed the original adjudication case report forms to confirm the reliability of the datasets, and the analyses that follow were based on the revised data.

Table 50: Number of Patients with MACE Adjudication Information (All Patients in Phase 3 Studies)

All patients in phase 3 studies	3229
Number of patients with an adjudication performed	54 (1.7%)
Number of patients adjudicated as having a MACE (broad)	37 (1.1%)
Number of patients adjudicated as having a MACE (narrow)	31 (1%)

Adjudicated MACE (broad) defined as non-fatal MI, non-fatal stroke, cardiovascular death, hospitalization for unstable angina, and hospitalization for TIA
Adjudicated MACE (narrow) defined as CV death, MI, and stroke.
Source: IR Response, page 5, submitted June 13, 2017

Through 18 weeks of exposure, there were 4 total MACE (narrow) across the treatment arms, and the incidence rate (per 100 PYs) was the same in the placebo and sirukumab 100 mg groups (0.34) and higher in the sirukumab 50 mg group (0.68). Similar findings were noted through 52 weeks of exposure and through SCS cutoff (Table 51) and in analyses utilizing Poisson regression (Table 53). The cumulative incidence of MACE over time is shown by treatment group in Figure 11.

When comparing the two doses in the larger dataset from studies ARA3001, ARA3002, ARA3003, ARA3004, and ARA3005, the incidence rate (per 100 PYs) of MACE was higher for sirukumab 50 mg (0.96) compared to sirukumab 100 mg (0.36) (Table 52). The reason for the slightly higher incidence rate of MACE with sirukumab 50 mg compared to sirukumab 100

mg is not clear, but does not appear to be due to lipid levels, which were similarly elevated in both treatment groups.

A total of 29 patients treated with sirukumab in the phase 3 RA studies experienced MACE (narrow) through the SCS cutoff: 21 in the sirukumab (combined) 50 mg q4w group and 8 in the sirukumab (combined) 100 mg q2w group (Table 52). Of the 29 sirukumab-treated patients who had one or more MACE, 7 had non-fatal MIs, 14 had non-fatal strokes, and 13 had CV death. Not surprisingly, there was a trend toward numerically greater MACE incidence with increasing age, and most subjects with MACE had at least one cardiovascular risk factor at baseline.

Table 51: Overview of Adjudicated MACE for Different Safety Pools and Follow-up Times

	ARA3002 and ARA3003			ARA3002 and ARA3003[1]					ARA3002 and ARA3003[1]	
	Through 18 weeks of exposure			Through 52 weeks of exposure					Through SCS cutoff	
	PBO N=850	SIR 50 mg[2] N=848	SIR 100 mg[3] N=850	PBO N=850	SIR 50 mg[2] N=848	SIR 100 mg[3] N=850	SIR Combined[4] 50 mg N=1214	SIR Combined[5] 100 mg N=1217	SIR Combined[4] 50 mg N=1214	SIR Combined[5] 100 mg N=1217
Total patient-years of exposure	292	292	294	520	787	784	1109	1111	1964	1975
Subjects with ≥1 event, N (%[6]), IR:										
Adjudicated MACE (broad)	1 (0.1%) 0.34	3 (0.4%) 1.03	1 (0.1%) 0.34	3, 0.58	11, 1.40	3, 0.38	16, 1.45	5, 0.45	24, 1 23	7, 0.35
Adjudicated MACE (narrow)	1 (0.1%) 0.34	2 (0.2%) 0.68	1 (0.1%) 0.34	2, 0.39	9, 1.15	3, 0.38	14, 1 27	4, 0.36	20, 1.02	6, 0.30
MI (non-fatal)	1 (0.1%) 0.34	0, 0.00	1 (0.1%) 0.34	1, 0.19	3, 0.38	1, 0.13	4, 0.36	1, 0.09	6, 0.31	1, 0.05
Stroke (non-fatal)	0, 0.00	1 (0.1%) 0.34	0, 0.00	1, 0.19	4, 0.51	1, 0.13	7, 0.63	2, 0.18	9, 0.46	3, 0.15
CV death	0, 0.00	1 (0.1%) 0.34	0, 0.00	0, 0.00	2, 0.25	2, 0.25	6, 0.54	3, 0.27	8, 0.41	4, 0.20

1 Includes data from ARA3004
2 Only includes patients randomized to sirukumab 50 mg q4w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w
3 Only includes patients randomized to sirukumab 100 mg q2w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w.
4 All patients who received at least one dose of sirukumab 50 mg q4w through the noted exposure time. This includes patients who were initially randomized to sirukumab 50mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w.
5 All patients who received at least one dose of sirukumab 100 mg q2w through the noted exposure time. This includes patients who were initially randomized to sirukumab 100 mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w.
6 Cumulative incidence percentages are only shown through 18 weeks and no other time periods given differences in exposure between sirukumab and placebo after 18 weeks.
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Adjudicated MACE (broad) defined as non-fatal MI, non-fatal stroke, cardiovascular death, hospitalization for unstable angina, and hospitalization for TIA
Adjudicated MACE (narrow) defined as CV death, MI, and stroke.
Abbreviations: PBO=placebo; SIR=sirukumab; EE=early escape; LE=late escape; CO=cross over; SCS=Summary of Clinical Safety; IR=incidence rate per 100 person years; MI=myocardial infarction; CV=cardiovascular; q2w=every 2 weeks; q4w=every 4 weeks
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: IR response, page 20, submitted June 16, 2017

Table 52: Adjudicated MACE from Studies ARA3001, ARA3002, ARA3003, ARA3004, and ARA3005

MACE	SIR Combined[1] 50 mg	SIR Combined[2] 100 mg
Total patient-years of exposure[3]	2193.3	2210.6
Subjects with ≥1 event, N, IR:		
Adjudicated MACE (broad)	25, 1.15	9, 0.41
Adjudicated MACE (narrow)	21, 0.96	8, 0.36
MI (non-fatal)	6, 0.27	1, 0.05
Stroke (non-fatal)	10, 0.46	4, 0.18
CV death	8, 0.37	5, 0.23

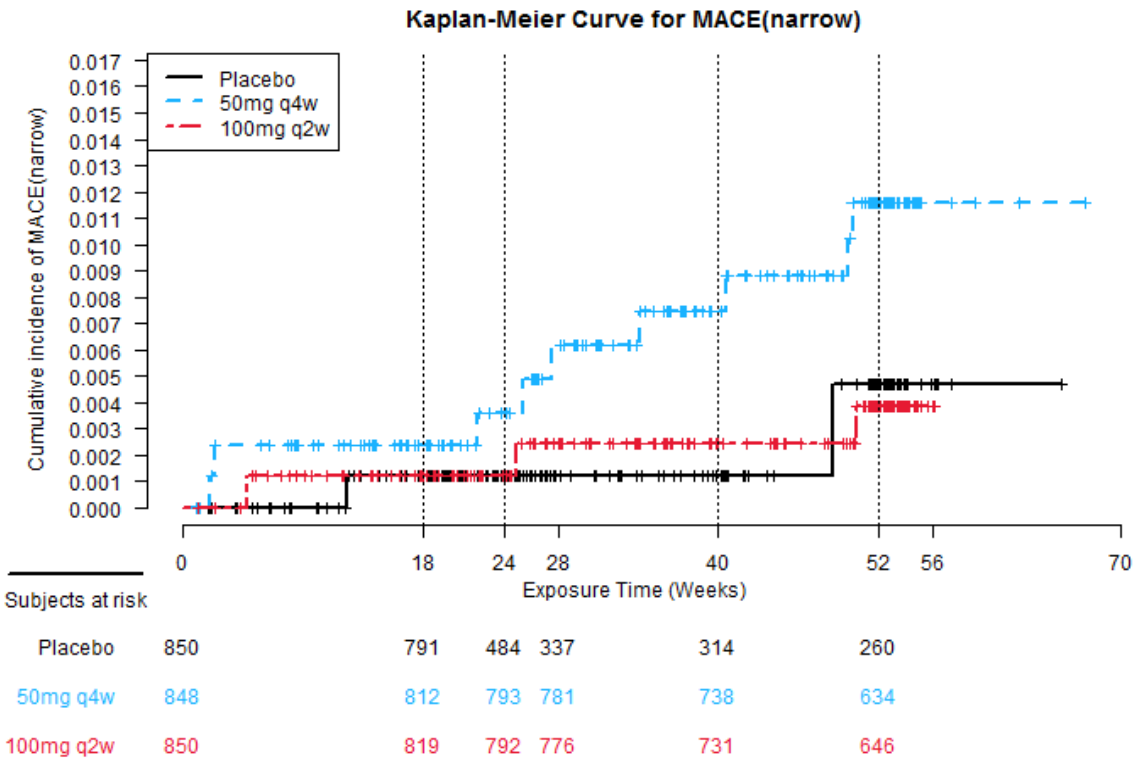
1. All patients who received at least one dose of sirukumab 50 mg q4w through the noted exposure time. This includes patients who were initially randomized to sirukumab 50 mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w.
2. All patients who received at least one dose of sirukumab 100 mg q2w through the noted exposure time. This includes patients who were initially randomized to sirukumab 100 mg q2w, patients randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w, and patients initially
randomized to sirukumab 50 mg q2w who escape to 100 mg q4w .
3. Total patient-years of exposure is calculated as the total amount of safety follow-up in the given window with censoring due to lost to follow-up, completion of planned follow-up, window cutoff, or death
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Abbreviations: PBO=placebo; SIR=sirukumab; EE=early escape; MI=myocardial infarction; CV=cardiovascular; LE=late escape; CO=cross-over; SCS=Summary of Clinical Safety; IR=incidence rate per 100 patient-years; q2w=every 2 weeks; q4w=every 4 weeks
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: IR response, page 22, submitted June 16, 2017

Table 53: Poisson Regression Modeling (Subject Based per 100 Patient-Years of Exposure) for MACE (narrow) Through 52 Weeks of Exposure (Studies ARA3002 and ARA3003)

	PBO	SIR start 50 mg q4w[1]	SIR start 100 mg q2w[2]
Treated patients	850	848	850
Number of patients with MACE	2	9	3
Total patient-years of exposure	519	785	784
Crude incidence rate per 100 patient-years	0.39	1.14	0.38
Ratio of incidence rates (95% CI) versus placebo group	--	2.9 (0.6, 13.6)	1.0 (0.2, 5.9)
Difference of incidence rates (95% CI) versus placebo group, per 100 patient-years	--	0.78 (-0.18, 1.73)	-0.01 (-0.73, 0.71)

Based on Poisson regression, with an offset for follow-up time, adjusting for study; difference in incidence rates calculated based on the delta method
1 Only includes patients randomized to sirukumab 50 mg q4w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w
2 Only includes patients randomized to sirukumab 100 mg q2w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w
Abbreviations: PBO=placebo; SIR=sirukumab; q2w=every 2 weeks; q4w=every 4 weeks; CI=confidence interval
Source: Statistical Reviewer

Figure 11: Kaplan-Meier Analysis of Time to Onset of MACE (narrow) Through 52 Weeks of Exposure in Studies ARA3002 and ARA3003



Based on all subjects who started off on placebo, sirukumab 50 mg q4w, or sirukumab 100 mg q2w. At-risk time for placebo patients extended up to the time at which placebo patients early escaped, late escaped, or crossed over to sirukumab. Patients who discontinued from the study were also censored. Cross-hairs represent the time at which patients were censored.
Abbreviations: 100mg q2w=sirukumab 100 mg every 2 weeks; 50mg q4w=sirukumab 50 mg every 4 weeks
Source: Statistical Reviewer

Anaphylaxis/Hypersensitivity

Hypersensitivity and anaphylaxis are adverse events that have been identified with all biologic drugs used in the treatment of rheumatoid arthritis, and, thus, these were adverse events of special interest in the sirukumab clinical development program. Through 18 weeks, 52 weeks, and SCS cutoff, there was a dose-response relationship between sirukumab and all hypersensitivity reactions and moderate or severe hypersensitivity reactions (Table 54). The most common hypersensitivity adverse event was dermatitis allergic. There were no cases of anaphylaxis (per Sampson[18] criteria) during the development program.

[18] Sampson HA, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium 2006;117(2):391-7.

