CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761037Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

BLA Number:	761037 (related IND 100632)
Submissions Date:	10/30/2015
Submission Type:	351(a)
Proposed Brand Name:	(b) (4)
Generic Name:	Sarilumab
Sponsor:	Sanofi
Route of Administration:	Subcutaneous Injection
Dosage Form:	Prefilled syringe
Dosage Strength:	Prefilled syringe (PFS, 150 mg and 200 mg)
Proposed Dosing Regimen:	Proposed dose is 200 mg SC every 2 weeks. Reduction of dose from 200 mg once every 2 weeks to 150 mg once every 2 weeks is recommended for management of neutropenia, thrombocytopenia and elevated liver enzymes.
Proposed Indication(s):	Treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to one or more DMARDs
OND Divisions:	Division of Pulmonary, Allergy, and Rheumatology Products
OCP Division:	Clinical Pharmacology II
Reviewers:	Jianmeng Chen, M.D., Ph.D., Sheetal Agarwal, Ph.D., RAC
Team Leader:	Anshu Marathe, Ph.D.
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Note –

In this review, early development name REGN88 or SAR153191 sometimes was used to refer to Sarilumab.

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1. EXECUTIVE SUMMARY

Sanofi has submitted an original BLA for sarilumab (development name REGN888/SAR153191, proposed brand name (b) (4) Sarilumab is a human IgG1 monoclonal antibody that binds to both soluble and membrane-bound IL-6 receptors. The proposed indication is treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to one or more DMARDs. The proposed dose is 200mg every 2 weeks. Dose may be reduced to 150mg every2 weeks in patients for management of neutropenia, thrombocytopenia, and elevated liver enzymes. The proposed available form is the pre-filled syringe (150 mg/1.14 mL and 200 mg/1.14 mL). (b) (4)

The clinical development program of this submission includes one Phase 1 studies in healthy subjects, eight Phase 1 studies in RA patients, and seven Phase 2/3 studies in RA patients.

The following are the major clinical pharmacology findings of the current review:

1. Based on the dose/exposure-response relationship for efficacy, the sarilumab 200 mg q2w dosing regimen has better efficacy compared to 150 mg q2w in RA patients. The dose/exposure-response relationship for safety supports sponsor's dose reduction scheme of reducing the dose to 150 mg q2w if laboratory abnormalities (neutropenia, thrombocytopenia, elevated liver enzymes) are observed.

2. The dosing regimen of sarilumab has been adequately explored. Prior to the confirmatory trials, a dose ranging trial was conducted in patients with RA. In this trial, 5 dosing regimens of sarilumab (100, 150, and 200 mg q2w; 100 and 150 mg qw) were compared with placebo over 12 weeks of treatment. The efficacy of sarilumab (ACR20, ACR50, and ACR70 scores and the DAS28-CRP) was only apparent at concentrations achieved with doses of 150 mg q2w or above. Moreover, a dose/exposure-response relationship was observed for certain AEs and laboratory abnormalities (neutropenia, thrombocytopenia, elevated liver enzymes) within the doses tested.

3. The absolute bioavailability for sarilumab SC injection was estimated to be ~80% for the to-be-marketed product ((b) (4)F3). Sarilumab exhibits nonlinear PK with the exposure increased more than dose proportional. The steady state exposure (AUC) for 200 mg q2w is approximately two fold higher compared to the steady state exposure of 150 mg q2w.

4. No adjustment of the starting dose is recommended for any intrinsic or extrinsic factors. The reviewer considers it reasonable to monitor absolute neutrophil count (ANC), platelet count, and liver enzyme for the tolerance of sarilumab, and to manage the adverse reactions by dose reduction, dose interruption, or discontinuation as necessary.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the BLA 761037 and finds the application acceptable from a clinical pharmacology perspective.

1.2 Phase 4 Commitments

None.

1.3. Summary of Clinical Pharmacology Findings

1.3.1 Background

Sarilumab is a recombinant human immunoglobulin (IgG)1 monoclonal antibody that binds specifically to both soluble and membrane-bound interleukin-6 (IL-6) receptors (sIL-6Rα and mIL-6Rα) and inhibits IL-6-mediated signaling. By binding to IL-6Rα with high affinity, sarilumab blocks the binding of IL-6 and interrupts the cytokine-mediated inflammatory signaling cascade.

1.3.2 Dose justification

The proposed dosing regimen for sarilumab seems reasonable. The proposed dose was supported by a dose ranging study (EFC11072 Part A) and two pivotal phase 3 studies (EFC11072 Part B and EFC10832).

Study EFC11072 Part A has provided evidence to support the selection of the 150 and 200 mg SC q2w dose for further evaluation in the pivotal efficacy studies. Following every week (100 and 150 mg qw) and every other week (100, 150, and 200 mg q2w) dose regimens in the Phase 2 dose-ranging study (EFC11072 Part A), the efficacy (ACR20, ACR50, and ACR70 scores and the DAS28 CRP) was apparent only at concentrations achieved with doses of 150 mg q2w or above (Figure 1, Figure 2). Furthermore, a plateau was reached for all efficacy endpoints at e sarilumab concentrations achieved at the 200 mg q2w dose, with further increase in exposure by as much 2.7-fold (150 mg qw) providing only marginal change in the responses. Thus, 150 mg q2w and 200 mg q2w doses were considered appropriate for the Phase 3 program.

A dose response relationship also was observed for ACR20, ACR50, and ACR70 over the dose range of 150 to 200 mg q2w in the Phase 3 studies (Table 3). Consistent with the dose-response, increased efficacy with respect to ACR20, ACR50, ACR70, CDAI, and DAS28 was observed with increasing exposure (Ctrough) in Phase 3 studies at the within the concentration range observed at 150 mg q2w and 200 mg q2w doses (Figure 3, Figure 4). For safety, there was a slight increase in the incidence of AEs with the 200 mg q2w dose compared to the 150 mg q2w dosing regimen of sarilumab. Per medical review, the risk/benefit assessment supports the starting dose of 200mg q2w for the proposed indication.

As increased lab abnormalities were associated with increasing dose of sarilumab, sponsor's proposed dose reduction scheme appears reasonable. Higher proportion of subjects with 1) increase in AST, ALT or GGT; 2) thrombocytopenia; 3) neutropenia was observed in the 200 mg q2w dose group compared to the 150 mg q2w dose group. The change from baseline in ANC and ALT was related to sarilumab concentration (Figure 5). The exposure –response relationship for these safety endpoints is consistent with the dose-response relationship observed in Phase 3 studies. Based on the exposure/dose response relationship for ANC, ALT and LDL, dose modification is an appropriate management strategy in the event of laboratory abnormalities that persist at the end of the dosing interval.

No dose adjustment is recommended for the starting dose in specific populations, with respect to sex, body weight, age, race, renal or hepatic function (See section 2.7.1).

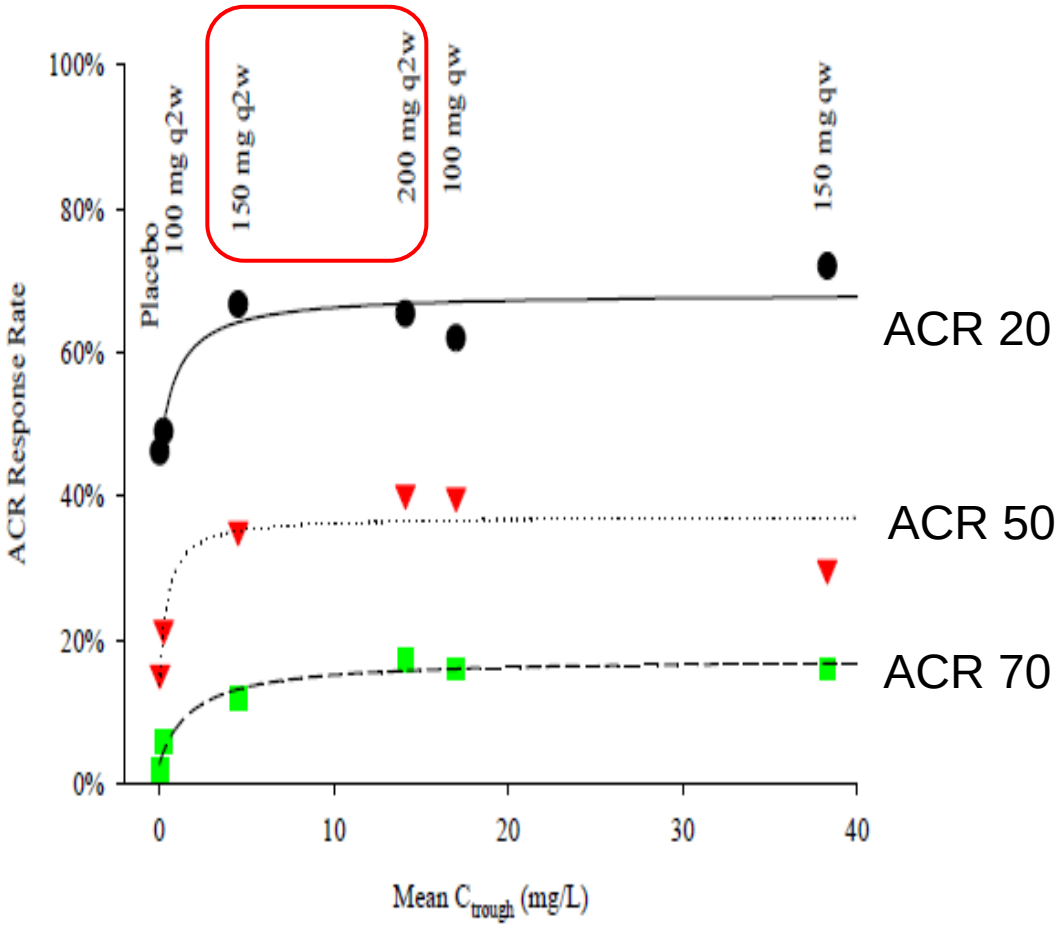

Figure 1.The response rate of American College of Rheumatology 20, 50 and 70 percent improvement versus trough concentrations of functional sarilumab at Week 12 in patients with rheumatoid arthritis (Study EFC11072 Part A)

(Source: Figure 16, summary of clin pharm)

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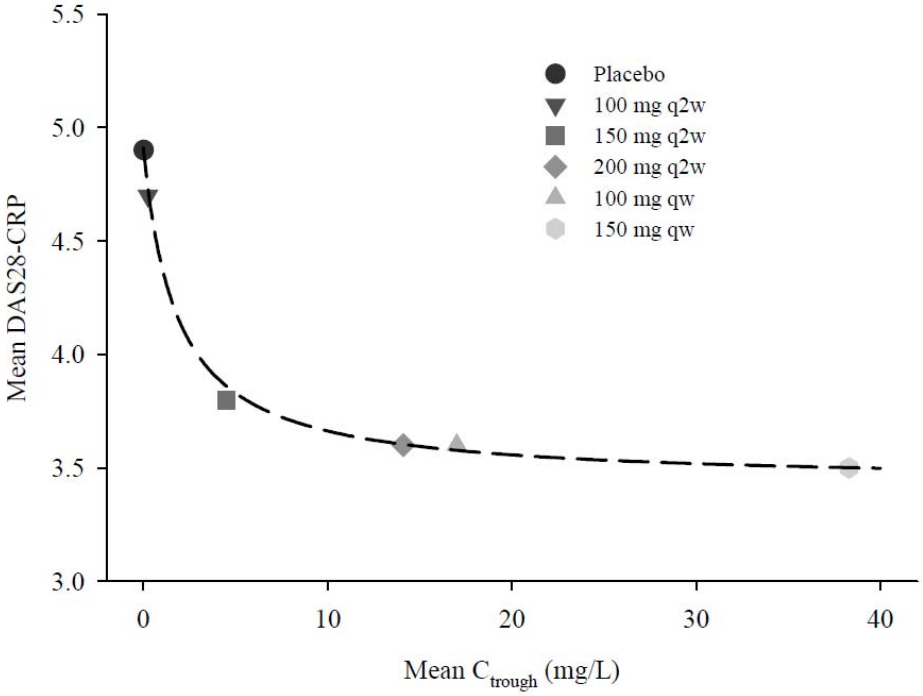

Figure 2. - DAS28-CRP versus trough concentrations of serum functional sarilumab at Week 12 in patients with rheumatoid arthritis (Study EFC11072 Part A)
(Source: Figure 20, summary of clin pharm)

1.3.3 Pharmacokinetics

Functional sarilumab serum concentrations in healthy subjects were higher than in patients with RA at the same dose of 100 mg by approximately 1.8-fold.

Pharmacokinetics in RA Patients
Sarilumab exhibits nonlinear PK with target mediated drug disposition. It is well absorbed after a single SC administration (T_{max} of 2 to 4 days and a bioavailability of 80%), exhibits a low apparent volume of distribution (7.3 L), which indicates distribution primarily in the circulatory system.