Table 54: Overview of Hypersensitivity Reactions for Different Safety Pools and Follow-up Times

	ARA3002 and ARA3003			ARA3002 and ARA3003[1]					ARA3002 and ARA3003[1]	
	Through 18 weeks of exposure			Through 52 weeks of exposure					Through SCS cutoff	
	PBO N=850	SIR 50 mg[2] N=848	SIR 100 mg[3] N=850	SIR PBO N=850	SIR 50 mg[2] N=848	SIR 100 mg[3] N=850	SIR Combined[4] 50 mg N=1214	SIR Combined[5] 100 mg N=1217	SIR Combined[4] 50 mg N=1214	SIR Combined[5] 100 mg N=1217
Total patient-years of exposure[7]	292.3	292.3	293.5	519 5	786.9	784.4	1109.4	1111.1	1963.8	1974.6
Subjects with ≥1 event, N (%[8]), IR:										
All hypersensitivity reactions	30 (3.5), 10.49	47 (5.5), 16.56	61 (7.2), 21.65	41, 8 18	91, 12.35	112, 15.5	124, 11.91	154, 14.97	153, 8.65	189, 10.84
Moderate or severe hypersensitivity reactions	3 (0.4), 1.03	7 (0.8), 2.41	13 (1.5), 4.46	4, 0.77	16, 2.05	25, 3.23	25, 2.28	34, 3.09	29, 1 5	45, 2.32

1 Includes data from ARA3004
2 Only includes patients randomized to sirukumab 50 mg q4w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w
3 Only includes patients randomized to sirukumab 100 mg q2w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w.
4 All patients who received at least one dose of sirukumab 50 mg q4w through the noted exposure time. This includes patients who were initially randomized to sirukumab 50mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w.
5 All patients who received at least one dose of sirukumab 100 mg q2w through the noted exposure time. This includes patients who were initially randomized to sirukumab 100 mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w.
6 Total patient-years of exposure is calculated as the total amount of safety follow-up in the given window with censoring due to lost to follow-up, completion of planned follow-up, window cutoff, or death
7 Cumulative incidence percentages are only shown through 18 weeks and no other time periods given differences in exposure between sirukumab and placebo after 18 weeks.
Abbreviations: PBO=placebo; SIR=sirukumab; EE=early escape; LE=late escape; CO=cross over; SCS=Summary of Clinical Safety; IR=incidence rate per 100 person years; q2w=every 2 weeks; q4w=every 4 weeks
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: IR response, page 55, submitted 5/30/17

Injection site reactions

Through 18 weeks of exposure, the proportion of patients with injection site reactions was higher in the sirukumab treatment arms (8% and 16% for 50 mg and 100 mg, respectively) compared to placebo (2%). Most injection site reactions were mild or moderate in severity. No patients in the sirukumab 50 mg group discontinued due to injection site reactions in studies ARA3002 and ARA3003, but five patients in the sirukumab 100 mg group discontinued due to injection site reactions that were moderate to severe. Injection site reactions are an anticipated adverse event for this biologic product.

Malignancy

Malignancy was an adverse event of special interest given that sirukumab is an immunosuppressant. Through 18 weeks of exposure, there were 4 total malignancies (including NMSC) observed across the treatment arms. The incidence rate of patients with any malignancy (including or excluding NMSC) was low and fairly similar between groups (Table 55). Through 52 weeks of exposure, the incidence rate (per 100 PYs) of malignancy (excluding NMSC) was higher on the 50 mg (0.64) and 100 mg (0.64) sirukumab groups compared to placebo (0.19). When including data after escape, this difference was slightly higher on the 100 mg sirukumab combined than the start arm. The types and frequencies of malignancies are shown in Table 56. Overall, the types of malignancies observed followed the

pattern of malignancies that would generally be expected in the underlying patient population. Solid tumors (such as breast and lung cancer) were the most commonly occurring cancers excluding nonmelanoma skin cancer. There were two hematologic malignancies through 52 weeks of exposure. Through the SCS cutoff, the incidence rate of malignancy was similar in the two sirukumab dose groups and did not increase from the incidence rate observed through 52 weeks of exposure.

Table 55: Overview of Malignancy for Different Safety Pools and Follow-up Times

	ARA3002 and ARA3003			ARA3002 and ARA3003[1]					ARA3002 and ARA3003[1]	
	Through 18 weeks of exposure			Through 52 weeks of exposure					Through SCS cutoff	
	PBO N=850	SIR 50 mg[2] N=848	SIR 100 mg[3] N=850	PBO N=850	SIR 50 mg[2] N=848	SIR 100 mg[3] N=850	SIR Combined[4] 50 mg N=1214	SIR Combined[5] 100 mg N=1217	SIR Combined[4] 50 mg N=1214	SIR Combined[5] 100 mg N=1217
Total patient-years of exposure[6]	292 3	292.3	293.5	519.5	786.9	784.4	1109.4	1111.1	1963.8	1974.6
Subjects with ≥1 event, N (%[7]), IR:										
All malignancy (including NMSC)	2 (0.2), 0.68	1 (0.1), 0.34	1 (0.1), 0.34	3, 0.58	8, 1.02	6, 0.77	11, 0 99	13, 1.17	20, 1.03	19, 0.97
Malignancy, excluding NMSC	1 (0.1), 0 34	0	1 (0.1), 0.34	1, 0.19	5, 0.64	5, 0.64	7, 0.63	11, 0.99	14, 0.71	15, 0.76
Hematologic malignancy	0	0	0	0	0	1, 0.13	0	2, 0.18	4, 0.20	2, 0.10
NMSC	1 (0.1), 0 34	1 (0.1), 0.34	0	2, 0.39	3, 0.38	1, 0.13	4, 0.36	2, 0.18	6, 0.31	4, 0.2

1 Includes data from ARA3004
2 Only includes patients randomized to sirukumab 50 mg q4w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w
3 Only includes patients randomized to sirukumab 100 mg q2w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w.
4 All patients who received at least one dose of sirukumab 50 mg q4w through the noted exposure time. This includes patients who were initially randomized to sirukumab 50mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w.
5 All patients who received at least one dose of sirukumab 100 mg q2w through the noted exposure time. This includes patients who were initially randomized to sirukumab 100 mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w.
6 Total patient-years of exposure is calculated as the total amount of safety follow-up in the given window with censoring due to lost to follow-up, completion of planned follow-up, window cutoff, or death
7 Cumulative incidence percentages are only shown through 18 weeks and no other time periods given differences in exposure between sirukumab and placebo after 18 weeks.
Abbreviations: PBO=placebo; SIR=sirukumab; EE=early escape; LE=late escape; CO=cross over; SCS=Summary of Clinical Safety; IR=incidence rate per 100 person years; NMSC=non-melanoma skin cancer; q2w=every 2 weeks; q4w=every 4 weeks
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: IR response, page 53, submitted 5/30/17

Table 56: Types of Malignancy Through 52 Weeks of Exposure

Malignancy type (MedDRA PT), n	PBO N=850	SIR 50mg[1] N=848	SIR 100mg[2] N=850
Basal cell carcinoma	1	2	1
Bladder cancer	0	0	1
Lung adenocarcinoma	0	0	1
Lung cancer metastatic	0	0	1
Lymphoproliferative disorder	0	0	1
Metastases to bone	0	0	1
Ovarian clear cell carcinoma	0	0	1
Bladder transitional cell carcinoma	0	1	0
Breast cancer metastatic	0	1	0
Glioblastoma multiforme	1	0	0
Invasive ductal breast carcinoma	0	1	0
Neuroendocrine carcinoma	0	1	0
Rectal adenocarcinoma	0	1	0
Squamous cell carcinoma	1	1	0

1 Only includes patients randomized to sirukumab 50 mg q4w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w
2 Only includes patients randomized to sirukumab 100 mg q2w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w
Abbreviations: PBO=placebo; SIR=sirukumab; PT=preferred term
Source: Summary of Clinical Safety, Table 30, page 97, submitted 9/22/16

Analyses were also performed in the larger dataset from studies ARA3001, ARA3002, ARA3003, ARA3004, and ARA3005. There was no relationship between sirukumab dose and incidence of malignancy (Table 57).

Table 57: Malignancy from Studies ARA3001, ARA3002, ARA3003, ARA3004, and ARA3005

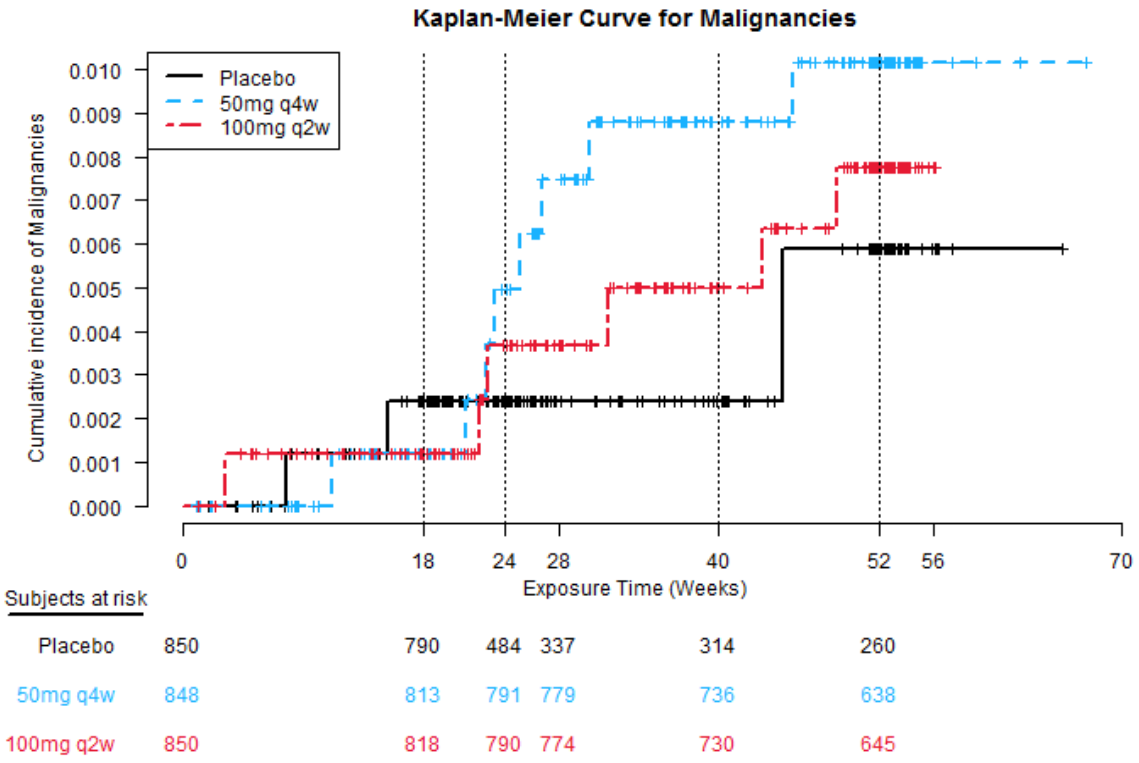
Malignancy	Combined[1] SIR 50 mg	Combined[2] SIR 100mg
Total patient-years of exposure[3]	2193.3	2210.6
Patients with ≥1 event, N, IR		
All malignancy (including NMSC)	22, 1.01	21, 0.95
Malignancy, excluding NMSC	16, 0.73	16, 0.72
Hematologic malignancy	4, 0.18	2, 0.09
NMSC	6, 0.27	5, 0.23

1 All patients who received at least one dose of sirukumab 50 mg q4w through the noted exposure time. This includes patients who were initially randomized to sirukumab 50 mg q2w and patients randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w.
2 All patients who received at least one dose of sirukumab 100 mg q2w through the noted exposure time. This includes patients who were initially randomized to sirukumab 100 mg q2w, patients randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w, and patients initially randomized to sirukumab 50 mg q2w who escape to 100 mg q4w.
3 Total patient-years of exposure is calculated as the total amount of safety follow-up in the given window with censoring due to lost to follow-up, completion of planned follow-up, window cutoff, or death
Abbreviations: PBO=placebo; SIR=sirukumab; EE=early escape; LE=late escape; CO=cross over; SCS=Summary of Clinical Safety; IR=incidence rate per 100 person years; NMSC=non-melanoma skin cancer; q2w=every 2 weeks; q4w=every 4 weeks
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: IR Response, Table 7, page 56, submitted 5/30/17

When evaluating the time to onset of all malignancies and malignancies excluding NMSC in the exposure time controlled analysis set, there was no apparent differences between the two doses of sirukumab (Figure 12, Figure 13). There was some separation between placebo and sirukumab in each analysis after approximately 26 weeks. Comparisons of incidence rates and hazards rates versus placebo for the two sirukumab dose groups are shown in Table 58 and

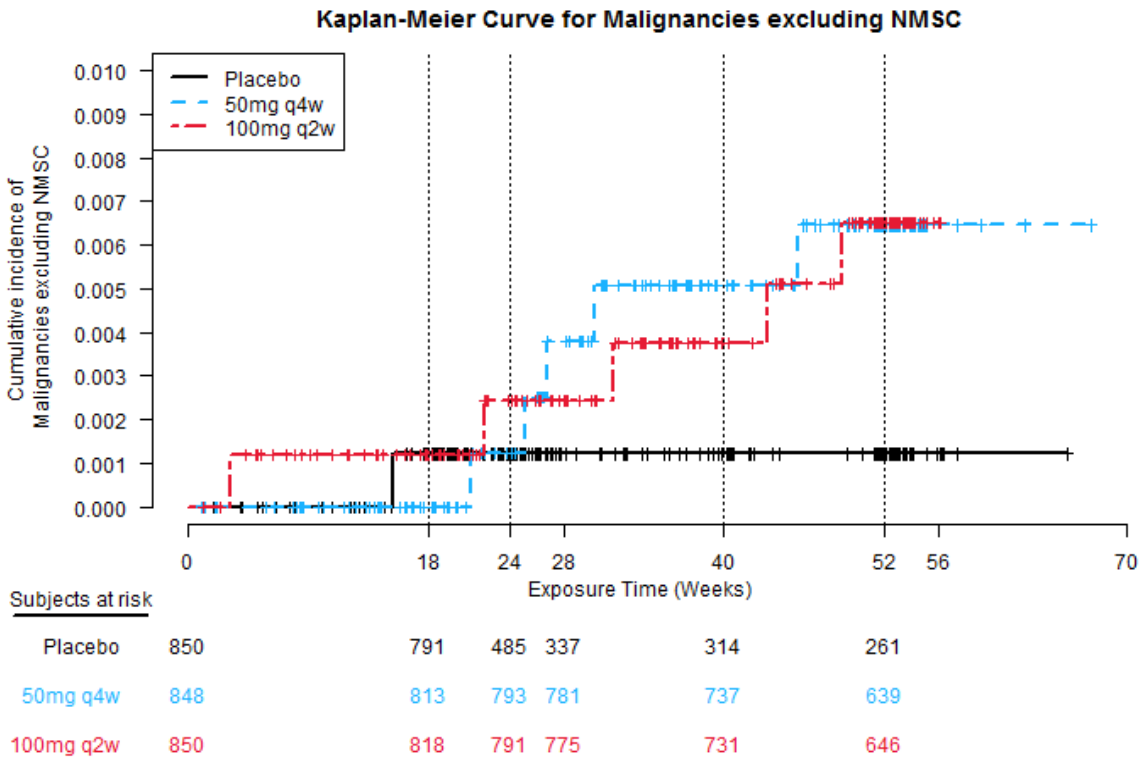
Table 59. As discussed previously, these comparisons are potentially confounded by the study design with patients escaping from placebo to sirukumab. The analyses estimate greater rates on the sirukumab arms as compared to placebo, but given the limited number of events, there is considerable uncertainty around the comparisons (as evident by the very wide confidence intervals around treatment comparisons).