Sarilumab exposure increases in a greater than dose proportional manner. At steady state, $AUC_{0\text{-}14\ days}$ is two -fold higher with sarilumab 200 mg q2w compared to sarilumab 150 mg q2w. Steady state appears to be achieved in 14 to 16 weeks following repeated q2w SC administration, with a 2- to 3-fold accumulation for $AUC_{0\text{-}14\ days}$. The effective half -life is ~17-19 day based on accumulation (AUC) at steady state.

Pharmacokinetics in Special Populations

No formal study was conducted in special populations (such as patients with renal or hepatic impairment), because the disposition of sarilumab, an IgG antibody, is not expected to be impacted by renal or hepatic function.

The main source of intrinsic PK variability identified in patients using population PK analysis is body weight, with a decrease in weight resulting in an increase in exposure, however no dose adjustment is needed (see section 2.7.2.2). None of the other demographic characteristics (age, race, or sex) have a relevant effect on the PK of sarilumab.

1.3.4 Immunogenicity

Positive ADA status has an impact on PK (a 24% to 28% lower exposure when compared to ADA negative patients), with concentrations in patients with persistent response being lower (by 32% to 41%) than in patients with transient response. Persistent ADA response was observed in 2.0%, 5.6%, and 4.0% of patients in the placebo and sarilumab 150 and 200 mg q2w treatment groups across the placebo controlled immunogenicity population (Pool 1), with 0.2%, 1.6%, and 1.0% of patients also exhibiting NAbs. Sarilumab concentrations in this small number of NAb positive patients appeared to be lower than in NAb negative patients (by 49% to 59%), but this did not impact discontinuations for lack or loss of efficacy (see section 2.7.4.4).

2. QUESTION BASED REVIEW

2.1 Regulatory History

Sarilumab is a recombinant human immunoglobulin (IgG)1 monoclonal antibody that binds specifically to both soluble and membrane-bound interleukin-6 (IL-6) receptors (sIL-6Rα and mIL-6Rα) and inhibits IL-6-mediated signaling. Sarilumab is indicated for 'treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more disease-modifying anti-rheumatic drugs (DMARDs).'' Sarilumab may be used as monotherapy or in combination with methotrexate (MTX) or other traditional DMARDs as a subcutaneous injection. The proposed dose of sarilumab is 200 mg once every 2 weeks (q2w) given as a subcutaneous (SC) injection. Reduction in the dose from 200 mg q2w to 150 mg q2w is recommended for management of elevated liver enzymes, neutropenia, and thrombocytopenia.

The sponsor discussed their development program with the Agency through several pre-submission meetings. Relevant Clinical Pharmacology related comments were conveyed during EOP2 meeting (Sep 15, 2011).

2.2 List the in vitro and in vivo Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA

The clinical pharmacology database for sarilumab comprises all PK and PD data collected from 53 healthy subjects from one Phase 1 study; 241 patients with RA from eight Phase 1 studies, and 2671 patients with RA from seven Phase 2/3 studies. Pre-specified population PK and population PK/PD analyses were conducted using pooled data from Phase 1, 2, and 3 studies.

Table 1. Sarilumab pharmacokinetic and pharmacodynamic assessments in clinical studies and analyses

Study type	Study identifier	Sarilumab dose regimen	Population	Number enrolled[l]
Biopharmaceutic studies (Phase 1)				
Single dose, comparative bioavailability	TDU11373[a]	100, 150, and 200 mg; a single SC dose	Healthy subjects	53
Single dose, comparative bioavailability	PKM12058[a]	200 mg; a single SC dose	RA patients	32
Pharmacokinetics and initial tolerability studies in patients (Phase 1)				
Single ascending dose IV	TDU10808/ 6R88-RA-0703	0.6 and 2.0 mg/kg; a single IV dose	RA patients	7[b]
Single ascending dose SC	TDU10809/ 6R88-RA-0801	50, 100, and 200 mg; a single SC dose	RA patients	15
Repeat ascending dose SC	TDR10805/ 6R88-RA-0802	50, 100, and 150 mg qw; 100, 150, and 200 mg q2w	RA patients	60
Intrinsic factors (Phase 1, population PK analysis)				
Race (Japanese)	TDU13402[c]	50, 100, and 200 mg; a single SC dose	RA patients	24
Age, gender, body weight, race, laboratory measurements.	POH0428[d]	50, 100, 150, and 200 mg, a single SC dose; 100, 150, and 200 mg q2w SC; 50, 100, and 150 mg qw SC	Pooled RA patients	1770
Extrinsic factors (Phases 1, 2, and 3 population PK analysis)				
Prior biologics, methotrexate	POH0428[d]	50, 100, 150, and 200 mg; a single SC dose	Pooled RA patients	1770
		100, 150, and 200 mg q2w SC; 50, 100, and 150 mg qw SC		
Effect of sarilumab on other drugs (Phase 1)				
Simvastatin (CYP3A4 substrate)	INT12684 Part A[e]	200 mg; a single SC dose	RA patients, MTX-IR	19
PD and PK/PD studies (Phase 1)				
PD for biomarkers, PK/PD for key safety parameters, biomarkers[f]	ACT10804/ 6R88-RA-0803	50, 100, and 200 mg; a single SC dose	RA patients	32
	6R88-RA-1309	150 and 200 mg; a single SC dose	RA patients	101[g]
Pharmacokinetics in efficacy/safety studies (Phases 2 and 3)				
Phase 2	EFC11072 Part A	100, 150, and 200 mg q2w; 100 and 150 mg qw SC	RA patients, MTX-IR	306

Study type	Study identifier	Sarilumab dose regimen	Population	Number enrolled[f]
Phase 3[e]	EFC11072 Part B	150 and 200 mg q2w SC	RA patients, MTX-IR	172 (Cohort 1) 1197 (Cohort 2)[h]
	EFC10832	150 and 200 mg q2w SC	RA patients, TNF-IR	546
	SFY13370	150 and 200 mg q2w SC	RA patients, TNF-IR	202[i]
	MSC12665[a]	150 and 200 mg q2w SC	RA patients, DMARD-IR	217
	EFC13752	150 and 200 mg q2w SC	RA patients, DMARD-IR	132
	LTS11210	150 and 200 mg q2w SC	RA patients who completed or transferred from 1 of 6 previous sarilumab trials	2008
Population PK and population PK/PD in clinical pharmacology and efficacy/safety studies				
Population PK	POH0428[d]	50, 100, 150, and 200 mg, a single SC dose; 100, 150, and 200 mg q2w SC; 100 and 150 mg qw SC	Pooled RA	1770
PK/PD for key efficacy and safety parameters	POH0455[j]	100, 150 and 200 mg q2w SC; 100 and 150 mg qw SC	Pooled RA patients	2221
Population PK/PD for absolute neutrophil count	POH0429[k]	50, 100, 150, and 200 mg, a single SC dose; 100, 150, and 200 mg q2w SC; 50, 100, and 150 mg qw SC	Pooled RA patients	1672
Population PK/PD for DAS28-CRP	POH0446[k]	100, 150 and 200 mg q2w SC; 100 and 150 mg qw SC	Pooled RA patients	2082

Source: Pages 13 and 14 of summary of clinical pharmacology, Module 2

2.3 General Attributes of the Drug

2.3.1 What are the highlights of the chemistry and physicochemical properties of the drug substance, and the formulation of the drug product?

Drug substance:

Sarilumab active pharmaceutical ingredient (IgG1 isotype monoclonal antibody) is a covalent heterotetramer consisting of two disulfide-linked human heavy chains, each covalently linked through a disulfide bond to a human kappa light chain. There is a single N-linked glycosylation site (Asn296) on each heavy chain, located within the CH2 domain of the Fc constant region in the molecule. Based on the primary sequence, the antibody without glycans possesses a predicted molecular weight of 143,873.7 Da, assuming the formation of 16 canonical disulfide bonds, and removal of Lys446 from each heavy chain C-terminus1. The complementarity-determining regions (CDRs) within the sarilumab heavy chain and light chain variable domains combine to form the binding site for its target, IL-6Rα (interleukin-6 receptor α subunit). Sarilumab is produced by (b) (4) suspension culture of recombinant Chinese Hamster Ovary (CHO) cells that have been engineered to constitutively express sarilumab heavy and light chains in culture.

Drug product:

Sarilumab solution for injection is a clear, colorless to pale yellow, aqueous [redacted] sterile solution, pH 6.0. Sarilumab solution for injection is supplied, for subcutaneous (SC) injection, as a single-use prefilled syringe (PFS) drug product (DP) presentation in two strengths, 131.6 mg/mL and 175 mg/mL, providing doses of 150 mg and 200 mg, respectively. [redacted]

Table 2. Sarilumab PFS Components and Presentations for the 150 mg and 200 mg Dose Forms

[redacted]

(Source: Page 8 of summary of drug product, Module 2)

2.3.2 What are the proposed mechanism of action and therapeutic indications?

Mechanism of action:

Sarilumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6Rα and mIL-6Rα), and inhibits IL-6 mediated signaling.

Proposed indication:

[redacted] is indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

2.3.3 What are the proposed dosage(s) and route(s) of administration?

Proposed dosing:

[redacted] may be used as monotherapy or in combination with methotrexate (MTX) or other traditional DMARDs as a subcutaneous injection. The recommended dose of [redacted] is 200 mg once every two weeks. Do not initiate [redacted] in patients with ANC < 2000/mm3, platelets < 150,000/mm3 or liver transaminases above 1.5 X ULN. Reduction of dose from 200

mg once every 2 weeks to 150 mg once every 2 weeks is recommended for management of neutropenia, thrombocytopenia, and elevated liver enzymes.

Route of administration: Subcutaneous injection.

2.3.4 What drugs (substances, products) indicated for the same indication are approved in the U.S.?

Actemra (tocilizumab, Solution for Subcutaneous Injection) was approved on October 21, 2013 under BLA 125472. Tocilizumab (RO4877533, TCZ) is a humanized anti-human IL-6 receptor (IL-6R) monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass produced using recombinant DNA technology. Tocilizumab is indicated for adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

2.4 General Clinical Pharmacology

2.4.1 What is the basis for selecting the response endpoints?

EFC11702 Part B (SARIL-RA-MOBILITY) and EFC10832 (SARIL-RA TARGET) are the 2 studies considered to be the pivotal studies to support the proposed indication. The following co-primary endpoints were discussed and agreed upon in the pre-submission meetings and were employed in these 2 studies:

EFC11702 Part B

1. American College of Rheumatology 20% improvement criteria (ACR20) responders at Week 24
2. Change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 16
3. Change from baseline in Sharp van der Heijde modified total Sharp score (mTSS) at Week 52

EFC10832

1. ACR20 responders at Week 24
2. Change from baseline in HAQ-DI at Week 12

2.4.2 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Functional sarilumab is assumed to represent the pharmacologically active drug. Plasma concentration of functional sarilumab was measured to assess its pharmacokinetic parameters

and exposure response relationships (See section 2.10). Per sponsor, functional sarilumab is defined as sarilumab with ≥1 free binding sites for IL-6Rα and capable of target binding.

The sponsor also measured bound sarilumab in earlier studies. The bound sarilumab and functional sarilumab are not mutually exclusive, as the fraction of sarilumab which has one binding site occupied with IL-6Rα and the other binding site free was both functional and bound. The bound sarilumab concentration is not stated in the label or used in the exposure-response analysis. Therefore, this review did not assess the concentration of bound sarilumab.

2.5 Exposure Response

2.5.1 What are the characteristics of the dose/exposure-response relationship for effectiveness?

Following every week (100 and 150 mg qw) and every other week (100, 150, and 200 mg q2w) dose regimens in the Phase 2 dose-ranging study (EFC11072 Part A), the efficacy (ACR20, ACR50, and ACR70 scores and the DAS28 CRP) was apparent only at concentrations achieved with doses of 150 mg q2w or above (Figure 1, Figure 2). Furthermore, a plateau was reached for all efficacy endpoints at e sarilumab concentrations achieved at the 200 mg q2w dose, with further increase in exposure by as much 2.7-fold (150 mg qw) providing only marginal change in the responses. Thus, 150 mg q2w and 200 mg q2w doses were considered appropriate for the Phase 3 program.

Table 3. ACR response rates in EFC11072 Part B, Cohort 2 and EFC10832

	EFC11072 Part B, Cohort 2			EFC10832		
	Placebo +MTX (N=398)	**Sarilumab 150 mg q2w + MTX (N=400)**	**Sarilumab 200 mg q2w + MTX (N=399)**	**Placebo +DMARD (N=181)**	**Sarilumab 150 mg q2w + DMARD (N=181)**	**Sarilumab 200 mg q2w + DMARD (N=181)**
ACR 20 at Week 24	33.4%	58.0%	66.4%	33.7%	55.8%	60.9%
ACR 50 at Week 24	16.6%	37.0%	45.6%	18.2%	37.0%	40.8%
ACR 70 at Week 24	7.3%	19.8%	24.8%	7.2%	19.9%	16.3%

(Source: Table 4, clinical overview)

A dose response relationship also was observed for ACR20, ACR50, and ACR70 over the dose range of 150 to 200 mg q2w in the Phase 3 studies (Table 3). Consistent with the dose-response, increased efficacy with respect to ACR20, ACR50, ACR70, CDAI, and DAS28 was observed with increasing exposure (Ctrough) in Phase 3 studies at the within the concentration range observed at 150 mg q2w and 200 mg q2w doses (Figure 3, Figure 4, similar results also shown for study EFC10832, see Appendix 4.1, Pharmacometrics review).

In the Phase 3 studies, the effect at the median serum trough concentration of 200 mg q2w was better than at the median trough concentration of 150 mg q2w for all endpoints (ACR20, ACR50, and ACR70 scores, the HAQ-DI, mTSS, CDAI, and DAS28-CRP) except for the HAQ-DI, where there was a minimal difference. For details see Pharmacometrics review section 2.2.

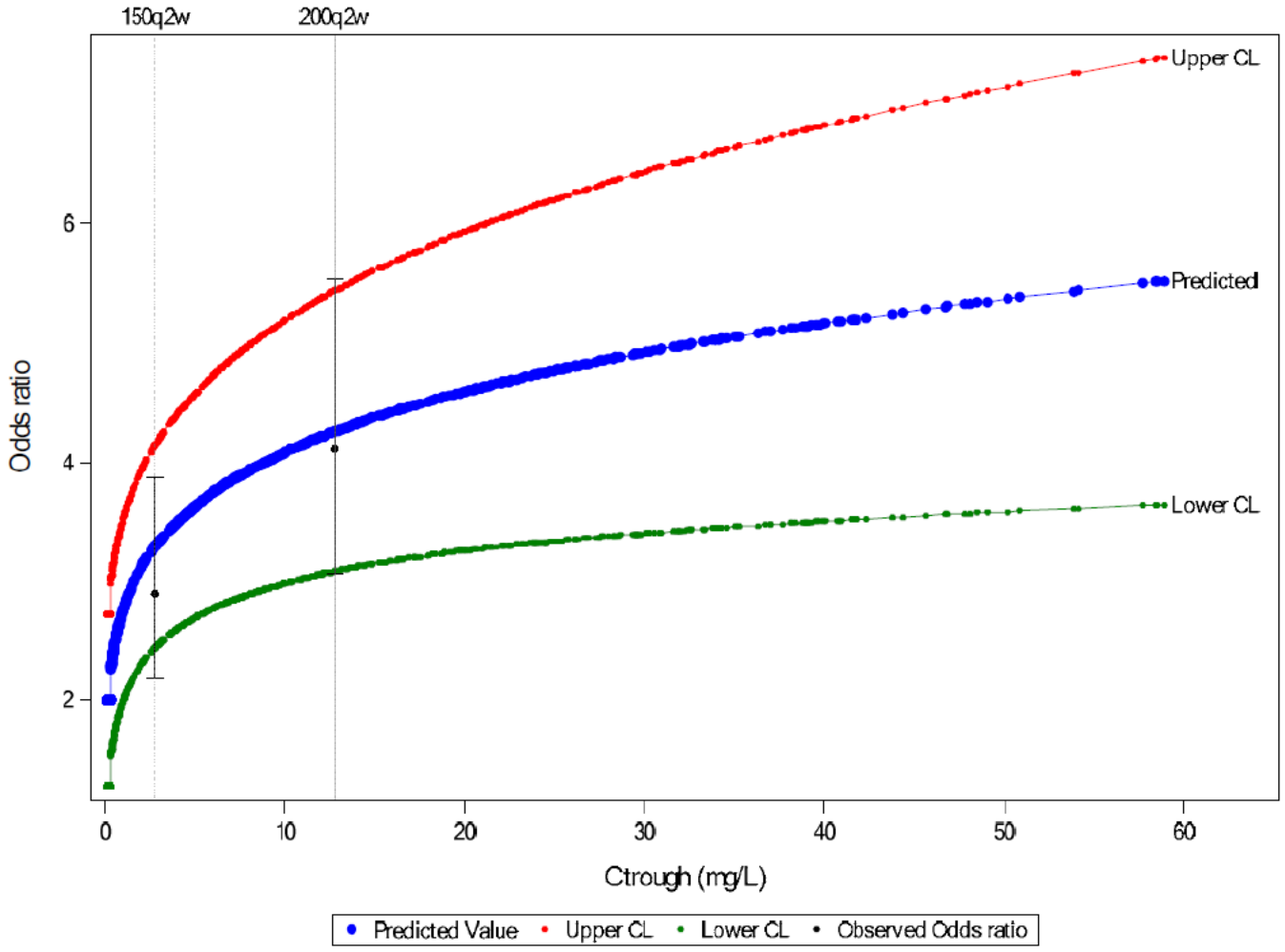

Figure 3. ACR20 responder at Week 24: PK/PD model predicted odds ratio (95% CI) from placebo versus trough concentration of functional sarilumab overlaying with observed treatment odds ratio (95% CI) (EFC11072 Part B Cohort 2)
(Source: Figure 1, study report poh0455)

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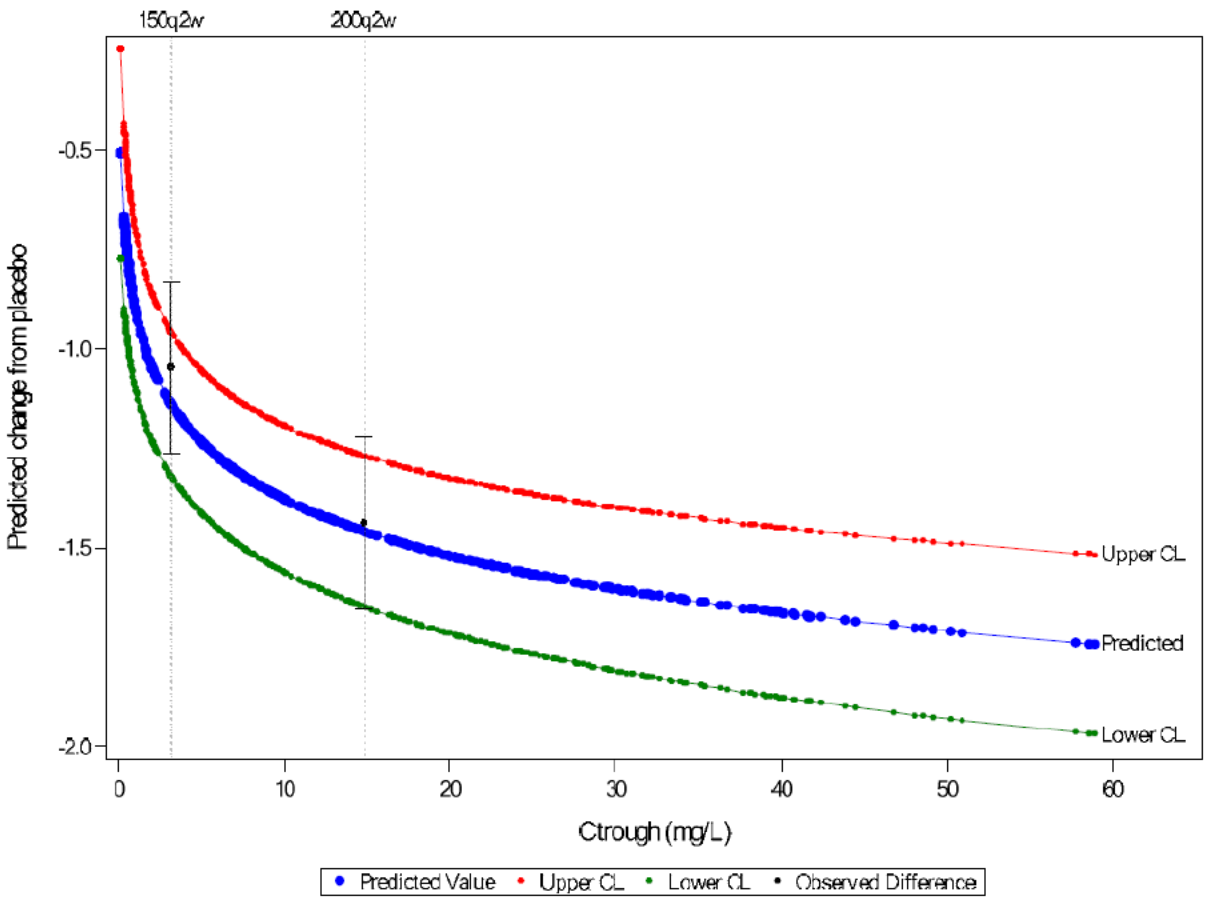

Figure 4. DAS28-CRP change from baseline at Week 24: PK/PD model predicted difference (95% CI) from placebo versus trough concentration of functional sarilumab overlaying with observed treatment difference (95% CI) (EFC11072 Part B Cohort 2)
(Source: Figure 12, study report poh0455)

2.5.2 What are the characteristics of the dose/exposure-response relationship for safety?

There was a slight increase in the incidence of AEs with the 200 mg q2w dose compared to the 150 mg q2w dosing regimen of sarilumab (See medical review). These differences were generally attributable to differences in the incidence of neutropenia (Table 4), which is anticipated based on the pharmacodynamic effects of IL-6 blockade on the peripheral neutrophil count. Consistent with the dose-response, the change from baseline in ANC was related to sarilumab concentration (Figure 5, Figure 6) within the concentration range observed in the Phase 2 and 3 studies at the studied dose regimens (100 and 150 mg qw; 100, 150, and 200 mg q2w). Based on the pharmacodynamics of the changes in ANC (Figure 7), laboratory results should be obtained at the end of the dosing interval when considering dose modification.

The change from baseline in ALT was related to sarilumab concentration (Figure 8). The exposure –response relationship is consistent with the dose-response relationship observed in

Phase 3 studies (150 mg and 200 mg q2w, Table 4). Based on the exposure/dose- response relationship for ANC and ALT, dose modification is an appropriate management strategy in the event of laboratory abnormalities that persist at the end of the dosing interval.

Table 4. Overview of lab abnormality TEAEs: number (%) of patients - Placebo-controlled safety population (Pool 1)

		Sarilumab	
	Placebo + DMARD	**150 mg q2w + DMARD**	**200 mg q2w + DMARD**
Total number of patients	**661**	**660**	**661**
Total treatment duration in pt-yrs	**382.3**	**440.7**	**441.4**
Neutropenia	3 (0.5%)	65 (9.8%)	94 (14.2%)
ALT			
> 1 - 1.5 ULN	127/661 (19.2%)	163/659 (24.7%)	178/657 (27.1%)
> 1.5 - 3 ULN	70/661 (10.6%)	124/659 (18.8%)	162/657 (24.7%)
> 3 and ≤ 5 ULN	10/661 (1.5%)	36/659 (5.5%)	31/657 (4.7%)
> 5 and ≤ 10 ULN	1/661 (0.2%)	9/659 (1.4%)	10/657 (1.5%)
> 10 and ≤ 20 ULN	0/661	4/659 (0.6%)	1/657 (0.2%)
> 20 ULN	0/661	0/659	1/657 (0.2%)
Total patients with ≥ 1 Thrombocytopenia (%)	0	6 (0.9%)	11 (1.7%)

(Source: Table 37, 40, 41, summary of clin safety)

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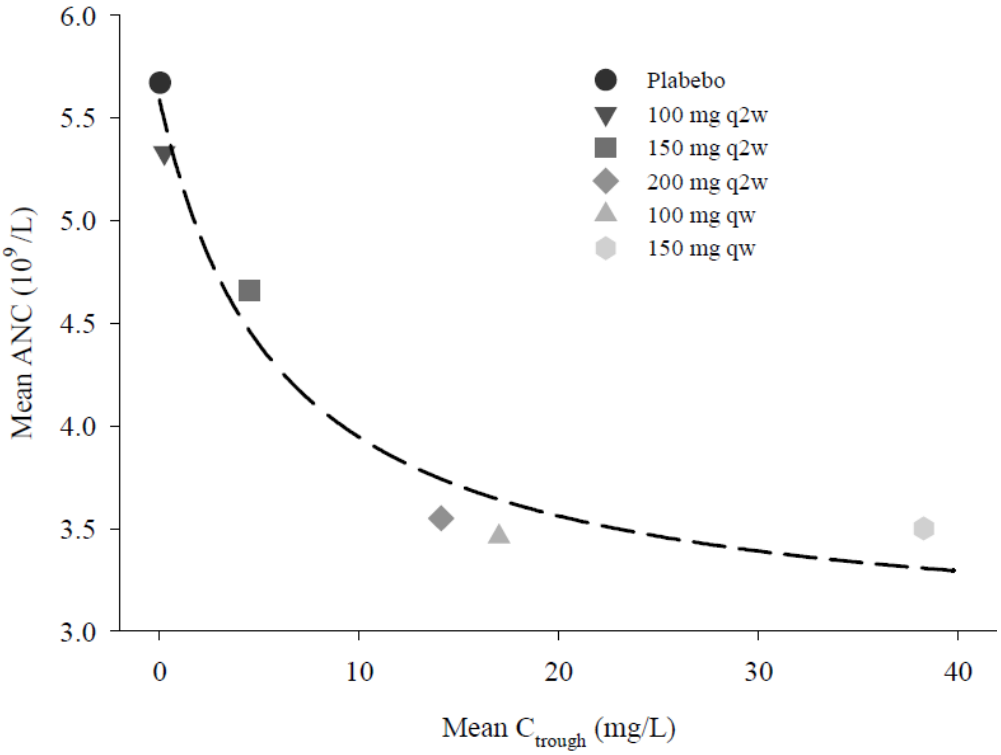