Figure 12: Kaplan-Meier Analysis of Time to Onset of all Malignancies Through 52 Weeks of Exposure in Studies ARA3002 and ARA3003



Based on all subjects who started off on placebo, sirukumab 50 mg q4w, or sirukumab 100 mg q2w. At-risk time for placebo patients extended up to the time at which placebo patients early escaped, late escaped, or crossed over to sirukumab. Patients who discontinued from the study were also censored. Cross-hairs represent the time at which patients were censored.
Abbreviations: 100mg q2w=sirukumab 100 mg every 2 weeks; 50mg q4w=sirukumab 50 mg every 4 weeks
Source: Statistical Reviewer

Figure 13: Kaplan-Meier Analysis of Time to Onset of Malignancies excluding NMSC Through 52 Weeks of Exposure in Studies ARA3002 and ARA3003



Based on all subjects who started off on placebo, sirukumab 50 mg q4w, or sirukumab 100 mg q2w. At-risk time for placebo patients extended up to the time at which placebo patients early escaped, late escaped, or crossed over to sirukumab. Patients who discontinued from the study were also censored. Cross-hairs represent the time at which patients were censored.
Abbreviations: 100mg q2w=sirukumab 100 mg every 2 weeks; 50mg q4w=sirukumab 50 mg every 4 weeks
Source: Statistical Reviewer

Table 58: Poisson Regression Modeling (Subject Based per 100 Subject Years of Exposure) for Malignancies Through 52 Weeks of Exposure (Studies ARA3002 and ARA3003)

	PBO	SIR start 50 mg q4w[1]	SIR start 100 mg q2w[2]
Treated patients	850	848	850
Total malignancies			
Number of patients with event	3	8	6
Total subject years of exposure	519	785	783
Crude incidence rate per 100 patient years	0.58	1.02	0.77
Ratio of incidence rates (95% CI) versus placebo group	--	1.6 (0.4, 6.1)	1.2 (0.3, 4.8)
Difference of incidence rates (95% CI) versus placebo group, per 100 patients-years	--	0.41 (-0.66, 1.48)	0.14 (-0.87, 1.14)
Malignancies excluding NMSC			
Number of patients with event	1	5	5
Total subject years of exposure	519	785	784
Crude incidence rate per 100 patient years	0.19	0.64	0.64
Ratio of incidence rates (95% CI) versus placebo group	--	3.1 (0.4, 26.9)	3.1 (0.4, 26.9)
Difference of incidence rates (95% CI) versus placebo group, per 100 patient-years	--	0.46 (-0.27, 1.19)	0.46 (-0.27, 1.19)

Based on Poisson regression, with an offset for follow-up time, adjusting for study; difference in incidence rates calculated based on the delta method

1 Only includes patients randomized to sirukumab 50 mg q4w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w

2 Only includes patients randomized to sirukumab 100 mg q2w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w

Abbreviations: PBO=placebo; SIR=sirukumab; q2w=every 2 weeks; q4w=every 4 weeks; EE=early escape; LE=late escape; CO=cross over

Source: Statistical Reviewer

Table 59: Proportional Hazards Regression Analysis of Time to Onset of Malignancies Through 52 Weeks of Exposure (ARA3002 and ARA3003)

	PBO N=850	SIR start 50 mg q4w[1] N=848	SIR start 100 mg q2w[2] N=850
Number of patients with ≥1 malignancy	3	8	6
Hazard ratio versus placebo group (95% CI)	--	1.54 (0.40, 5.96)	1.15 (0.28, 4.74)
Number of patients with ≥1 malignancy excluding NMSC	1	5	5
Hazard ratio versus placebo group (95% CI)	--	2.54 (0.29, 22.59)	2.54 (0.29, 22.57)

Based on Cox proportional hazards regression, stratified by study

1 Only includes patients randomized to sirukumab 50 mg q4w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 50 mg q4w

2 Only includes patients randomized to sirukumab 100 mg q2w and does not include data after escape/CO in patients initially randomized to placebo who EE/LE/CO to sirukumab 100 mg q2w

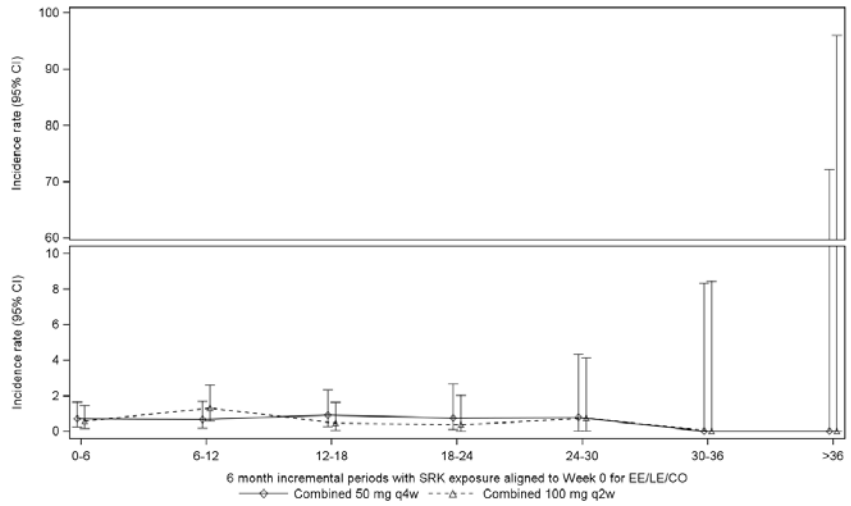
Abbreviations: PBO=placebo; SIR=sirukumab; EE=early escape; LE=late escape; CO=cross over; NMSC=non-melanoma skin cancer; q2w=every 2 weeks; q4w=every 4 weeks; CI=confidence interval

Source: IR Response, Tables 5 and 6, page 9, submitted 6/23/17

Source: IR Response, Tables 5 and 6, page 9, submitted 6/23/17

The rate of malignancies (excluding NMSC) was stable over time (Figure 14), however the confidence intervals widen over time, indicating greater uncertainty surrounding the point estimates.

Figure 14: Incidence Rate (Patient Based per 100 Patient Years of Exposure) of Malignancies excluding NMSC in 6 Month Incremental Periods During the Sirukumab Controlled Period



Source: IR response, page 25, submitted 5/30/17

Demyelinating disorders

Demyelinating disorders have been reported with other immunomodulatory biologic agents and the tocilizumab prescribing information includes a warning for demyelinating disorders, noting that multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in RA clinical studies. In the sirukumab clinical program, there were no events of demyelination.

7.6 Comparison to Adalimumab

In trial ARA3005, Janssen compared sirukumab (50 mg q4w and 100 mg q2w) and adalimumab. The trial randomized a total of 559 patients (186 adalimumab 40 mg q2w, 186 sirukumab 50 mg q4w, and 187 sirukumab 100 mg q2w). At Week 16, patients in all treatment groups who had <20% improvement from baseline in both swollen and tender joint counts qualified for early escape (EE). The EE regimens were adalimumab 40 mg q1w for patients originally randomized to the adalimumab 40 mg q2w group, sirukumab 100 mg q2w for patients originally randomized to sirukumab 50 mg q4w; patients originally randomized to sirukumab 100 mg q2w stayed on this regimen. Safety data are displayed for the "combined" groups for adalimumab and sirukumab. Specifically, safety data are displayed for the treatment arms based on the group a patient was originally randomized to and including data after EE to either adalimumab 40 mg q1w or sirukumab 100 mg q2w. For patients randomized to sirukumab 100 mg q2w, there was no option for escape and data are shown for all patients

randomized to sirukumab 100 mg q2w. These analyses therefore compare three treatment regimens: (1) adalimumab 40 mg q2w, with the possibility of up-titration to adalimumab 40 mg q1w at Week 16; (2) sirukumab 50 mg q4w, with the possibility of up-titration to sirukumab 100 mg q2w at Week 16; and (3) sirukumab 100 mg q2w. In this section of the review, data are shown based on the 24 week study report submitted to the BLA.

The proportion of patients with AEs, SAEs (except the sirukumab 100 mg group), AEs leading to discontinuation, serious infections (except the sirukumab 100 mg group), infections requiring oral or parenteral antibiotic treatment, and malignancy was higher in the sirukumab groups than the adalimumab group, but the imbalances tended to be small (Table 60). Adverse events of herpes zoster were reported in numerically more patients on adalimumab 40 mg combined (1.6%) than on sirukumab 50 mg q4w combined or sirukumab 100 mg q2w (0.5% each); none of these cases were disseminated. There were no deaths, opportunistic infections, or GI perforations through 24 weeks. There were a total of two patients with tuberculosis (one treated with adalimumab and one treated with sirukumab). One patient in the sirukumab 50 mg q4w group had an SAE of adenocarcinoma (metastatic adenocarcinoma of the lung) that led to discontinuation of study agent. The event started prior to Week 24, but the subject died after Week 24 and that death is not included in the table. There was one MACE event that occurred in the sirukumab 100 mg group. Importantly, given the small size and short duration of the trial limited conclusions are possible regarding the comparative safety of sirukumab and adalimumab.

Table 60: Overall Summary of Treatment-emergent Adverse Events through Week 24 in ARA3005

	Combined adalimumab[1]	Combined sirukumab 50 mg[2]	Sirukumab 100 mg[3]
N	186	186	187
Patients with ≥1 event, n, %			
Treatment emergent AEs	103 (55.4)	106 (57.0)	119 (63.6)
MedDRA SOC			
Infections and infestations	31 (16.7)	35 (18.8)	40 (21.4)
General disorders and administration site conditions	24 (12.9)	28 (15.1)	42 (22.5)
SAEs	8 (4.3)	13 (7.0)	5 (2.7)
MedDRA SOC			
Infections and infestations	2 (1.1)	6 (2.7)	0
Injury, poisoning, and procedural complications	1 (0.5)	1 (0.5)	1 (0.5)
AEs leading to discontinuation	9 (4.8)	15 (8.1)	12 (6.4)
Infection			
Treatment-emergent infection	35 (18.8)	38 (20.4)	45 (24.1)
Serious infection	2 (1.1)	6 (3.2)	0
Infection requiring oral or parenteral antibiotic treatment	19 (10.2)	24 (12.9)	32 (17.1)
Opportunistic infection	0	0	0
Tuberculosis	1 (0.5)	1 (0.5)	0
Herpes zoster	3 (1.6)	1 (0.5)	1 (0.5)
MACE	0	0	1 (0.5)
Malignancy	0	2 (1.1)	1 (0.5)
GI perforation	0	0	0
Death[4]	0	0	0

1 Includes patients randomized to adalimumab who continued adalimumab 40 mg q2w or escaped to adalimumab 40 mg q1w
2 Includes patients randomized to sirukumab 50 mg q4w who continued sirukumab 50 mg q4w or escaped to sirukumab 100 mg q2w
3 Includes patients randomized to sirukumab 100 mg q2w (this group did not have the option to escape)
4 Subject 50118 had an AE starting prior to Week 24, but died due to it after Week 24. This death is not included in this table since it occurred after week 24
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: Study report ARA3005, Table 38 (page 167-168), Table 39 (page 169), Table 41 (page 175), Table 44 (page 185), TSFAE07 (page 744), TSFAE09 (page 751), submitted 9/22/16

Through Week 24, the mean change from baseline in neutrophil count (x10^3/µL) was greater for the combined sirukumab 50 mg (-1.9) and sirukumab 100 mg (-1.8) groups compared to adalimumab (-0.5). In addition, a greater proportion of patients in the sirukumab 50 combined and sirukumab 100 groups had grade 1, 2, and 3 neutrophil count decreases compared to the adalimumab combined group (Table 61).

Table 61: Change in Neutrophil Counts through Week 24 in ARA3005

	Combined adalimumab[1]	Combined Sirukumab 50 mg[2]	Sirukumab 100 mg[3]
N	186	186	187
Mean change from baseline in neutrophil count at Week 24 (x10^3/μL)	-0.5	-1.9	-1.8
Neutrophils (decreased)			
Toxicity grade 0 (≥LLN)	162 (87.1)	120 (64.5)	128 (68.4)
Toxicity grade 1 (<LLN-1,5000/mm^3)	14 (7.5)	36 (19.4)	31 (16.6)
Toxicity grade 2 (<1,500-1,000/mm^3)	9 (4.8)	26 (14.0)	21 (11.2)
Toxicity grade 3 (<1,000-500/mm^3)	1 (0.5)	4 (2.2)	6 (3.2)
Toxicity grade 4 (<500/mm^3)	0	0	1 (0.5)

1 Includes patients randomized to adalimumab who continued adalimumab 40 mg q2 w or escaped to adalimumab 40mg q1w
2 Includes patients randomized to sirukumab 50 mg q4w who continued sirukumab 50 mg q4w or escaped to sirukumab 100 mg q2w
3 Includes patients randomized to sirukumab 100 mg q2w (this group did not have the option to escape)
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: Study report ARA3005, TSFLABH01 (page 826), and TSFLABH07 (page 854), submitted 09/22/16

Through Week 24, a numerically greater proportion of patients in the sirukumab 50 mg q4w combined (40%) and sirukumab 100 mg q2w (42%) groups had any post-baseline ALT>1 to ≤3x ULN compared to the adalimumab 40 mg combined group (20%). However, the incidence of >5x ULN ALT values was low across treatment groups. Similarly, through Week 24, a numerically greater proportion of patients in the sirukumab 100 mg q2w group (30%) followed by the sirukumab 50 mg q4w group (25%) had any post-baseline elevation in AST >1 and ≤3x ULN compared with the adalimumab 40 mg combined group (15%). However, the incidence of >5x ULN AST values was low across treatment groups (Table 62).

Table 62: Maximum Post-baseline ALT and AST Measurements through Week 24 in ARA3005

	Combined adalimumab[1]	Combined Sirukumab 50 mg[2]	Sirukumab 100 mg[3]
N	186	186	187
Patients with ≥1 event, n, %			
ALT			
Mean (SD) change from baseline at Week 2	1 (13.5)	9 (13.9)	10.5 (16.8)
Elevations of ALT			
>8x ULN	1 (0.5)	0	0
>5 to ≤8x ULN	2 (1.1)	1 (0.5)	2 (1.1)
>3 to ≤5 ULN	3 (1.6)	6 (3.2)	9 (4.8)
>1 to ≤3 ULN	38 (20.4)	75 (40.3)	78 (41.7)
≤1 ULN	142 (76.3)	104 (55.9)	98 (52.4)
AST			
Mean (SD) change from baseline at Week 2	1.2 (7.6)	5.1 (8.6)	5.7 (10.9)
Elevations of AST			
>8xULN	1 (0.5)	0	0
>5 to ≤8x ULN	0	0	0
>3 to ≤5 ULN	2 (1.1)	4 (2.2)	4 (2.1)
>1 to ≤3 ULN	28 (15.1)	46 (24.7)	56 (29.9)
≤1 ULN	155 (83.3)	136 (73.1)	127 (67.9)

1 Includes patients randomized to adalimumab who continued adalimumab 40 mg q2 w or escaped to adalimumab 40mg q1w
2 Includes patients randomized to sirukumab 50 mg q4w who continued sirukumab 50 mg q4w or escaped to sirukumab 100 mg q2w
3 Includes patients randomized to sirukumab 100 mg q2w (this group did not have the option to escape)
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: Study report ARA3005, Table 48 (page 205), TSFLABC05 (page 813), Table 50 (page 210), TSFLABC06 (page 817), submitted 09/22/16

Through Week 24, patients treated with sirukumab had greater mean changes increases in total cholesterol, LDL, and HDL cholesterol compared to patients treated with adalimumab (Table 63).

Table 63: Change in Selected Lipid Parameters through Week 24 in ARA3005

	Combined adalimumab[1]	Combined Sirukumab 50 mg[2]	Sirukumab 100 mg[3]
N	186	186	187
Mean Change from baseline at Week 24 (mg/dL)			
Total cholesterol	1.5	24.4	24.3
LDL	-2.2	11.2	14.2
HDL	2.3	5.6	3.6

1 Includes patients randomized to adalimumab who continued adalimumab 40 mg q2 w or escaped to adalimumab 40mg q1w
2 Includes patients randomized to sirukumab 50 mg q4w who continued sirukumab 50 mg q4w or escaped to sirukumab 100 mg q2w
3 Includes patients randomized to sirukumab 100 mg q2w (this group did not have the option to escape)
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: Study report ARA3005, TSFLABL02 (page 871, 874), TSFLABL04 (page 877), submitted 9/22/16

7.7 Safety conclusions

The safety data submitted for sirukumab suggest it is associated with significant immunosuppression, as manifested by increased risks of serious infection, as well as important laboratory abnormalities, such as neutropenia and lipid parameter elevations. Some of these risks appeared to have a dose-response, but there was no evidence of increased risk with longer duration of exposure. Through 52 weeks of exposure, there was an imbalance in deaths and malignancy. There was an imbalance in MACE when comparing the placebo group to the 50 mg dose group, but not the 100 mg dose group. Wide confidence intervals around treatment comparisons for serious rare events such as death, malignancy, and MACE indicate that the imbalances could be due to chance but also that relatively large increases in risks on sirukumab cannot be ruled out based on the data alone. Such imbalances raise concern regarding these important safety risks. Additional safety signals related to events of GI perforation and hypersensitivity were also observed.

While Janssen studied two doses in phase 3, Janssen has only proposed approval of the 50 mg q4w dose given similar efficacy of the two doses, despite higher exposure with the 100 mg q2w dose group. A discussion point at the advisory committee meeting will be the imbalances noted through 52 weeks of exposure for death, MACE, and malignancy. Further, the advisory committee will discuss the overall risk/benefit profile of the proposed dose of 50 mg q4w for rheumatoid arthritis.

8. Appendix

8.1 Statistical Considerations in the Evaluation of Radiographic Progression

Statistical Reviewer: William Koh, PhD; Statistical Team Leader: Gregory Levin, PhD

Progression of radiographic structural damage in inflammatory arthritis, for example, as assessed by changes in the van der Heijde modified Sharp score over one year, is an important clinical trial endpoint, as it is considered a surrogate for meaningful long-term patient outcomes, such as decline in function and risk of disability. This section elaborates on the determination of the most appropriate statistical methodology for evaluating drug effects on radiographic progression.

Estimand of Interest

Before considering the choice of statistical methodology, it is critical to discuss and identify the estimand of interest, i.e., the specific measure of drug effect on radiographic progression that is of interest. The importance of selecting an estimand that is meaningful and can be estimated with plausible assumptions was emphasized in the 2010 National Research Council Report *The Prevention and Treatment of Missing Data in Clinical Trials*. During the sirukumab review, we have considered two potential estimands: (1) the *de facto* or *treatment policy* estimand, i.e., the difference in mean change in vdH-S over 52 weeks between all

patients assigned to sirukumab and all patients assigned to placebo *regardless of escape*; and (2) the difference in mean change in vdH-S over 52 weeks between all patients assigned to sirukumab and all patients assigned to placebo *in a setting where patients on placebo do not receive biologic escape therapy.*

There are pros and cons of each of these potential estimands. Despite the inclusion of data after placebo escape (cross-over) to sirukumab, evaluation of the treatment policy estimand (#1) is expected to be sensitive to drug effects, given that structural damage is generally understood to be irreversible, i.e., any joint space or erosion changes occurring on placebo in the first four months of the trial are not expected to go away after escape to sirukumab. This is in contrast to evaluations of symptomatic endpoints, such as joint counts and functional assessments, which may show considerable improvement toward baseline values within a few weeks of biologic treatment. Furthermore, the treatment policy estimand (#1) reflects a real-world effect of assignment to sirukumab versus assignment to placebo as an add-on to MTX in MTX inadequate responders. However, the relevance of this comparison to actual real-world treatment decisions is unclear, given that the control arm may not be receiving a treatment consistent with standard of care—inadequate responders to MTX would typically receive an escalation in treatment, such as the addition of a biologic or small-molecule drug, in clinical practice.

Estimand #2, the difference between treatment groups *in the absence of escape therapy on placebo,* has appeal in that it is not impacted by cross-over between treatment arms and thus its evaluation may be more sensitive to drug effects than the evaluation of estimand #1. However, its relevance to inform actual real-world treatment decisions is also unclear, given that it involves a comparison against a control arm (placebo + MTX, without biologic escape, in inadequate responders to MTX) that is a hypothetical rather than real-world treatment regimen. Furthermore, any evaluation of this estimand needs to rely on unverifiable assumptions because clinical trials in RA typically offer escape options with established efficacy for inadequate responders within 3–4 months of randomization due to ethical considerations.

Statistical Methodology

The pre-specified statistical analysis of the effect of sirukumab on radiographic progression utilized an approach often termed *linear extrapolation* to handle missing data and post-escape data on the placebo arm. The linear extrapolation approach, which has been used in previous RA trials, imputes a single Week 52 value in patients who escape or withdraw from the study prior to Week 52. In the applicant's analysis, patient data after early escape on the placebo arm were considered missing. Then, the applicant fit a line through the baseline score and the last observed radiographic score before escape and used that line to assign a Week 52 value to the patient. If the interest is in estimand #2, the linear extrapolation approach requires the assumption that placebo patients' scores on average would, in the absence of escape, continue to change at the same linear rate as was observed through the time of escape. This assumption is strong and unverifiable, and may tend to overstate true progression on placebo. In addition, the linear extrapolation approach is a single-imputation method that does not appropriately take into account the statistical uncertainty in the imputation process. This leads to

underestimates of the variability and overestimates of the degree of evidence of a treatment effect. There are alternative analyses that may more reliably evaluate estimand #2 than the pre-specified linear extrapolation approach.

In particular, we believe there is merit in a supportive linear mixed effects model carried out by the applicant. The analysis utilized a linear mixed effects model and included all radiographic data observed prior to escape, including such data collected at any time point during the 52-week double-blind period. Patient data on the placebo arm after early escape were considered missing. Observed data on both sirukumab arms after meeting escape criteria were included in the analysis. Observed data after treatment discontinuation on all arms (in patients who did not escape) were included. The model included the following as covariates: visit week, treatment, and treatment-by-week interaction. The treatment-by-week interaction coefficients for the two sirukumab dosing regimens represent differences in slopes (differences in mean changes per year) versus placebo and are of primary interest. This analysis still relies on strong and unverifiable assumptions, e.g., that progression is on average roughly linear over time and that missing values after escape in placebo patients who early escape are similar to values over time among placebo patients with observed data, conditional on a linear model of the baseline covariates and the time of the x-ray, and the observed value prior to escape. However, the analysis more appropriately handles statistical uncertainty (presuming the assumptions hold) than the single-imputation linear extrapolation approach. We note that there are a number of alternative methodological approaches that could be considered for evaluating estimand #2—additional research regarding the most appropriate analysis is warranted.

An alternative approach includes in the analysis all observed Week 52 x-ray data, including data collected after treatment discontinuation or escape, with patients analyzed according to their randomized treatment group. This analysis reliably targets estimand #1, the treatment policy estimand. This analysis might also be expected to conservatively target estimand #2, given that patients on placebo who meet escape criteria would be expected to have less future progression in the absence of escape to an effective biologic therapy.