Figure 5. Absolute neutrophil count versus serum trough concentration of functional sarilumab at Week 12 in patients with rheumatoid arthritis (Study EFC11072 Part A)
(Source: Figure 22, summary of clin pharm)

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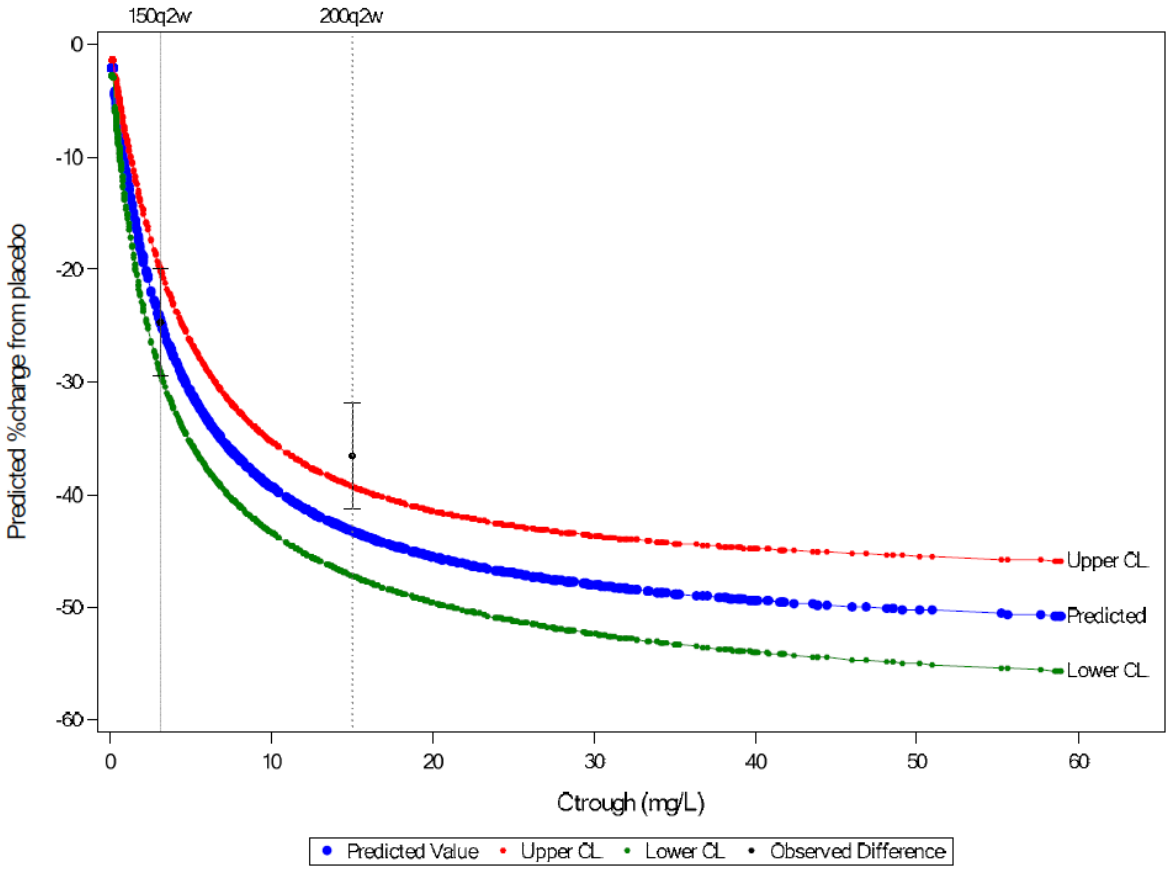

Figure 6. ANC %change from baseline at Week 24: PK/PD model predicted difference (95% CI) from placebo versus trough concentration of functional sarilumab overlaying with observed treatment difference (95% CI) (Safety Pool)
(Source: Figure 15, Study report POH0455)

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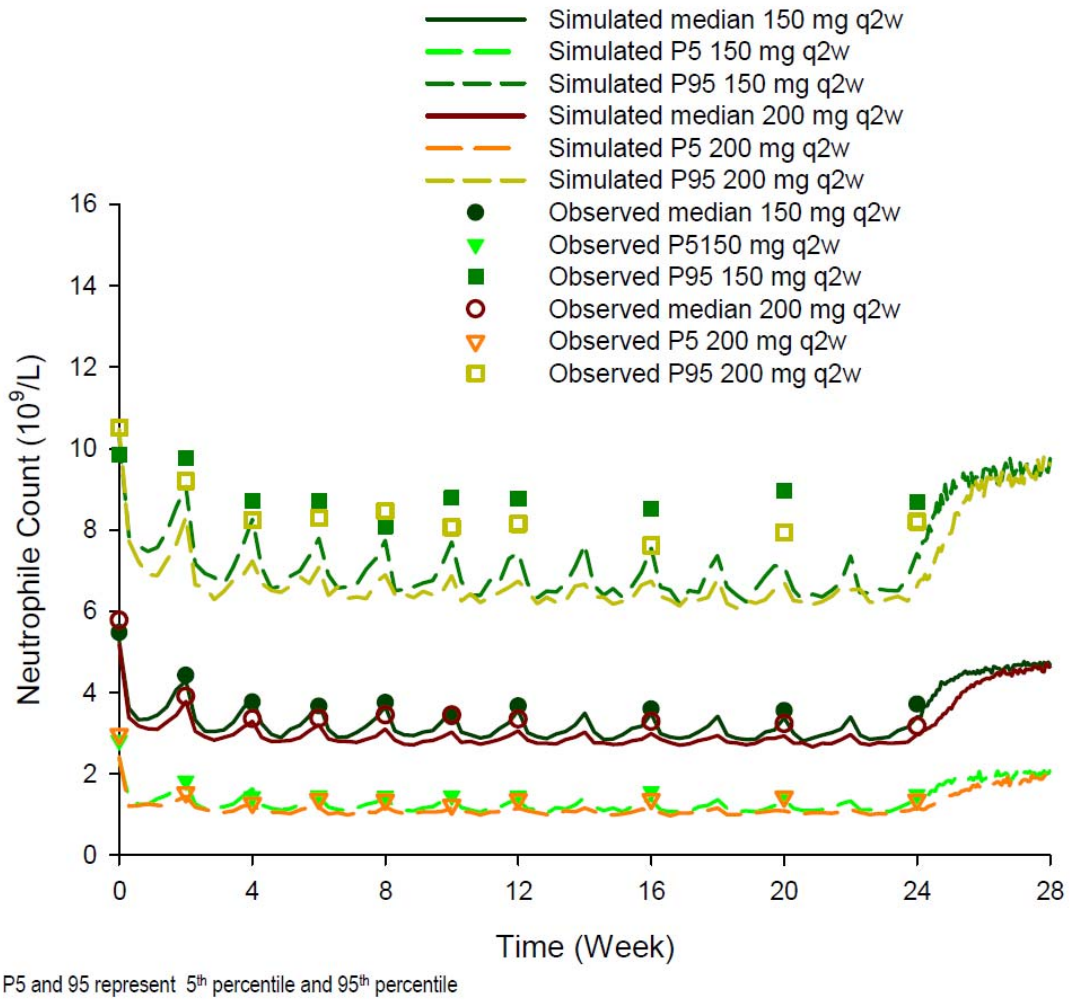

Figure 7. ANC level-time profiles (observed vs model predicted median, 5th and 95th percentiles)
(Source: Figure 9, study report POH0429)

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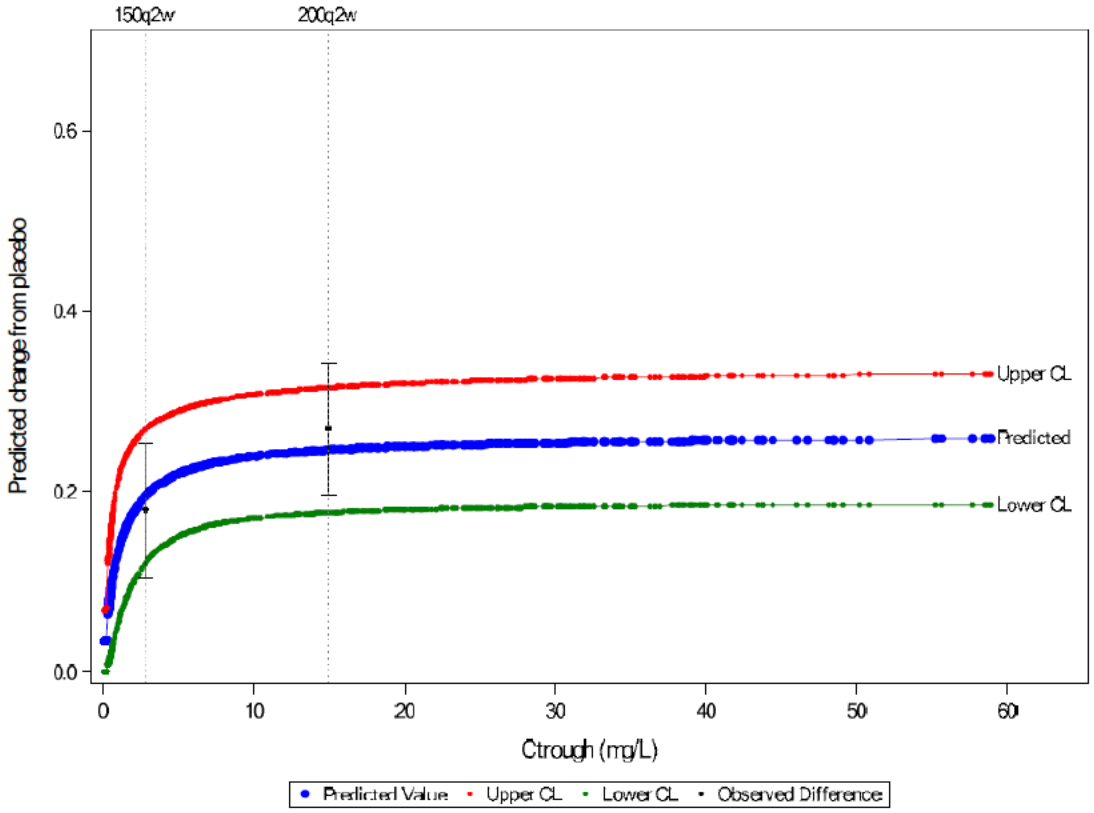

Figure 8. ALT (ULN) change from baseline at Week 24: PK/PD model predicted difference (95% CI) from placebo versus trough concentration of functional sarilumab overlaying with observed treatment difference (95% CI) (Safety Pool)
(Source: Figure 18, Study report POH0455)

2.5.3 Does the dose/exposure-response relationship for effectiveness and safety endpoints support the proposed dose and dose modification scheme?

The proposed dosing regimen for sarilumab seems reasonable. The proposed dosing recommendation is to initiate dosing with sarilumab 200 mg q2w and to decrease the dose to 150 mg q2w for laboratory abnormalities. The proposed dose was supported by a dose ranging study (EFC11072 Part A) and two pivotal phase 3 studies (EFC11072 Part B and EFC10832). There is increased efficacy for the 200 mg q2w compared to a dose of 150 mg q2w and lower in phase 2 and 3 studies (see section 2.5.1). Similar trend was observed in the exposure-response analysis where increased sarilumab exposure is associated with increased efficacy in the observed 150 mg q2w and 200 mg q2w concentration range of Phase 3 studies.

For safety, there was a slight increase in the incidence of AEs with the 200 mg q2w dose compared to the 150 mg q2w dosing regimen of sarilumab. Per medical review, the risk/benefit assessment supports the starting dose of 200mg q2w for the proposed indication. Additionally, increased lab abnormalities with increasing dose/exposure supports sponsor's dose reduction scheme (See section 2.5.2). Higher proportion of subjects with greater than 3xULN increase in

AST, ALT or GGT; 2) thrombocytopenia 3) neutropenia was observed in the 200 mg q2w dose group compared to the 150 mg q2w dose group. Thus sponsor's dose modification based on lab abnormalities is reasonable.

No dose adjustment was recommended for the starting dose in specific populations, with respect to sex, body weight, age, race, renal or hepatic function (See section 2.7.1).

2.6 PK Characteristics of the Drug

2.6.1 What are the single and multiple dose PK parameters of drug?

Sarilumab PK was characterized through IV (single dose) and SC (single and multiple doses) routes.

Single IV dose PK

When dosed intravenously at 0.6, and 2 mg/kg (lyophilized powder) in patients with RA who were concomitantly treated with MTX (study TDU10808), nonlinear kinetics of functional sarilumab were observed. The terminal half-life and mean residence time increased with dose, whereas the clearance decreased with dose. The terminal half-life was 1.73 and 4.49 days in the 0.6 mg/kg and 2.0 mg/kg dose groups, respectively. As the formulation and administration route is different from the to-be-marketed product, the PK information collected in this study was not presented in the label for (b) (4)

Table 5. Summary of Observed Noncompartmental Pharmacokinetic Parameters of Functional REGN88 by Dose

Parameter [unit]		Dose							
		0.6 mg/kg				2 mg/kg			
		N	Median	SE	CV%	N	Median	SE	CV%
$t_{1/2}$	[day]	3	1.73	0.491	47.2	2	4.49	0.582	18.3
CL	[L/day/kg]	3	0.0124	0.00142	20.3	2	0.00596	0.000139	3.30
V_z	[L/kg]	3	0.0359	0.00622	35.7	2	0.0385	0.00410	15.1
V_{ss}	[L/kg]	3	0.0325	0.00433	25.0	2	0.0359	0.00385	15.2
C_{max}	[mg/L]	4	19.3	0.433	4.48	2	58.7	5.55	13.4
C_{max}/Dose	[kg/L]	4	32.1	0.722	4.48	2	29.3	2.78	13.4
C_{last}	[mg/L]	4	0.315	1.27	167.	2	5.97	0.625	14.8
t_{last}	[day]	4	7.06	2.51	62.6	2	13.5	0.511	5.35
AUC_{last}	[day*mg/L]	4	41.1	7.44	34.5	2	296.	1.23	0.586
AUC_{all}	[day*mg/L]	4	44.0	6.23	26.8	2	317.	0.806	0.359
AUC_{inf}	[day*mg/L]	3	48.3	6.32	21.5	2	336.	7.82	3.30
AUC_{last}/AUC_{all}	N/A	3	0.980	0.102	19.9	2	0.884	0.0243	3.88
MRT_{inf}	[day]	3	2.49	0.485	33.0	2	6.05	0.787	18.4

N/A = not applicable

(Source: Table 9, TDU10808 CSR)

Single SC dose PK

Pharmacokinetic parameters of functional sarilumab after single doses of sarilumab, obtained from noncompartmental analyses of data from individual Phase 1 studies, are summarized in **Table 6**. The PK of functional sarilumab in patients with RA over the dose range of 50 to 200 mg was generally consistent across a number of studies. Generally, sarilumab appears to be absorbed well after SC administration and exhibits nonlinear PK, with two distinct processes for elimination: a slow, linear, and nonsaturable elimination phase at higher serum concentrations, when target binding is at or near saturation; and a fast, nonlinear, and target mediated elimination phase at lower serum concentrations. The fast elimination is presumably a result of internalization via endocytosis of target-bound sarilumab.

Table 6. Pharmacokinetic parameters of serum functional sarilumab after a single (or first) subcutaneous dose of sarilumab to healthy subjects or patients with rheumatoid arthritis

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Study identifier (Population)	Dose	N	C_{max} (mg/L)[a]	AUC_{last} (mg•day/L)[a]	AUC (mg•day/L)[a]	t_{max}[b] (days)	$t_{1/2z}$ (days)[a]
TDU11373 (Healthy subjects)	100 mg	14	7.77 (3.65)	45.0 (22.7)	55.0 (25.0)	2.50 (1.00 - 6.00)	2.23 (1.07)
TDU10809/6R88-RA-0801 (RA patients)	50 mg	4	1.16 (1.82)	2.36 (3.94)	NR	2.04(1.99 - 2.10)	NR
	100 mg	4	4.89 (4.53)	25.5 (36.2)	NR	3.05 (2.01 - 3.11)	NR
	200 mg	6	10.9 (2.38)	90.0 (15.3)	NR	3.01 (2.96 - 3.05)	NR
ACT10804/6R88-RA-0803 (RA patients)	50 mg	8	0.516 (0.745)	0 (0)	NR	2.91 (1.83 - 2.93)	NR
	100 mg	8	3.96 (2.70)	18.4 (10.5)	NR	4.41 (1.90 - 4.88)	NR
	200 mg	8	12.9 (4.81)	93.2 (48.9)	NR	3.85 (1.98 - 5.00)	NR
TDU13402 (Japanese RA patients)	50 mg	6	1.36 (0.411)	4.69 (2.43)	NR	3.00 (2.00 - 3.00)	NR
	100 mg	6	4.54 (2.97)	33.0 (30.4)	70.1 (NC)[d]	3.00 (3.00 - 7.00)	1.62 (NC)
	200 mg	6	27.7 (12.6)	339 (173)	409 (126)[e]	3.00 (2.00 - 7.00)	3.49 (1.35)
PKM12058 (RA patients)	200 mg	15	15.8 (7.02)	153 (92.5)	179 (108)	4.00 (2.00 - 6.04)	4.58 (2.51)
6R88-RA-1309 (RA patients)	150 mg	26	13.9 (9.28)	106 (91.9)	108 (92.2)	3.02 (2.00 - 6.16)	1.70 (0.457)
	200 mg	26	21.6 (11.7)	169 (105)	173 (105)	3.99 (1.99 - 6.17)	1.96 (1.10)
MSC12665 (RA patients)	150 mg	51	16.7 (13.0)	152 (76.7)[c]	NR	2.88 (0.90 - 6.88)	NR
	200 mg	53	23.7 (12.7)	227 (94.9)[c]	NR	3.67 (1.71 - 10.9)	NR

a Mean (standard deviation) for observed values from noncompartmental analysis

b Median (minimum - maximum) for observed values from noncompartmental analysis

c $AUC_{0\text{-}14\ days}$ instead of AUC_{last}

d N = 1

e N = 5

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

(Source: Table 8, summary of clin pharm)

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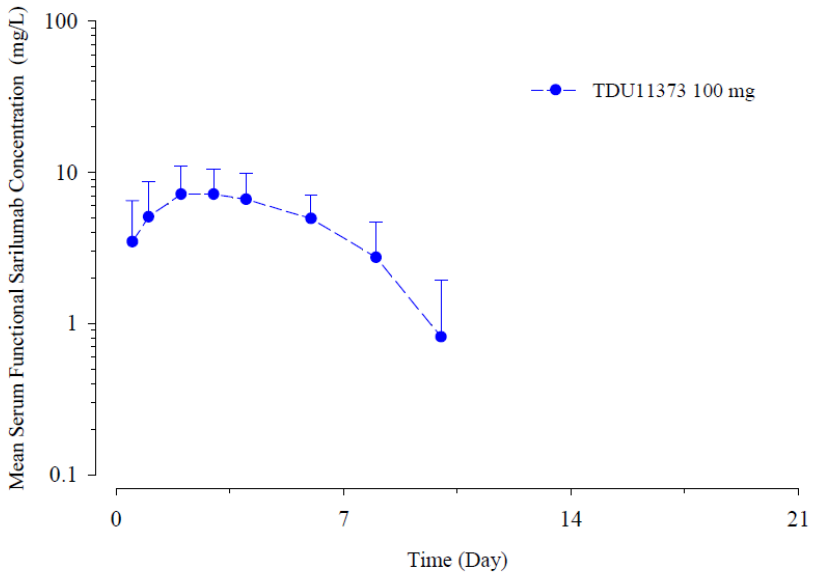
Healthy subjects: Study TDU11373



Patients with rheumatoid arthritis: Studies TDU10809/6R88-RA-0801, ACT10804/6R88-RA-0803, 6R88-RA-1309, and PKM12058

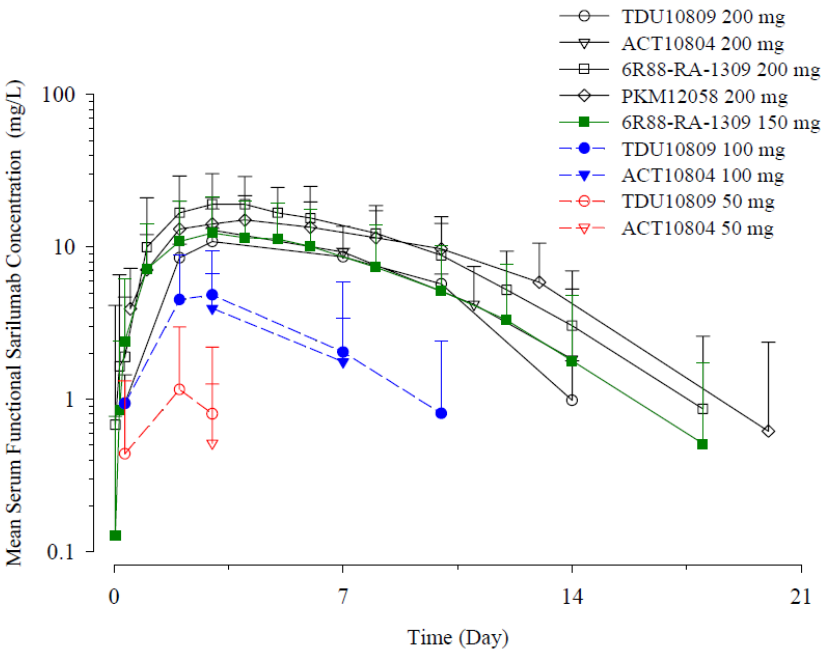


Figure 9. Concentrations of serum functional sarilumab following a single subcutaneous dose in healthy subjects (Study TDU11373) and patients with rheumatoid arthritis (rest of studies)
(Source: Figure 4, summary of clin pharm)

Multiple SC dose PK

In a multiple ascending dose (50, 100, 150 mg QW and 100, 150, 200 mg q2w, dose for 4 weeks) study in patients with RA who were concomitantly treated with MTX, the concentration of functional sarilumab increased in a more than dose-proportional manner, as expected with nonlinear pharmacokinetics due to target mediated clearance at low concentrations. The mean steady-state trough concentrations of functional sarilumab after the last dose are summarized in table below.

Table 7. Mean steady-state trough concentrations of functional sarilumab after the last dose

Treatment	Visit	Trough Concentration (mg/L)
50 mg qw	Day 36	1.14
100 mg qw	Day 36	18.4
100 mg q2w	Day 43	0.601
150 mg qw	Day 36	38.0
150 mg q2w	Day 43	2.47
200 mg q2w	Day 43	11.0

(Source: Table 16, CSR6R88-RA-0802)

In the phase 2 and 3 studies, the observed mean trough serum concentrations of functional sarilumab, based on a limited sampling scheme, indicated that steady state was reached between Week 12 and the next sampling time at Week 24 after repeated SC q2w administration of sarilumab to patients with RA (**Figure 10**), with approximately 3- to 4-fold accumulation.

Population PK analysis was utilized to simulate the population mean concentrations for sarilumab for a reference patient (female, body weight 71 kg, ADA negative, BSA normalized CLCR 100 mL/min, baseline CRP 14.2 mg/L, serum albumin 38 g/L and administered drug product of other than (b) (4) F2) upon repeated administration of sarilumab at 150 or 200 mg q2w doses . The PK profile can be visualized in **Figure 11**. The exposure (AUC0-14 day, Cmax, Ctrough) at each dose interval was listed in **Table 8**. The time to steady state in a typical patient, estimated from population PK analysis, was 14 to 16 weeks for $AUC_{0\text{-}14\ days}$ and 18 to 20 weeks for C_{trough} (**Figure 11**). The accumulation ratios, based on post hoc individual predicted PK parameters, were determined to be 2.3 and 2.5 for $AUC_{0\text{-}14\ days}$ and 3.0 for C_{trough} after sarilumab 150 and 200 mg q2w dosing regimens, respectively.