Conclusions and Additional Thoughts

We believe that either the analysis including all observed data or the analysis comparing slopes of progression based on a mixed effects model are more appropriate choices for evaluating radiographic progression than the linear extrapolation approach. We have concerns with the reliability of results based on linear extrapolation because such results rely on strong and unverifiable scientific assumptions and the use of inappropriate statistical methodology. Furthermore, use of either of the alternative analyses would be more consistent with the recommendations in the 2010 NRC missing data report. Our considerations are based on the goals of evaluating an estimand of interest with minimal and plausible missing data assumptions and ensuring that results are convincing even if those assumptions are violated. The observed data analysis reliably targets one estimand of interest and conservatively targets an alternative estimand of interest, with minimal assumptions. The mixed effects model analysis excluding post-escape data on placebo and comparing slopes is also considered reasonable in this setting—it targets a clear estimand of interest, and although underlying

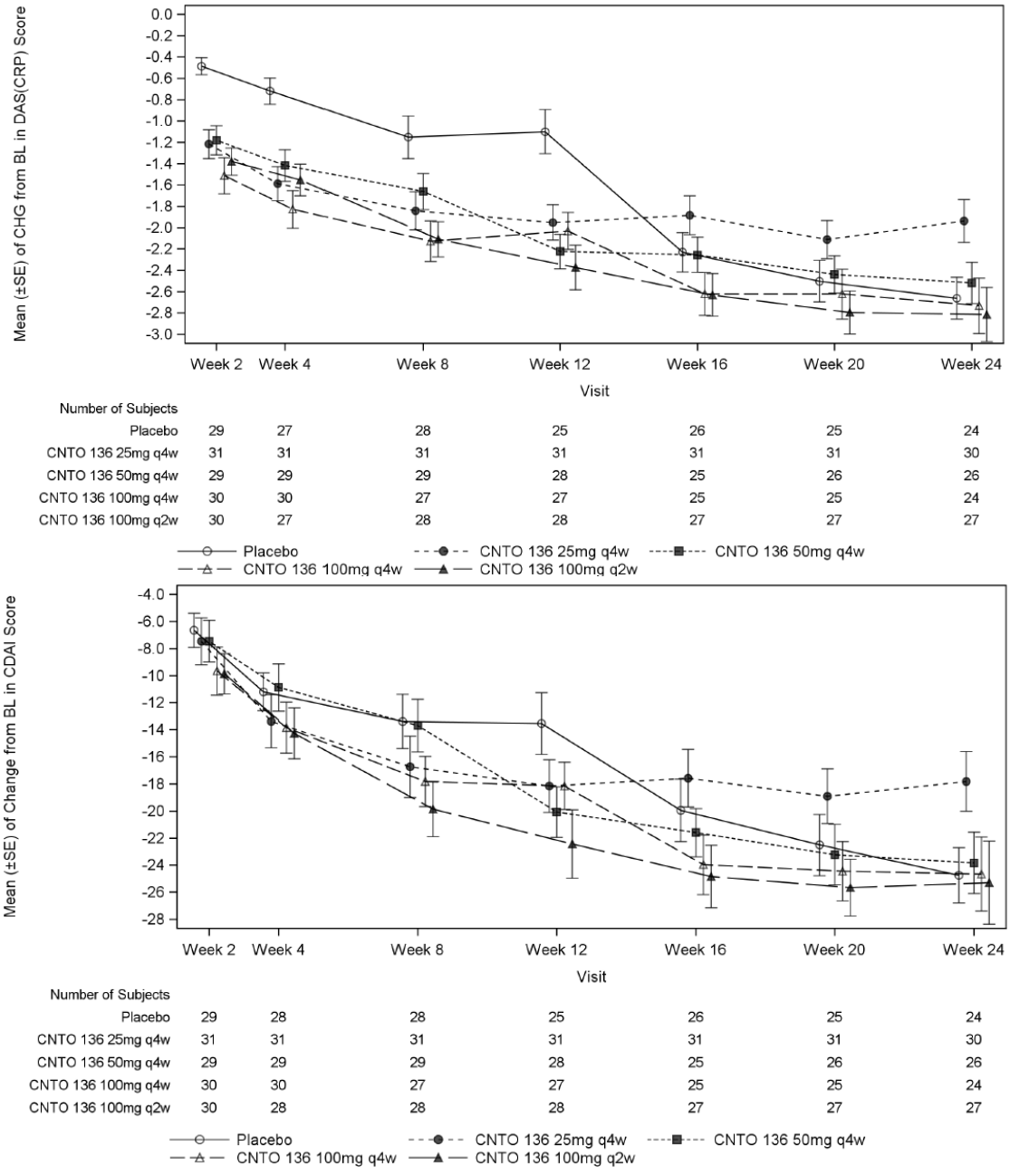
assumptions are unverifiable, sensitivity analyses can be carried out to establish that results are convincing under plausible, alternative assumptions.

We also note that considerations about the estimand(s) of interest in a specific clinical trial setting are greatly impacted by the study design and in particular, the choice of control group.[19] For example, as discussed above, the relevance of the treatment policy estimand might be questioned in the sirukumab phase 3 trial due to the comparison against a treatment policy (placebo + MTX, in inadequate responders to MTX) not reflective of true standard of care. However, if the control arm instead receives a reasonable representation of standard of care, the treatment policy estimand compares patient outcomes between two potential real-world treatment regimens and is of clear interest from a public health perspective. For example, a trial could compare a new biologic to an active biologic control in MTX inadequate responders, or could compare a new biologic to optimally titrated MTX in MTX-naïve patients. The evaluation of the treatment policy estimand in trials with these designs would provide information relevant to actual treatment decisions being made in clinical practice. Consideration should therefore be given to such alternative designs for generating evidence of and evaluating the extent of drug effects on radiographic progression. In particular, we encourage additional discussions about whether non-inferiority margins against approved, effective products can be adequately justified such that active-controlled trials (for example, in a population enriched for radiographic progression) can provide persuasive evidence of drug effects on this important clinical outcome.

[19] Ideally, the discussion about the estimand of interest would happen *before* the discussion about the design and choice of control group.

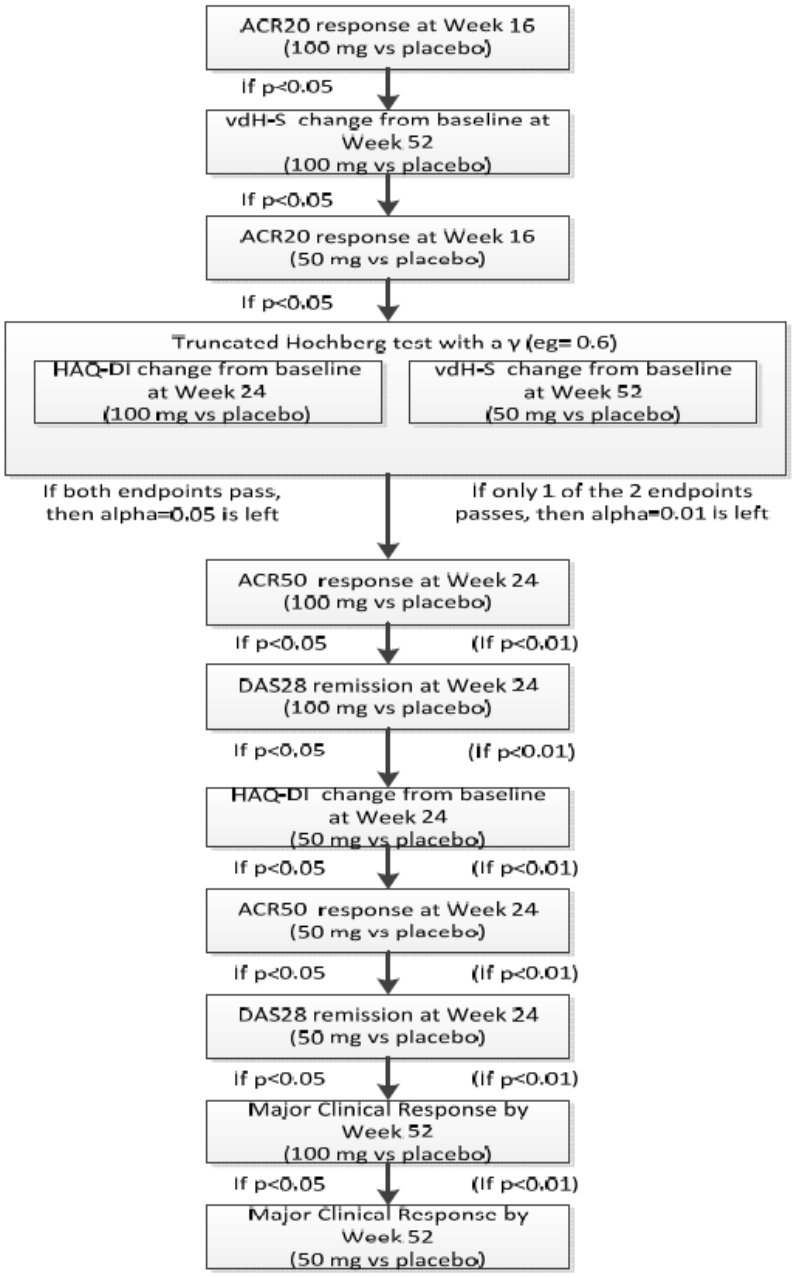
8.2 Additional Tables and Figures

Figure 15: Mean (±SE) Changes from Baseline in DAS28(CRP) and CDAI through week 24 in Study C1377T04 Part B



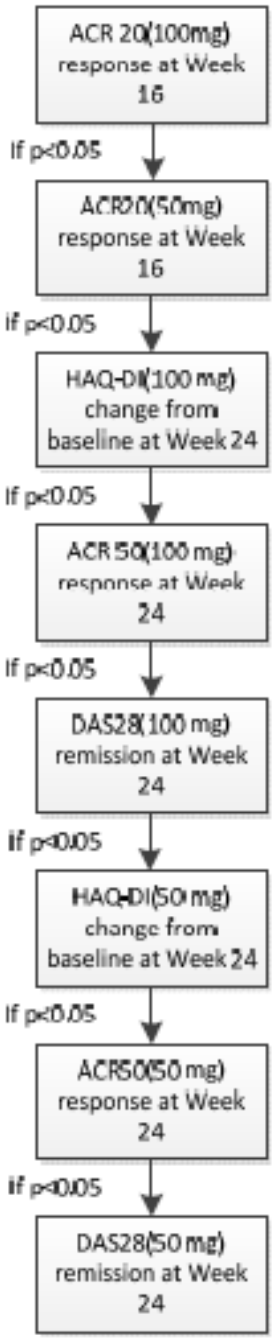
Abbreviations: DAS28 (CRP)=Disease activity index score 28 using C-reactive protein; CDAI=clinical disease activity index; CHG= change; BL= Baseline; SE= standard error; q2/q2w=every two weeks; q4/q4w=every four weeks
The DAS28 (CRP) values were based on observed data excluding data collected after treatment termination.
The CDAI scores were based on observed data excluding data collected after treatment termination.
Subjects in placebo group crossed over to sirukumab 100 mg q2w group at Week 12.
Source: Response to IR, Figure: GEFDASCHG01T04A & GEFCDACHG01T04A, page 19 and 23, submitted 7/6/17.

Figure 16: US-specific Multiplicity Adjustment Procedure in ARA3002



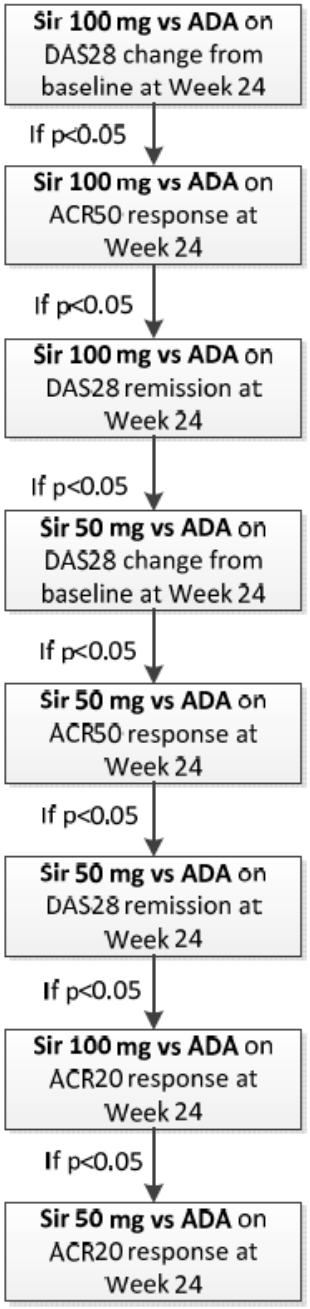
Abbreviations: ACR=American College of Rheumatology; ADA=adalimumab; DAS28=disease activity index score 28; HAQ-DI=health assessment questionnaire-disability index; vdH-S=van der Heijde-modified Sharp
Source: ARA3002 Statistical Analysis Plan dated October 15, 2015

Figure 17: US-specific Multiplicity Adjustment Procedure in ARA3003



Abbreviations: ACR=American College of Rheumatology; ADA=adalimumab; DAS28=disease activity index score 28; HAQ-DI=health assessment questionnaire-disability index; vdH-S=van der Heijde-modified Sharp
Source: ARA3003 Statistical Analysis Plan dated June 13, 2014

Figure 18: US-specific Multiplicity Adjustment Procedure in ARA3005



Abbreviations: ACR=American College of Rheumatology; ADA=adalimumab; DAS28=disease activity index score 28
Source: ARA3005 Statistical Analysis Plan dated September 30, 2015