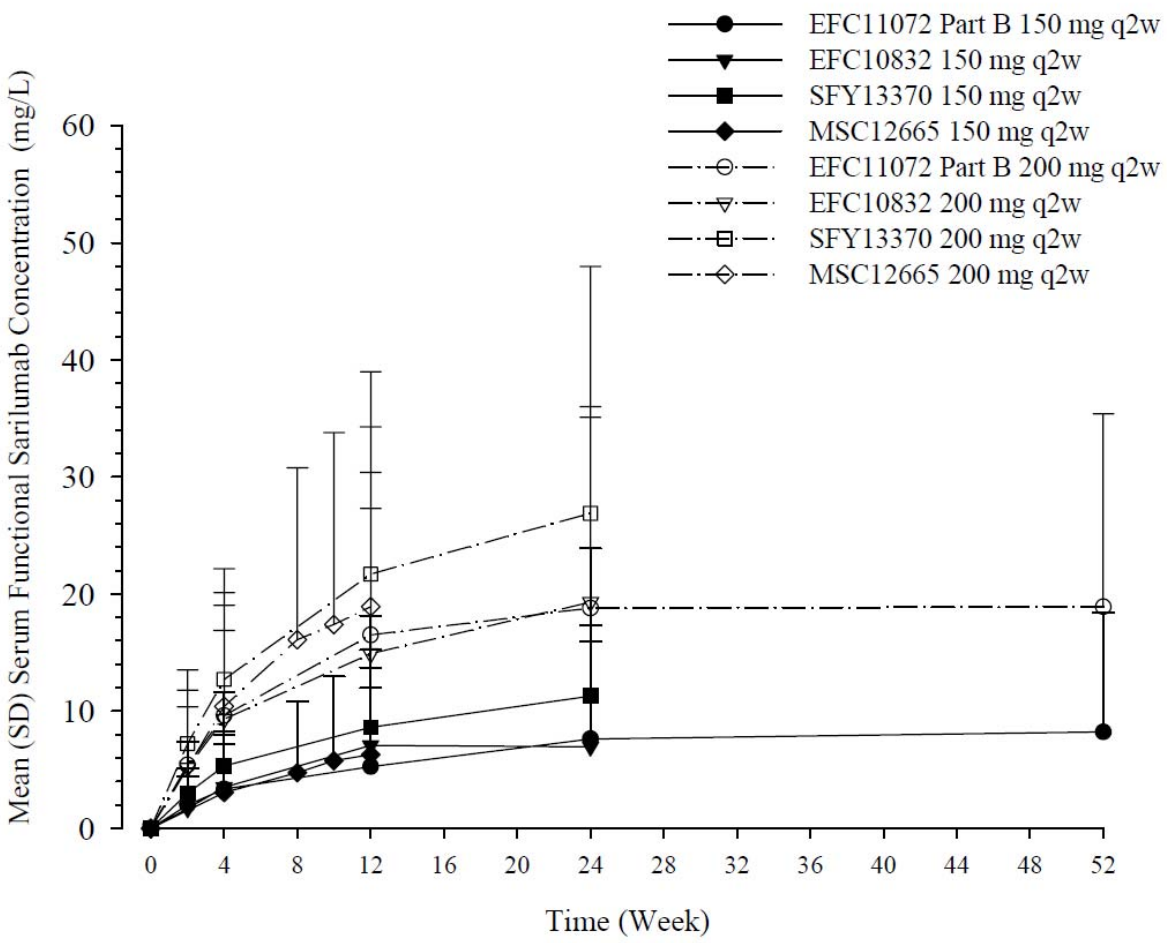


Figure 10. Trough serum concentrations of serum functional sarilumab up to steady state following repeated subcutaneous doses in patients with rheumatoid arthritis
(Source: Figure 6, summary of clin pharm)

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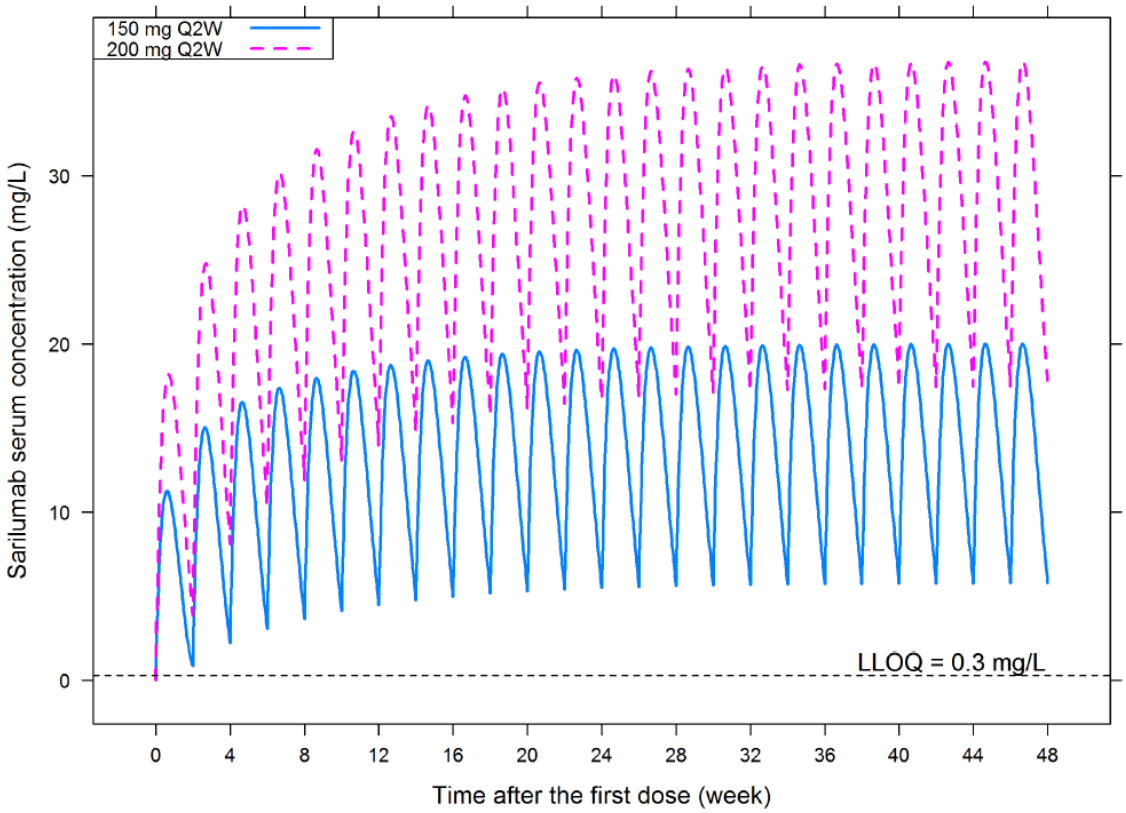


Figure 11. Sarilumab concentrations versus time curve in reference patient post repeated 150 or 200 mg q2w sarilumab treatment

(Source: Figure 29, pop PK report POH0428)

Table 8. Pharmacokinetic parameters of serum functional sarilumab following first and repeated subcutaneous administration of sarilumab to patients with rheumatoid arthritis (Study POH0428)

Dose regimen	Pharmacokinetic parameter (unit)	N	First dosing interval[a]	Steady state[a]	R_{ac}
150 mg q2w	C_{max} (mg/L)	547	10.7 (4.68)	20.0 (9.20)	1.87
	$AUC_{0\text{-}14\ days}$ (mg•day/L)		87.4 (42.8)	202 (120)	2.31
	C_{trough} (mg/L)		2.44 (3.29)	6.35 (7.54)	2.60
200 mg q2w	C_{max} (mg/L)	609	17.5 (6.47)	35.6 (15.2)	2.03
	$AUC_{0\text{-}14\ days}$ (mg•day/L)		159 (62.5)	395 (207)	2.48
	C_{trough} (mg/L)		5.54 (5.71)	16.5 (14.1)	2.98

a Mean (standard deviation) for post hoc individual pharmacokinetic parameters for patients in Studies EFC11072 Part B and EFC10832 were estimated from population pharmacokinetic analysis.

$AUC_{0\text{-}14\ days}$: area under the serum concentration versus time curve from 0 to 14 days; C_{max}: maximum serum concentration; C_{trough}: serum concentration observed before drug administration during repeated dosing; R_{ac} accumulation ratio

(Source: Table 10, summary of clin pharm)

2.6.2 How does the PK of the drug in healthy adults compare to that in patients with the target disease?

As seen in Figure 9 and Table 6, cross-study comparison showed that functional sarilumab serum concentrations in healthy subjects were higher than in patients with RA at the same dose of 100 mg by approximately 1.8-fold. This is likely due to an elevated abundance of the target in patients with RA, as evidenced by about a 1000-fold higher sIL-6Rα serum concentration in patients with RA (41.3 ng/mL) when compared to healthy subjects (21.4 pg/mL) which is likely to increase the clearance of drug in RA patients compared to healthy subjects.

2.6.3 What are the characteristics of drug absorption?

The absolute bioavailability for sarilumab SC injection was estimated to be ~80% for the to-be-marketed product ((b) (4) F3) based on the final pop-PK model (cross study comparison , Population PK analysis, study POH0428, see details in PM review). Median Tmax is achieved at 2-4 days.

2.6.4 What are the characteristics of drug distribution?

Sarilumab Vss at steady state after IV administration was ~0.03 L/kg (approximately 2.1 to 2.5 L in a 70 kg individual) at 0.6 and 2.0 mg/kg, respectively, based on observed data in 6 patients with RA after a single administration. Population PK analysis results (Study POH0428) were consistent with an estimated apparent central volume of distribution (Vc/F) of 2.08 L and an apparent peripheral volume of distribution (Vp/F) of 5.23 L, resulting in a total volume of distribution (the sum of Vc/F and Vp/F) of 7.31 L. This low value suggests that the distribution of sarilumab is primarily limited to the circulatory system.

2.6.5 What are the characteristics of drug metabolism?

No specific in vitro or in vivo metabolism or excretion studies were conducted for sarilumab as it is an IgG1 monoclonal antibody that is catabolized by ubiquitous proteolytic enzymes, not restricted to hepatic tissue.

2.6.6 What are the characteristics of drug elimination?

Sarilumab exhibits nonlinear PK with target mediated drug disposition. Sarilumab clearance is governed by two parallel pathways: a nonlinear, target mediated pathway predominating at lower concentrations and a nonspecific, linear pathway predominating at higher concentrations (Figure 12). Based on population PK analysis, in the range of serum concentrations achieved over the dosing interval at therapeutic doses of sarilumab, target mediated clearance represents a large

portion of total clearance, while linear clearance represents only 7% to 26% of total clearance at 150 mg q2w and 22% to 40% of total clearance at 200 mg q2w (Figure 12).

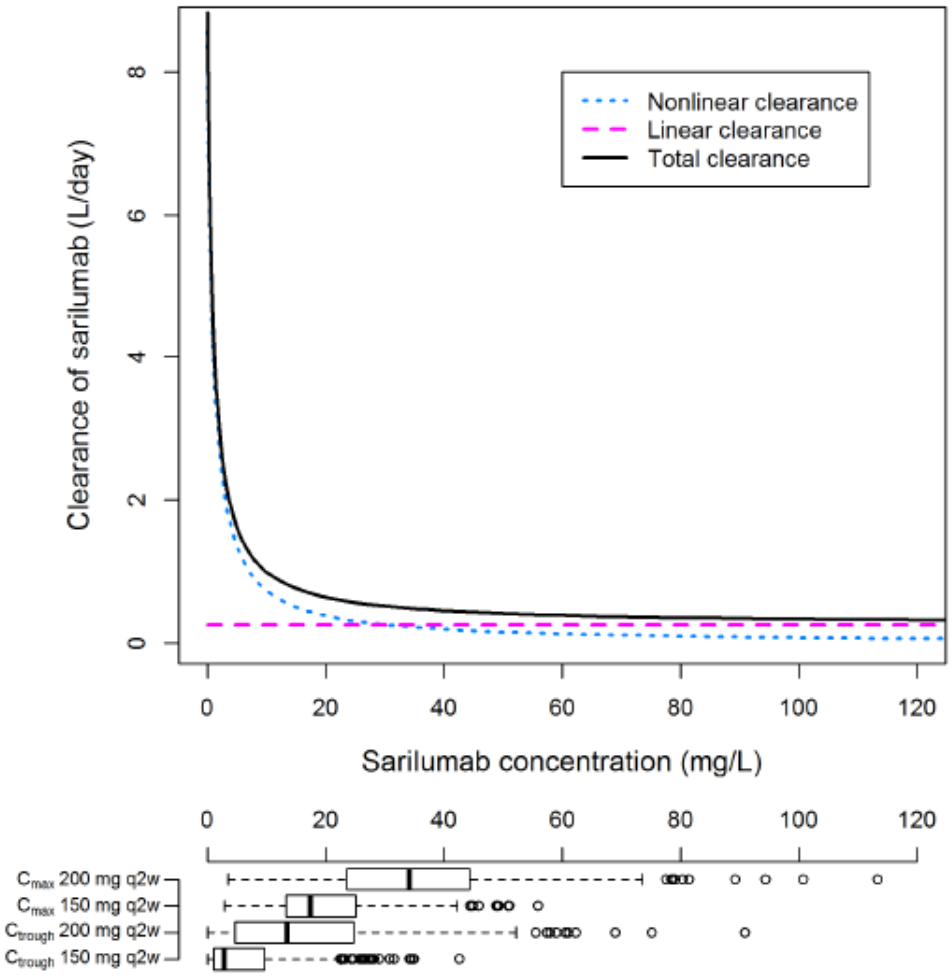
In the sponsor's proposed label, it is stated that "(b) (4) sarilumab doses based on population PK analysis (Study POH0428). The half- life values of sarilumab should be interpreted with caution due to nonlinear PK. The effective half -life is ~17-19 day based on accumulation (AUC) at steady state, as calculated by this reviewer. The effective half- life of 17-19 day is consistent with the time to reach steady state. Sarilumab serum concentrations after the last steady state dose were measurable up to a median time of 28 and 43 days for 150 and 200 mg q2w, respectively.