Table 64: Mean Change from Baseline at Week 16 for ACR20 Components in ARA3002

	Placebo[a] (N=556)	Sirukumab 50 mg q4w[a] (N=557)	Sirukumab 100 mg q2w[a] (N=557)	Sirukumab 50 mg q4w vs Placebo[b]	Sirukumab 100 mg q2w vs Placebo[b]
SJC66	-4.60 (8.56) (n=513)	-8.38 (7.36) (n=527)	-8.68 (7.76) (n=517)	-3.78 (-4.62, -2.95) <0.0001	-3.87 (-4.71, -3.03) <0.0001
TJC68	-7.04 (12.81) (n=513)	-11.36 (11.97) (n=527)	-11.59 (11.83) (n=517)	-4.40 (-5.71, -3.10) <0.0001	-4.95 (-6.26, -3.64) <0.0001
Physician VAS (0 – 10)	-2.05 (2.35) (n=512)	-2.98 (2.18) (n=526)	-3.20 (2.16) (n=516)	-0.97 (-1.21, -0.72) <0.0001	-1.20 (-1.45, -0.95) <0.0001
Patient VAS (0 – 10)	-1.29 (2.59) (N=514)	-2.30 (2.82) (n=528)	-2.27 (2.67) (n=517)	-1.02 (-1.30, -0.74) <0.0001	-1.01 (-1.29, -0.73) <0.0001
HAQ-DI (0 – 3)	-0.22 (0.54) (n=514)	-0.42 (0.58) (n=528)	-0.45 (0.55) (n=517)	-0.21 (-0.27, -0.15) <0.0001	-0.24 (-0.30, -0.18) <0.0001
Patient Pain (0 – 10)	-1.21 (2.58) (n=514)	-2.25 (2.82) (n=528)	-2.39 (2.64) (n=517)	-1.05 (-1.32, -0.77) <0.0001	-1.14 (-1.42, -0.86) <0.0001
CRP (mg/dL)	-0.57 (3.25) (n=514)	-2.31 (2.43) (n=526)	-2.31 (2.52) (n=515)	-1.87 (-2.02, -1.72) <0.0001	-1.90 (-2.05, -1.76) <0.0001

Abbreviations: ACR=American College of Rheumatology; SJC=swollen joint count; TJC=tender joint count; VAS=visual analog scale; HAQ-DI=health assessment questionnaire-disability index; CRP=C-reactive protein; q2w=every 2 weeks; q4w=every 4 weeks

a Cell contents are mean (standard deviation) (n=number of non-missing observations); negative values indicate improvement

[b] Comparison to placebo based on linear regression, adjusting for baseline value and categorical baseline methotrexate use

Source: Statistical Reviewer

Table 65: Mean Change from Baseline at Week 16 for ACR20 Components in ARA3003

	Placebo[a] (N=294)	Sirukumab 50 mg q4w[a] (N=292)	Sirukumab 100 mg q2w[a] (N=292)	Sirukumab 50 mg q4w vs Placebo[b]	Sirukumab 100 mg q2w vs Placebo[b]
SJC66	-5.52 (9.35) (n=260)	-7.02 (11.40) (n=252)	-8.49 (10.06) (n=254)	-0.76 (-2.23, 0.71) 0.314	-2.14 (-3.60, -0.67) 0.004
TJC68	-7.52 (15.29) (n=260)	-11.90 (15.16) (n=252)	-11.24 (15.05) (n=254)	-3.46 (-5.83, -1.09) 0.004	-3.21 (-5.57, -0.84) 0.008
Physician VAS (0 – 10)	-1.82 (2.43) (n=258)	-2.59 (2.35) (n=252)	-3.15 (2.32) (n=255)	-0.68 (-1.06, -0.30) 0.000	-1.16 (-1.53, -0.78) <0.0001
Patient VAS (0 – 10)	-1.09 (2.33) (n=261)	-1.82 (2.77) (n=251)	-2.22 (2.88) (n=255)	-0.58 (-0.99, -0.17) 0.005	-1.08 (-1.49, -0.68) <0.0001
HAQ-DI (0 – 3)	-0.16 (0.45) (n=261)	-0.28 (0.54) (n=249)	-0.35 (0.52) (n=255)	-0.11 (-0.19, -0.02) 0.013	-0.18 (-0.26, -0.09) <0.0001
Patient Pain (0 – 10)	-1.10 (2.31) (n=261)	-1.87 (2.61) (n=251)	-2.33 (2.73) (n=255)	-0.59 (-0.99, -0.18) 0.004	-1.14 (-1.54, -0.74) <0.0001
CRP (mg/dL)	-0.08 (2.28) (n=260)	-1.88 (2.29) (n=252)	-2.08 (2.42) (n=254)	-1.85 (-2.08, -1.63) <0.0001	-1.94 (-2.17, -1.72) <0.0001

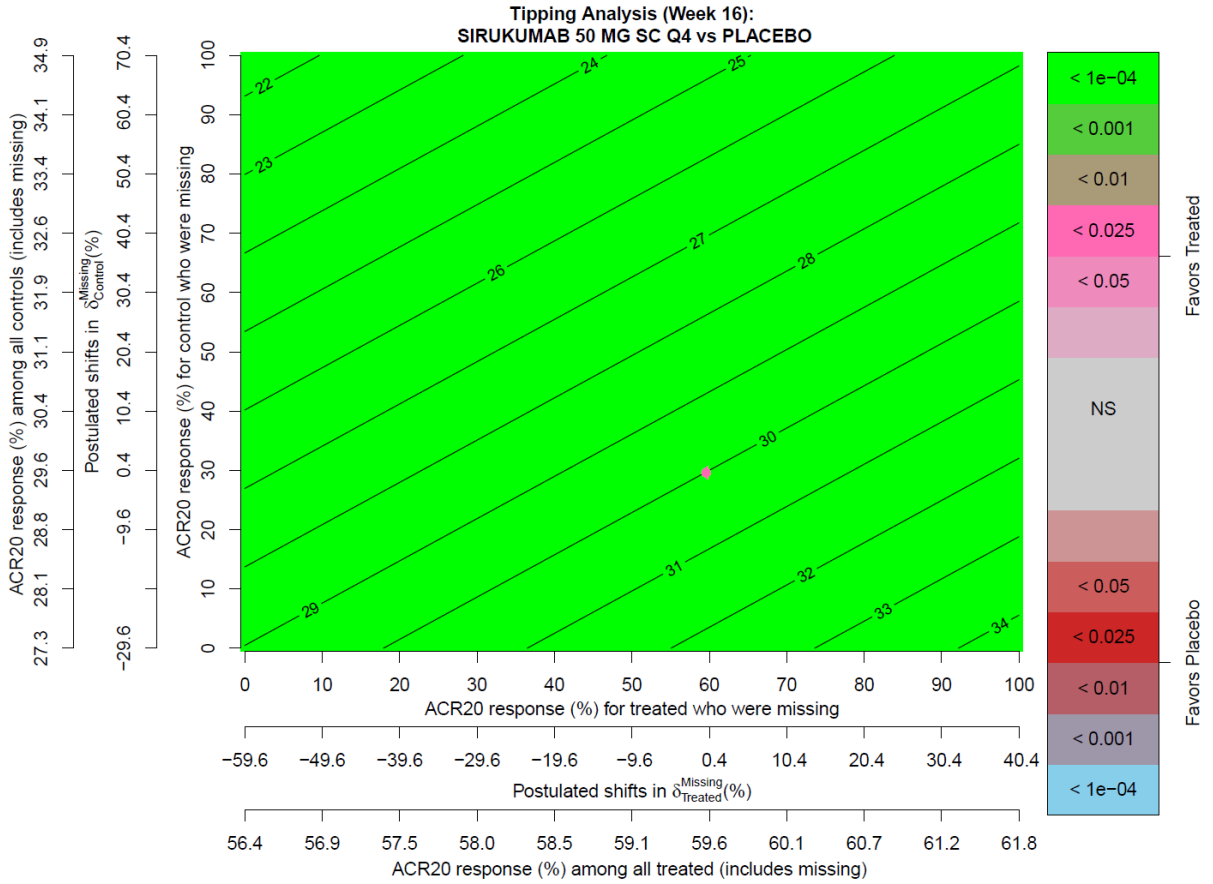
Abbreviations: ACR=American College of Rheumatology; SJC=swollen joint count; TJC=tender joint count; VAS=visual analog scale; HAQ-DI=health assessment questionnaire-disability index; CRP=C-reactive protein; q2w= every two weeks; q4w=every four weeks

[a] Cell contents are mean (standard deviation) (n=number of non-missing observations); negative values indicate improvement

[b] Comparison to placebo based on linear regression, adjusting for baseline value and categorical baseline methotrexate use

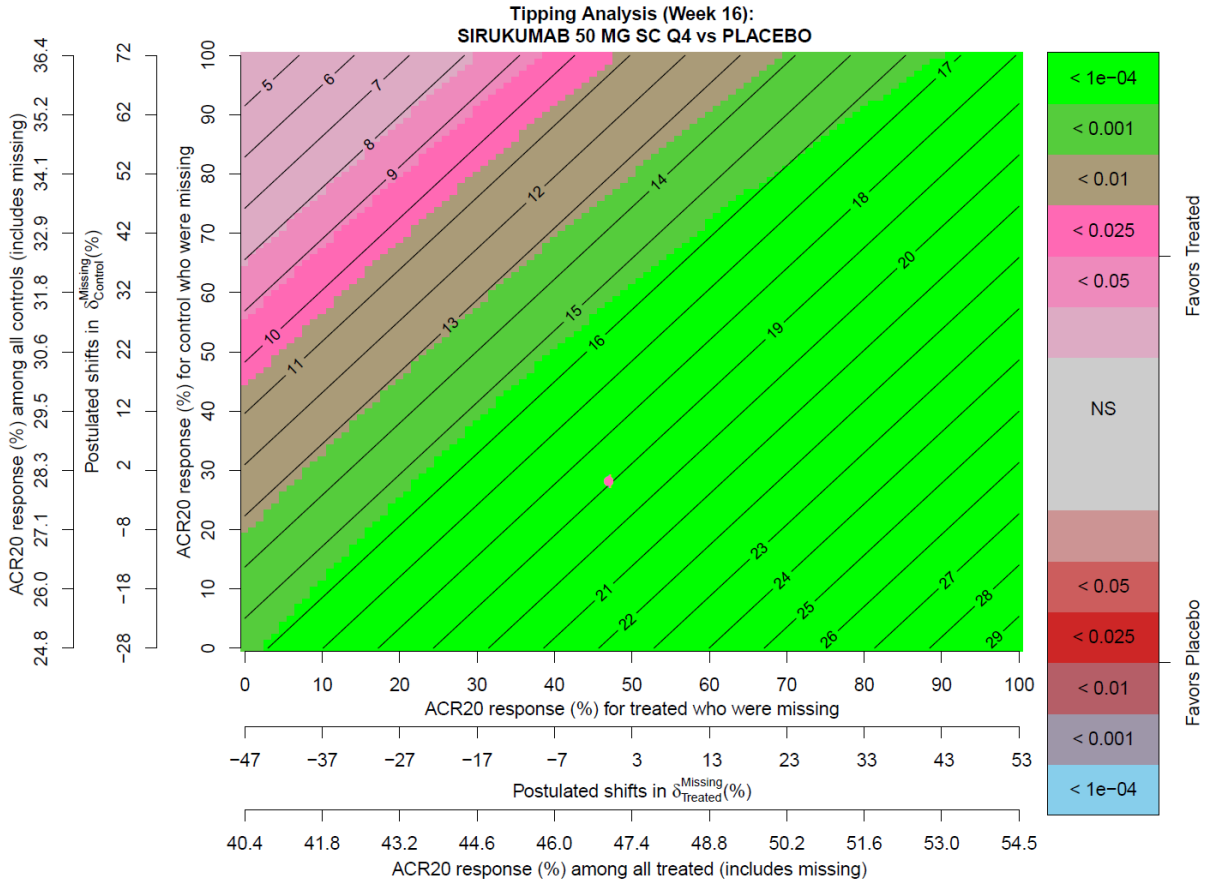
Source: Statistical Reviewer

Figure 19: Tipping Point Sensitivity Analysis for ACR20 Comparing Sirukumab 50 mg q4w to Placebo at Week 16 in ARA3002



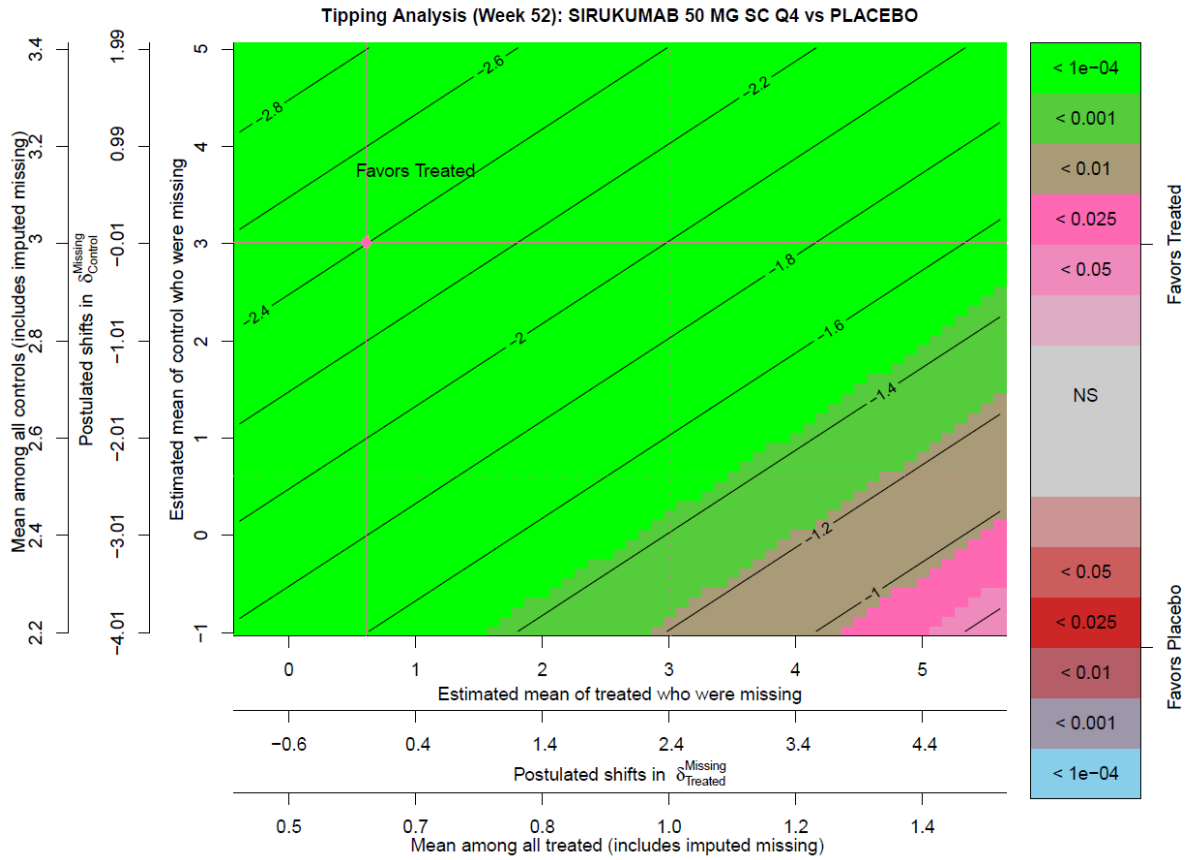
The pink point corresponds to the coordinates of the estimated proportion of ACR20 responders based on all observed data for each treatment arm. Contour lines represent the estimated treatment effect relative to placebo for a given set of missing data assumptions.
Abbreviations: ACR=American College of Rheumatology; SC=subcutaneously; Q4/Q4W=every four weeks; NS=Not significant (p>0.1) in gray
Source: Statistical Reviewer

Figure 20: Tipping Point Sensitivity Analysis for ACR20 Comparing Sirukumab 50 mg q4w to Placebo at Week 16 in ARA3003



The pink point corresponds to the coordinates of the estimated proportion of ACR20 responders based on all observed data for each treatment arm. Contour lines represent the estimated treatment effect relative to placebo for a given set of missing data assumptions.
Abbreviations: ACR=American College of Rheumatology; SC=subcutaneously; Q4/Q4W=every four weeks; NS=Not significant (p>0.1) in gray
Source: Statistical Reviewer

Figure 21: Tipping Point Sensitivity Analyses for Week 52 Change from Baseline in vdH-S Comparing Sirukumab 50 mg q4w to Placebo Based on all Observed Data Regardless of Escape or Treatment Discontinuation in ARA3002



The pink point corresponds to the coordinates of the estimated mean changes based on all observed data for each treatment arm. Contour lines represent the estimated treatment effect relative to placebo for a given set of missing data assumptions.
Abbreviations: vdH-S=van der Heijde-modified Sharp score; SC=subcutaneously; Q4/Q4W=every four weeks; NS=Not significant (p>0.1) in gray
Source: Statistical Reviewer

Table 66: Mean Changes from Baseline in ACR20 Components[a] and DAS28(ESR) Components[b] at Week 24 in ARA3005

Component	Adalimumab 40 mg q2w (N=186)[c]	Sirukumab 50 mg q4w (N=186)[c]	Sirukumab 100 mg q2w (N=187)[c]	Sirukumab 50 mg q4w vs Adalimumab[d]	Sirukumab 100 mg q2w vs Adalimumab[d]
TJC68	-18.39 (13.49) (n=174)	-16.67 (14.08) (n=172)	-19.40 (13.91) (n=176)	2.53 (0.12, 4.94) 0.040	0.03 (-2.36, 2.43) 0.977
SJC66	-12.60 (9.47) (n=174)	-12.01 (10.72) (n=172)	-13.86 (10.29) (n=176)	1.35 (-0.27, 2.97) 0.104	-0.28 (-1.90, 1.33) 0.732
HAQ-DI	-0.52 (0.67) (n=174)	-0.51 (0.61) (n=172)	-0.53 (0.67) (n=174)	0.04 (-0.08, 0.17) 0.510	-0.03 (-0.15, 0.09) 0.621
Pain Assessment *(0 – 10 unit VAS)*	-2.89 (2.67) (n=174)	-2.72 (2.67) (n=171)	-2.82 (2.65) (n=174)	0.18 (-0.31, 0.68) 0.468	-0.06 (-0.56, 0.43) 0.804
Patient Global *(0 – 10 unit VAS)*	-2.79 (2.84) (n=174)	-2.65 (2.82) (n=171)	-2.82 (2.72) (n=174)	0.08 (-0.42, 0.59) 0.748	-0.14 (-0.64, 0.36) 0.589
Physician Global *(0 – 10 unit VAS)*	-3.81 (2.16) (n=174)	-3.75 (2.33) (n=172)	-4.02 (2.09) (n=176)	0.03 (-0.37, 0.43) 0.884	-0.17 (-0.57, 0.22) 0.387
CRP *(mg/dL)*	-0.84 (2.95) (n=175)	-1.78 (2.79) (n=173)	-1.71 (2.34) (n=176)	-0.95 (-1.29, -0.61) <0.0001	-1.06 (-1.40, -0.73) <0.0001
TJC28	-10.60 (7.05) (n=174)	-8.83 (6.75) (n=172)	-10.73 (7.25) (n=176)	1.74 (0.42, 3.05) 0.010	0.16 (-1.14, 1.47) 0.809
SJC28	-8.68 (5.86) (n=174)	-7.83 (6.56) (n=172)	-9.14 (6.37) (n=176)	1.23 (0.16, 2.31) 0.025	0.11 (-0.96, 1.18) 0.846
ESR *(mm/h)*	-13.73 (26.86) (n=175)	-34.10 (28.56) (n=173)	-34.68 (22.65) (n=176)	-19.5 (-24.0, -15.0) <0.0001	-22.7 (-27.1, -18.2) <0.0001

Analysis based on linear regression using all observed data regardless of escape
Abbreviations: ACR=American College of Rheumatology; CRP=C-reactive protein; DAS28 (ESR)=disease activity index score 28 using ESR; ESR=erythrocyte sedimentation rate; HAQ-DI=Health Assessment Questionnaire-Disability Index; SJC66=swollen joint count out of 66 joints; TJC68=tender joint count out of 68 joints; SJC28=swollen joint count out of 28 joints; TJC28=tender joint count out of 28 joints; VAS=visual analogue scale
[a] ACR20 components include TJC68, SJC66, HAQ-DI, pain assessment, patient global, physician global, and CRP
[b] DAS28(ESR) components include TJC28, SJC28, patient global, and ESR
[c] Cell contents are mean (standard deviation) (n=number of non-missing observations); negative values indicate improvement
[d] Comparison to placebo based on linear regression, adjusting for baseline value and baseline reason for methotrexate failure
Source: Statistical Reviewer

9. Structural Damage Progression in Rheumatoid Arthritis

Structural Damage Progression Studies in Rheumatoid Arthritis

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Date: 05 July 2017

Prevention or reduction in radiographic evidence of structural damage progression assessed in relatively short-duration randomized controlled trials (RCTs) is thought to be a predictor of long-term benefit in preventing or delaying the progression to disability related to joint damage in rheumatoid arthritis (RA). Radiographic evidence of benefit in RA was first reported in a RCT for intramuscular gold in the 1970s (Singler 1974), and subsequently for many small-molecule and large-molecule biologic products for RA. Radiographic progression is assessed by a well developed and standardized scoring system utilizing x-rays of the hands and feet and is graded based on joint space narrowing and erosion (Boini 2001). For pharmaceutical industries developing drugs for RA, assessment of radiographic progression of structural damage is an important consideration. Demonstration of inhibition of radiographic structural damage has essentially become defining whether a drug is considered to be a disease-modifying anti-rheumatic drug (DMARD) or not.

Despite conduct of many RCTs with DMARDs showing positive benefit in structural damage assessed radiographically, changes in radiographic progression have not been directly related to clinical response (as assessed by criteria developed by American College of Rheumatology at 20% threshold or ACR-20, or by Disease Activity Score or DAS) or physical function changes (as assessed by Health-Assessment Questionnaire-Disability Index or HAQ-DI). The benefit in structural damage assessed radiographically in relatively short-duration RCTs thus can be considered as a biomarker that likely predicts destructive joint damage. The ultimate manifestation of disability in patients with RA is crippling destructive joint damage. Since the marketing of biologic DMARDS (bDMARDs) from the late 1990s (Enbrel or etanercept by Amgen in 1998, and Remicade or infliximab by J&J Company in 1999), general clinical impression suggests that crippling destructive joint damage is less common in patients with RA and probably will become even rarer in the future. In 2003, in a systemic review of radiographic data from recently conducted RCTs at that time for four drugs (leflunomide, infliximab, etanercept, and anakinra), it was thought that with the availability of better and more effective treatments for RA, radiographic progression rates in RA would decrease in future RCTs (Strand 2003). This has indeed become the case, as noted in a publication from 2016, which states that radiographic progression rates observed in RCTs have become smaller, and the authors raised the question of whether radiographic progression in modern RA trials is still a robust outcome (Landewe 2016). Early introduction of bDMARDs is now the standard of care as recommended by the American College of Rheumatology (Singh 2012; Singh 2016), and with patients treated early with bDMARDs, the conduct of studies and finding

appropriate patients who are likely to show radiographic progression in RCTs have become challenging.

RCTs for assessing radiographic progression with bDMARD before 2000, the early trials:

The early trials of bDMARDs evaluating benefit in structural damage assessed radiographically were with etanercept (Enbrel by Amgen, approved for marketing in 1998) and infliximab (Remicade by J&J Company, approved for marketing in 1999). The etanercept trial (etanercept versus methotrexate in the treatment of early rheumatoid arthritis or ERA) and the infliximab trial (anti-tumor necrosis factor trial in rheumatoid arthritis or ATTRACT) were conducted in the late 1990s (Bathon 2000, Lipsky 2000). These RCTs showed a decrease in radiographic evidence of structural damage progression when etanercept or infliximab was added to methotrexate. Methotrexate at that time was a tried-and-true DMARD. The magnitude of benefit in composite score (erosion and joint space narrowing) in these RCTs varied – approximately 0.5 points for etanercept and 6.5 points for infliximab. Both trials enrolled patients with a high probability of radiographic progression, and the trial duration was approximately 12 months. Beneficial effects were evident at 6 months, which became more pronounced during the second 6 months. Patients enrolled in the ERA trial had early disease with either erosion or high-titer rheumatoid factor positivity and were therefore more likely to demonstrate radiographic progression. Patients enrolled in the ATTRACT trial had relatively long disease duration and failed multiple courses of cDMARD (conventional small molecule DMARD) therapy and had high radiographic scores at baseline. Added benefit over methotrexate with these bDMARDs was considered a remarkable finding at that time, which impacted the subsequent standard of care of patients with RA and future RCTs to assess radiographic progression in RA.

Patient dropout in these 12-month RCT was a problem. At that time, sensitivity analyses were performed often with substituting the worst values from the placebo group for the missing value in the active-treatment group, and the best value from the active-treatment group for the missing values in the placebo group. Sensitivity analyses confirmed the robustness of the finding.

RCTs for assessing radiographic progression with DMARDs after 2000, the changing landscape:

Some representative RCTs conducted for assessing radiographic progression with DMARDs after the approval of etanercept and infliximab are shown in the Appendix Table at the end of this document. Most of the RCTs for assessing radiographic progression conducted between approximately 2000 and 2007 (for anakinra, adalimumab, abatacept, certolizumab, and tocilizumab) were still 12 months in duration, but the magnitude of benefit for these products was lower than that seen for other products in earlier RCTs (noting the limitations in comparing across RCTs conducted at different times, in patients with different disease severities, and different methods used to score radiographs).

With the availability and widespread acceptance and use of etanercept (approved in 1998), infliximab (approved in 1999), and many other similar bDMARDs approved subsequently,

questions were raised in 2009 about the appropriateness of conduct of RCTs that lasted 12 months and even 6 months where patients were not given a bDMARD or a similarly potent drug that has known benefit on structural damage progression (Boers 2009, Strand 2009). Structural damage is known to be permanent and irreversible. Even loss of physical function in these 6- to 12-month RCT is thought to be permanent and irreversible. The American College of Rheumatology organized a clinical trial priorities and design conference in 2010 to discuss the changing RA treatment landscape (conference summary published in 2011). The conference summary stated that to fulfill regulatory requirements, short-term placebo (usually methotrexate alone) treatment arms in RCTs will be necessary, but such placebo treatment should be limited to 3 or 4 months, and early rescue treatment should be provided. The conference summary stated that to enroll patients in protocols where placebo is used for prolonged periods when proven therapies exist does not provide clinically useful information and is not ethically defensible. On duration of treatment, noting the 12-month trials for assessing radiographic progression, the conference summary stated that keeping to standard clinical practice, patients who did not receive target benefits would be switched to effective therapy at 3-6 months. Reflecting the changing clinical practice with the availability of bDMARDs, the American College of Rheumatology updated its recommendation for the treatment of RA in 2012 stating that all patients with early RA and moderately to highly active RA with poor prognostic factors should be started with a bDMARD (with or without methotrexate) or combination cDMARD therapy (double or triple therapy) early in treatment with the aim of achieving disease remission or low disease activity (Singh 2012). The FDA also updated the Guidance for Developing Products for the Treatment of RA in 2013 to accommodate the changing standard of clinical care for patients with RA and expectation of the American College of Rheumatology (FDA RA guidance 2013). The FDA Guidance says that studies longer than 3-months should have provisions for escape therapy to rescue patients with active disease.