2.6.7 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Sarilumab clearance from the central compartment is governed by two parallel pathways: concentration independent linear clearance and concentration-dependent nonlinear clearance. **Figure 12** depicts the contributions of linear and nonlinear clearance at different sarilumab concentrations.

It can be seen that most sarilumab concentrations at steady state are in the range where nonlinear clearance portion is greater or equal to the linear clearance portion. This suggests that target-mediated sarilumab disposition plays a significant role at the dose regimen of both 150 and 200 mg q2w.

Functional sarilumab exposure increased in a greater than dose proportional manner in patients with RA, due to an appreciable contribution of nonlinear clearance to the total clearance in the therapeutic dose range. After a single SC dose of sarilumab, observed mean AUClast increased by 38.1- to 72.3-fold over a 4-fold increase in dose over the range of 50 to 200 mg (**Table 6**). A 33% increase in dose over the therapeutic dose range of 150 to 200 mg resulted in ~96% increase of mean AUCtau of functional sarilumab (**Table 8**).



*In this figure, linear and nonlinear clearance refer to the values in the reference RA patient based on median/mean values in the population (female, body weight 71 kg, negative ADA, BSA normalized CLCR 100 mL/min, baseline C-reactive protein 14.2 mg/L and albumin 38 g/L). Linear clearance equals to CLO/F and nonlinear clearance was computed by Vm/(Km + concentration) (see detailed definition of CLO/F, Vm and Km in Appendix 4.1, Pharmacometrics review).

Figure 12. The contribution of linear and nonlinear clearance at different sarilumab concentrations
(Source: Figure 28, study report POH0428)

2.6.8 How do the PK parameters change with time following chronic dosing?

The observed mean trough serum concentrations of functional sarilumab, based on a limited sampling scheme, did not have significant change with time after reaching steady state (**Figure 13**).

In population PK analysis, none of the model parameters change with time other than ADA (see Pharmacometrics review for details). Overall, there is no evidence of time-dependent PK for sarilumab.

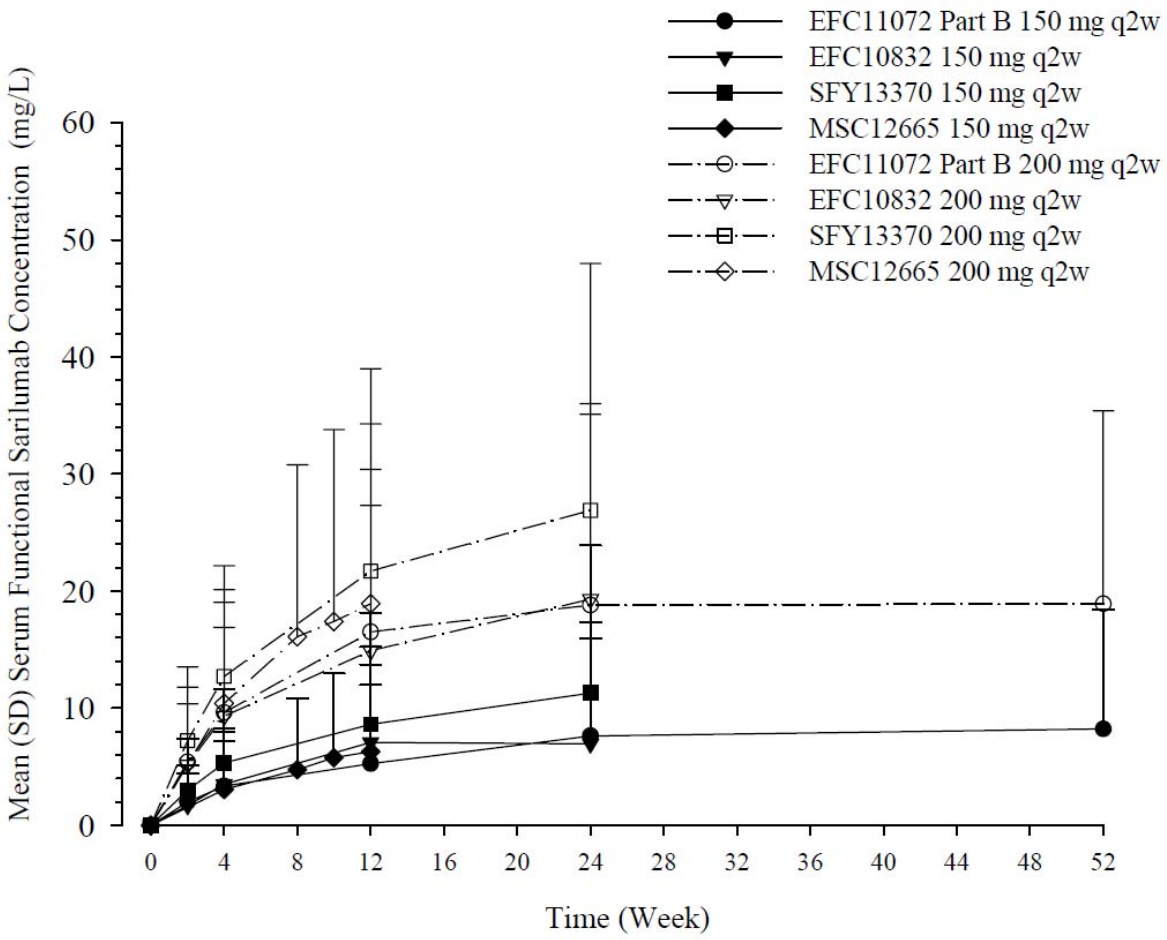


Figure 13. Trough serum concentrations of serum functional sarilumab up to steady state following repeated subcutaneous doses in patients with rheumatoid arthritis
(Source: Figure 6, summary of clin pharm)

2.6.9 Is there evidence for a circadian rhythm of the PK?

The circadian rhythm of sarilumab PK was not assessed in this submission. Some literature suggested that there may be circadian secretion of IL-6 in human.

2.6.10 What are the PD characteristics of sarilumab in patients?

Based on graphical analysis, it was observed that inflammation biomarkers CRP, SAA, fibrinogen and ESR decreased with time and with increasing exposure; mechanism based biomarker sIL-6R levels increased with time and with increasing exposure (**Figure 14**).

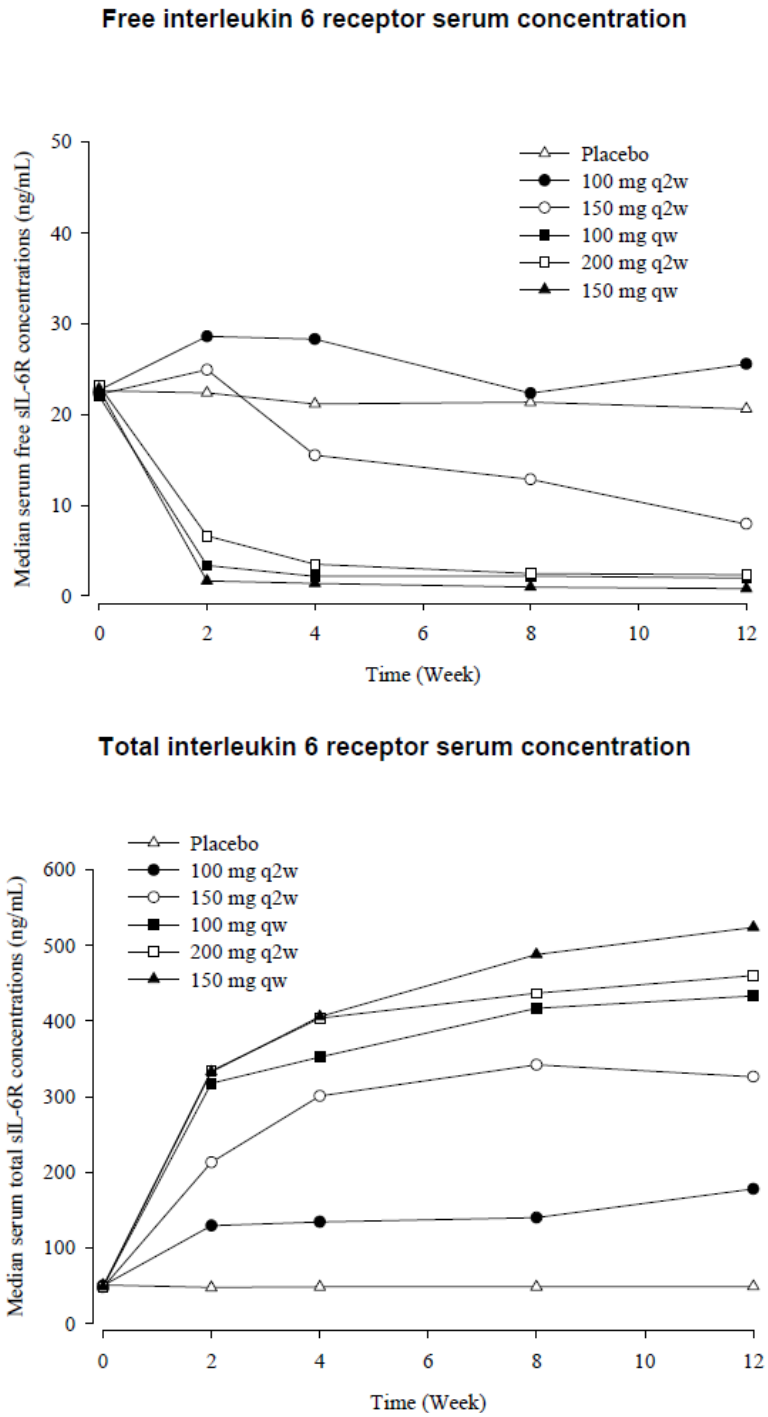


Figure 14. Serum concentrations of free soluble interleukin 6 receptor and total soluble interleukin 6 receptor following repeated doses of sarilumab in patients with rheumatoid arthritis (Study EFC11072 Part A)

(Source: Figure 11, summary of clin pharm)

After repeated q2w SC administration of 150 or 200 mg sarilumab, a dose dependent decrease in CRP levels were observed as early as Week 2, reached steady state by Week 24, and were sustained until the end of treatment. Both dose regimens of sarilumab suppressed CRP levels to a

similar degree 2 to 4 days after administration. The 200 mg dose suppressed CRP levels throughout the 2 week dosing interval, while CRP levels had a tendency to rebound towards the end of the dosing interval at the 150 mg dose, suggesting a lower IL-6Rα blockade at this dose (Figure 47).

Consistent with the changes observed in CRP levels, a dose dependent reduction in other acute phase reactants, such as SAA, fibrinogen, and the ESR, was observed in patients with RA after a single SC administration or repeated SC q2w administration of 150 or 200 mg sarilumab (See individual study review ACT10804/6R88-RA-0803).

2.7 Intrinsic Factors

2.7.1 What are the covariates contributing to the inter-subject PK variability of sarilumab based on population PK analyses?

Population PK analysis identified that body weight, ADA, drug product (b) (4) F2 and sex had an impact on linear clearance (CL). Non-linear clearance (Vmax) was impacted by body weight, albumin, BSA-normalized creatinine clearance and baseline CRP levels. Absorption (Ka) was impacted by drug product (b) (4) F2.

No dose adjustment is recommended for the starting dose with respect to any of the covariates. The posthoc analysis showed that age, sex, race, albumin, baseline CRP and concomitant methotrexate did not meaningfully influence the pharmacokinetics of sarilumab (see Pharmacometrics review). Compared to ADA negative patients, ADA positive status decreased the steady state AUC0-14, Cmax, and Ctrough by 24%, 18%, and 48% respectively for the 150 mg q2w dose, and 28%, 22%, and 43% respectively for the 200 mg q2w dose. Although body weight and creatinine clearance influenced the pharmacokinetics of sarilumab, no dose adjustments are recommended for any of these demographics, as discussed below (section 2.7.2).

2.7.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

No dose adjustment is warranted with regard to intrinsic factors.

2.7.2.1 Severity of Disease state

No dose adjustment is warranted based on disease severity.

It can be seen from Figure 34 and 35 that sarilumab exposure are not apparently associated with baseline DAS28 and prior biologics.

Because sarilumab is eliminated in part through target mediated clearance, the baseline CRP level reflecting disease activity in patients with RA is correlated to the target (IL-6Rα) level. Thus, patients with higher baseline CRP levels would have higher IL-6Rα levels, resulting in

greater target-mediated clearance and lower sarilumab exposure. Although in the pop PK analysis, baseline CRP level was identified as a statistically significant covariate of nonlinear maximum rate of clearance (Vm) of sarilumab,, this did not result in a meaningful change in functional sarilumab steady state exposure. The steady state AUC0-14 days changed by less than 20% in patients with high CRP levels (>31) compared to patients with low CRP levels (<8).