Given the changing landscape in the care of patients with RA, the pharmaceutical industry also shifted the conduct of RCTs for assessing radiographic progression in RA with the aim of recruiting patients appropriate for these RCTs and limiting the duration of exposure of patients to potentially ineffective treatment. From approximately 2005 to 2010 most of the RCTs were 6-months in duration. For example, there were two RCTs conducted with golimumab (Simponi by J&J Company): one trial 12-months in duration conducted in methotrexate-naïve patients, and another trial 6-months in duration conducted in methotrexate-inadequate responder patients (Emery 2011). Conducting a 12-month RCT in methotrexate-naïve RA patients would be reasonable because these patients would be treated with methotrexate for the first time in the trial, and methotrexate has a known benefit on radiographic progression that may take 3-6 months to manifest. Other trials conducted in late 2000s and early 2010s (such as an IV formulation of golimumab and JAK-inhibitors tofacitinib) were also 6-months in duration.

Another change, keeping with the evolving landscape in care of patients with RA and expectations of the RCT for RA discussed above, was the application of the criteria based on which patients from placebo (cDMARD, usually methotrexate alone) treatment were allowed to escape to active treatment (Appendix Table). For some relatively recent programs (since about 2005), the criterion was <20% improvement in tender joint count and swollen joint

count, which was applied usually at the 3-month time point to decide whether a patient would remain on placebo (cDMARD, usually methotrexate alone) or not. In an operational sense, if a patients with 10 "hot joints" (tender joint and swollen joint) was randomized in a RCT to placebo, at approximately the 3-month time point, if this patients had 8 "hot joints" (20% improvement), the patient would be continued on placebo with the rationale that this patient has shown some improvement and is likely to improve further with time. However, if this patient had 9 "hot joints" (<20% improvement), the patients would escape from placebo (cDMARD, usually methotrexate alone) to active treatment. At the 6-month time point, all patients would escape from placebo (cDMARD, usually methotrexate alone) to active treatment. With this escape criterion, no patient with active RA would stay on placebo (cDMARD, usually methotrexate alone) for more than 3 months, and no patient would remain on placebo (cDMARD, usually methotrexate alone) for more than 6 months.

RCTs for assessing radiographic progression with bDMARDs after 2010, the sarilumab and sirukumab trials:

A probable deviation from the change in RCTs for assessing radiographic progression discussed above seems to have occurred for sarilumab (Sanofi product, Approved June 22, 2017) and sirukumab (J&J Company product under FDA review). The sarilumab RCT was conducted from 2011 to 2013, and the sirikumab RCT was conducted from 2012 to 2015 (Appendix Table). Both RCTs continued patients who had at least 20% improvement in tender joint count and swollen joint count on placebo through approximately the 3-month and the 6-month time-point. In an operational sense, keeping to the analogy described above, if a patient with 10 "hot joints" (tender joint and swollen joint) was randomized in a RCT to placebo, at approximately the 3-month time point, if this patients had 8 "hot joints" (20% improvement), the patient could be continued on placebo. At 6-month time point, if this same patient still had 8 "hot joints" (still 20% improvement), the patient could still be continued on placebo. With this design, patients could stay on placebo (cDMARD, usually methotrexate alone) through and beyond 6-months with 20% improvement (8 "hot joints" out of 10 "hot joints" at randomization). In these two trials, at 12-month time-point approximately 50% patients remained on placebo (cDMARD, usually methotrexate alone). The radiographic progression on placebo (cDMARD, usually methotrexate alone) was high and the treatment effect size (difference between cDMARDs and drug) was also high at month 12. The treatment effect sizes for these two products were larger than the treatment effect size of other RCTs done relatively recently (using the same methods to score radiographs), and even older RCTs conducted with the very early bDMARDs in the late 1990s (noting the limitations in comparing across RCTs conducted at different times, in patients with different disease severities, and different methods used to score radiographs).

Current challenges with RCTs for assessing radiographic progression:

RCTs to demonstrate benefit in radiographic progression have become increasingly difficult for several reasons. First, use of placebo (cDMARD, usually methotrexate alone) in RCTs lasting for longer than 6-months without an escalation in treatment in patients with ongoing disease activity seems to be no longer acceptable. Second, RA patients with high disease severity who are more likely to show progression during RCTs are not available in large

numbers because the current standard of care recommends early institution of DMARDs with the aim of achieving disease remission or low disease activity. Third, the extent of progression in the placebo (cDMARD, usually methotrexate alone) comparator group is low in the more recently conducted 6-month long RCTs, thus making it difficult for the drug to show a benefit. Fourth, patient dropout from the treatment arms makes analysis of the data complicated. Finally, patients are increasingly switched from placebo (cDMARD, usually methotrexate alone) to active treatment or standard-of-care treatment early during RCTs to prevent irreversible harm to study patients, thus compounding the missing data problem.

There is no good analysis method for accounting for the missing data for patients who dropout from the trial or the data from patients who are actively switched from placebo (cDMARD, usually methotrexate alone) to active-treatment arms. The traditional historical method used is the "linear extrapolation method" where data post-dropout are imputed assuming a linear progression assumption from data before the dropout. Various alternate methods are being explored. One such method is the "observed data method" where actual data from after the dropout are used. Both these methods have problems. In the "linear extrapolation method", the difference between the treatment groups may be inflated if the actual progression after the drop out was not linear, but less. In the "observed data method", the difference between the treatment groups may be deflated because after dropout, patients (likely more in placebo group) are treated with bDMARDs that have a known benefit. In most of the RCTs conducted after 2010, the "linear extrapolation method" has been used for reporting radiographic progression data.

Future of RCTs for assessing radiographic progression:

RCTs as being done today are becoming increasingly difficult to conduct, analyze, and interpret. We need to consider alternate methods to assess radiographic progression, or perhaps assume radiographic progression from other measures, such as higher level of benefit in signs and symptoms by ACR or DAS criteria, or higher level of benefit in physical function by the HAQ-DI measure.

If we are to continue using x-ray radiographic progression as the endpoint, RCTs will need to be redesigned and alternate methods employed. One approach would be to conduct an active-comparator RCT where a new drug (with adequate and convincing phase 2 data suggestive of benefit) can be compared to an existing and well-studied DMARD in a 12-month study. Such study could be of a non-inferiority design. Demonstration of superiority would also be possible with appropriate statistical methodologies built into the RCT. Another approach may be to use portions of the x-ray data post-hoc to increase sensitivity, such as data from patients with radiographic progression (FDA guidance 2013), or a trimmed analysis where the extremes of the data (outliers) are excluded (Landewe 2016). Multiple methods can also be used in the same RCT where the two treatment arms are compared using the standard matrix as used today, and then post-hoc using data from patients with radiographic progression or with a trimmed analysis excluding extremes of the data. Furthermore, prognostic factors to identify patients likely to progress during the RCT can be used as well.

Alternate imaging modalities, such as magnetic resonance imaging (MRI) or ultrasonography may allow for demonstration of a positive benefit in structural damage progression in a RCT of shorter duration than what has been required in previous RCTs examining x-ray radiographic data. There are data on MRI that seem promising (Peterfy 2016).

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DMARD radiographic changes (Total Sharp Score or its modification)* in representative clinical trials conducted for product registration in the United States since 2000. Studies listed chronologically based on year the studies were started.

Drug Name, † (Sponsor), year first approved	Study ID Study patients ‡ (Study years)	Month of endpoint measure	Mean change from baseline score *			Methotrexate/Placebo to Drug escape criteria		% Patients on mtx/pbo at month 12
			Mtx	Mtx + Drug	Δ [95% CI] or (p-value) §	Early escape at ≈ month 3-4	Late escape at ≈ month 6-7	
Anakinra (Kineret) Amgen 2001	Study 1 Mtx-IR	12	2.6	1.7	0.9 [0.3, 1.6]	Allowed rescue analgesics like acetaminophen, codeine, or propoxyphene except within 12 hours of a scheduled study evaluation. Intra-articular corticosteroids to 2 joints was permitted on 2 separate occasions >2 weeks before the next assessment visit.	Allowed rescue analgesics like acetaminophen, codeine, or propoxyphene except within 12 hours of a scheduled study evaluation. Intra-articular corticosteroids to 2 joints was permitted on 2 separate occasions >2 weeks before the next assessment visit.	≈ 65 %
Adalimumab (Humira) AbbVie, 2002	Study RA III Mtx-IR (2000-2002)	12	2.7	0.1	-2.6 [1.4, 3.8]	At or after the Week 16 visit, DMARDs (except TNF antagonists) could be added for non-responding patients at the discretion of the investigator.	At or after the Week 16 visit, DMARDs (except TNF antagonists) could be added for non-responding patients at the discretion of the investigator.	≈ 70 %
Abatacept (Orencia) BMS, 2005	Study III Mtx-IR (2002-2004)	12	2.43	1.07	-1.36 [xxxx, xxxx] (p<0.01)	Lack of efficacy or discretion of the investigator, but with no specified time point	Lack of efficacy or discretion of the investigator, but with no specified time point	≈ 75 %
	Study VI Mtx-naive (2005-2008)	12	1.1	0.6	-0.5 [xxxx, xxxx] (p=0.04)	None	After first 6-months, small molecule cDMARDs allowed at investigator discretion; no bDMARDs allowed	≈ 90 %
Cetrolizumab (Cimzia) UCB, 2008	C87027 or RA-I MTX-IR (2005-2008)	12	2.8	0.4	-2.4 [xxxx, xxxx] (p<xxxx)	None. Provisions were made to treat RA flare with NSAIDS and narcotics.	None. Provisions were made to treat RA flare with NSAIDS and narcotics.	≈ 20 %
Tocilizumab 8 IV (Actemra) Genentech, 2010	17823 or II Mtx-IR (2005-2007)	12	1.17	0.25	-0.90 [-0.59, -1.20]	<20% improvement in tender joint count and swollen joint count	<20% improvement in tender joint count and swollen joint count	≈ 40 %
Golimumab 50 (Simponi) Janssen, 2009	Go-before or 5 Mtx-naïve (2005-2008)	12	1.37	0.74	-0.60 [xxxx, xxxx] (p=0.015)	None	<20% improvement in tender joint count and swollen joint count	≈ 85 %

	Go-forward or 6 Mtx-IR (2005-2009)	6	0.55	0.60	-0.10 [xxxx, xxxx] (p=0.953)	<20% improvement in tender joint count and swollen joint count	All placebo patients were escaped to drug	NA
Tofacitinib 5 mg (Xeljanz) Pfizer, 2012	1044 or IV Mtx-IR (2009-2011)	6	0.47	0.12	-0.34 [-0.73, 0.04]	None. Use of NSAIDs or opioids for 10 consecutive days led to withdrawal.	All placebo patients were escaped to drug	NA
	1069 or VI Mtx-naïve (2010-2012)	6	0.84	0.18	-0.66 [-1.03, -0.28]	None. Use of NSAIDs or opioids for 10 consecutive days led to withdrawal.	All placebo patients were escaped to drug	NA
Golimumab 2/kg (Simponi Aria) Janssen, 2013	Study 3001 or I Mtx-IR (2009-2011)	6	1.09	0.03	-1.06 [xxxx, xxxx] (p<0.001)	<20% improvement in tender joint count and swollen joint count	All placebo patients were escaped to drug	NA
Sarilumab 200 Kevzara Sanofi, NA	11072-Part B Mtx-IR (2011-2013)	12	2.78	0.25	-2.52 [-3.18, -1.88]	<20% improvement in tender joint count and swollen joint count	<20% improvement in tender joint count and swollen joint count	≈ 50 %
Sirukumab Janssen, NA	ARA3002 cDMARD-IR (2012-2015)	12	3.69	0.50	-3.19 [-4.00, -2.38]	<20% improvement in tender joint count and swollen joint count	<20% improvement in tender joint count and swollen joint count	≈ 50 %

* Total Sharp Score (TSS) is a composite of Erosion Score and Joint Space Narrowing Score, modifications (mTSS) include the Genant and van der Heijde. Linear extrapolation method use for missing data and post-rescue data. Not appropriate to compare scores across studies because in the differences in study patients, and differences in modifications of the TSS used in different studies.

† Excluded from this list are methotrexate approved in 1986 and some other small molecule older DMARDs, etanercept approved in 1998, and infliximab approved in 1999.

‡ Mtx is methotrexate; IR is inadequate responder; cDMARD is conventional small molecule (usually methotrexate) disease modifying anti-rheumatic drug; bDMARD is biologic (usually TNF blocker) disease modifying anti-rheumatic drug;

§ Either 95% confidence interval or p-value comparing drug to drug+mtx is shown