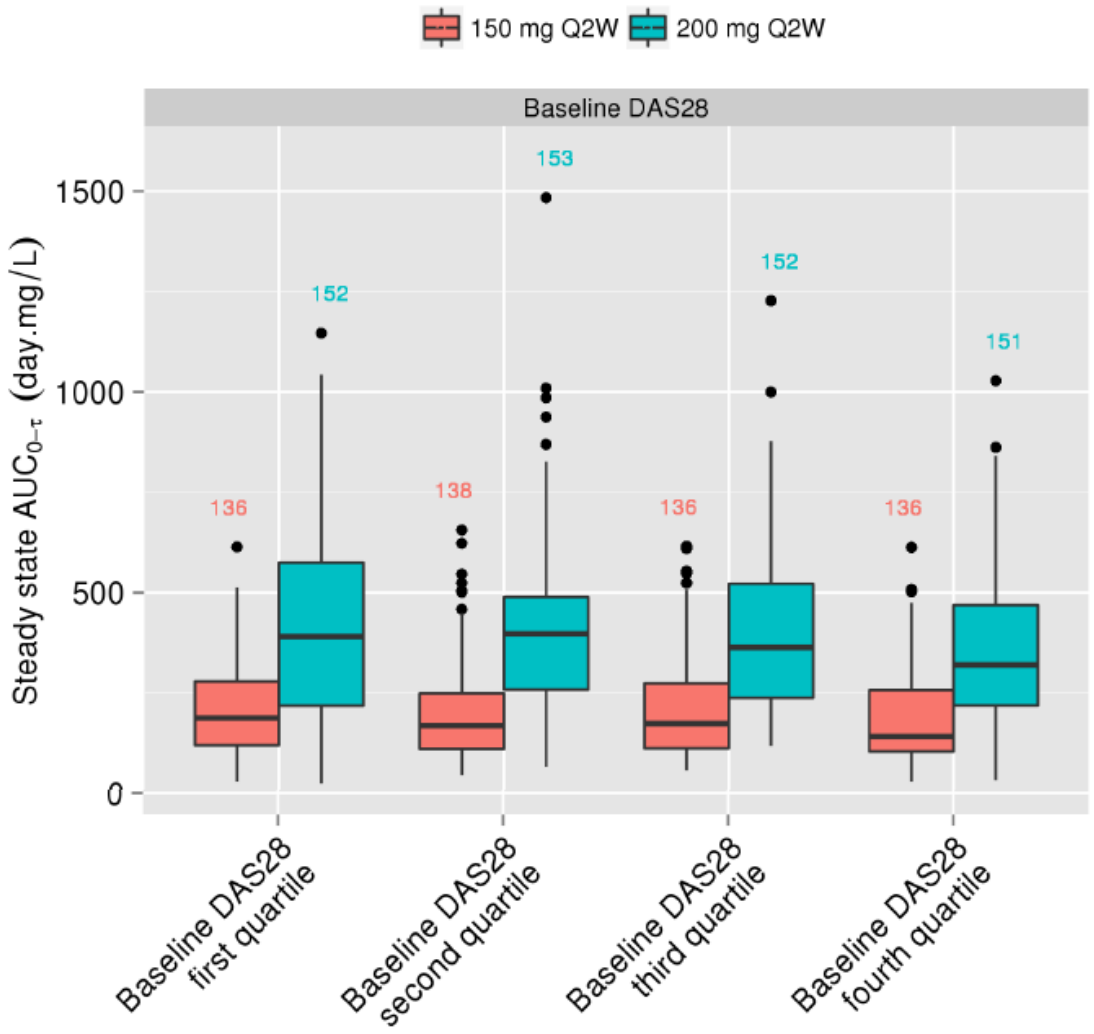


Figure 15. Comparison of sarilumab exposure across baseline DAS28 quartiles
(Source: Figure 34, Study report POH0428)

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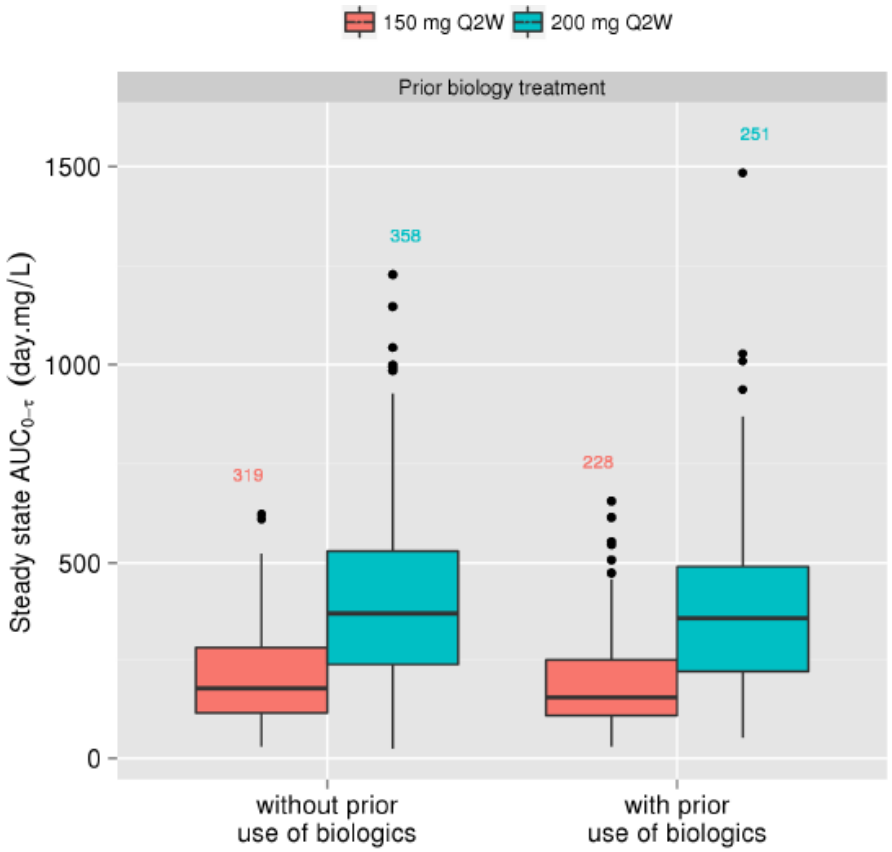


Figure 16. Comparison of sarilumab exposure with or without prior use of biologics
(Source: Figure 35, Study report POH0428)

2.7.2.2 Body Weight

No dose adjustments are recommended based on body weight as it did not result in a clinically meaningful impact on efficacy or safety.

Individual studies suggested a trend toward a decrease in functional sarilumab serum concentration with increase in body weight. In agreement with the observed data, population PK analysis (Study POH0428) of sarilumab serum concentration data from patients with RA from 32 to 177 kg identified body weight as significant covariate influencing apparent linear clearance (CL_0/F) and nonlinear maximum rate of clearance (V_m), resulting in an increase in exposure with decrease in body weight.

A summary of individual post hoc parameters predicted by population PK analysis for patients in Phase 3 studies are presented by body weight category in the table below. The steady state AUC 0-14 days at the 200 mg q2w dose is 1.6-fold higher and 0.53 fold lower in patients with body weight less than 60 kg (<60 kg) and patients with body weight greater than 100 kg (>100 kg) compared to patients with body weight ranging between 60 to 100 kg.

Table 9. Population PK analysis for patients in Phase 3 studies by body weight

Body weight	150 mg q2w				200 mg q2w			
	N	C_{max} (mg/L)	$AUC_{0\text{-}14\ days}$ (mg•day/L)	C_{trough} (mg/L)	N	C_{max} (mg/L)	$AUC_{0\text{-}14\ days}$ (mg•day/L)	C_{trough} (mg/L)
<60 kg	112	28.4 (10.3) [28.0]	314 (142) [318]	12.8 (10.3) [11.5]	129	49.6 (15.8) [47.1]	590 (226) [556]	29.2 (16.5) [27.1]
60 to <100 kg	380	18.8 (7.44) [16.8]	185 (93.7) [160]	5.21 (5.77) [2.55]	410	33.7 (12.4) [32.3]	368 (164) [347]	14.5 (11.2) [12.2]
≥100 kg	55	11.1 (3.30) [10.9]	90.3 (31.0) [91.7]	1.11 (0.83) [1.03]	70	20.8 (8.23) [20.0]	196 (96.4) [178]	4.69 (5.61) [2.54]

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

$AUC_{0\text{-}14\ days}$: area under the serum concentration versus time curve from 0 to 14 days; C_{max}: maximum serum concentration; q2w: every 2 weeks; C_{trough}: serum concentration observed before drug administration during repeated dose administration

(Source: Table 11 on page 51/112 of summary of clinical pharmacology)

1) Although lower exposure is observed in higher weight patients (≥100 kg) compared to patients with body weigh ranging between 60-100 kg at the 200 mg q2w dose, there is no need for dose adjustment/increase because reasonable efficacy in terms of ACR 20 response rate is observed in high body weight patients compared to lower body weigh patients (**Table 10** below). The ACR20 were 58.2% and 63.0% in patients with body weight ≥ 100 kg and patients with body weight ranging between 60-100 kg. The placebo response was similar in both weight categories.

2) Similar safety profiles were observed across the different weight groups in general (**Table 11**, see medical review), so there is no need for dose adjustment/decrease for lower weight patients. In the subgroup analysis of safety, a numerically higher incidence of ANC <1.0 Giga/L was observed in patients with weight <60 kg (17.6%) compared to higher weight patients. However, there is no increase of serious infection in the lower weight group (2.2%). Also, a lower starting dose at 150 mg q2w does not significantly lower the risk of neutropenia (14.1%). Therefore, dose adjustment is not required for the starting dose in patients with weight <60kg.

Also, in the long-term extension study11210, ~20% of the lower weight patients (<60kg) required a dose reduction from 200 mg q2w to 150 mg q2w due to AE (**Table 12**). This is similar to the percentage of patients (~18%) who had dose reduction due to AE in the higher body weight group (60-100kg).

Table 10. ACR20 response rate by patients with different baseline body weight (pooled data of EFC11072 and EFC10832)

	Placebo (N=579)	Sarilumab 150 mg q2w (N=581)	Sarilumab 200 mg q2w (N=583)

< 60 kg (N=363)	29.5%	69.0%	73.4%
≥60 and <100 kg (N=1186)	34.4%	56.9%	63.1%
≥100 kg (N=191)	35.9%	40.0%	58.2%

(Source: Figure 4 from Summary of Clinical Efficacy)

Table 11. Summary of AE of interest by subgroups during the entire TEAE period - Sarilumab+DMARD long-term safety population (Pool 2)

		Placebo + DMARD (N=661)	Sarilumab 150 mg q2w + DMARD (N=660)	Sarilumab 200 mg q2w + DMARD (N=661)
Serious infection	Weight			
	<60 kg	2/135 (1.5%)	2/128 (1.6%)	3/136 (2.2%)
	≥60 and <100 kg	9/454 (2.0%)	8/467 (1.7%)	11/451 (2.4%)
	≥100 kg	1/72 (1.4%)	2/65 (3.1%)	5/74 (6.8%)
ANC<1G/L	Weight			
	<60 kg	1/135 (0.7%)	18/128 (14.1%)	24/136 (17.6%)
	≥60 and <100 kg	0/454 (0.0%)	20/467 (4.3%)	32/451 (7.1%)
	≥100 kg	0/72 (0.0%)	2/65 (3.1%)	5/74 (6.8%)
ALT>3XULN	Weight			
	<60 kg	2/135 (1.5%)	7/128 (5.5%)	9/136 (6.6%)
	≥60 and <100 kg	7/454 (1.5%)	38/467 (8.1%)	33/451 (7.3%)
	≥100 kg	2/72 (2.8%)	4/65 (6.2%)	1/74 (1.4%)

(Source: Table 80, 82, 84, summary of Clin safety)

Table 12. Dose reduction due to AE in different weight groups in the long term extension study

WT GRP (kg)	Total patients	Patients who had dose reduction due to AE	% Dose reduction patients
<60	353	72	20.40%
>=60 - 100	1437	256	17.81%
>=100	215	25	11.63%

(Source: reviewer summary based on dataset:

\\cdsesub1\evsprod\bla761037\0000\m5\datasets\lts11210\analysis\legacy\datasets\adsl.xpt)

2.7.2.3 Sex

Population PK analysis (Study POH0428) of functional sarilumab serum concentration data from 304 male and 1466 female patients with RA identified sex as a significant covariate impacting apparent linear clearance (CL0/F). However, the effect of sex was minimal after accounting for differences in body weight between males and females. The sarilumab steady state exposures (AUC0-14 days) are 12% and 14% lower after repeated 150 and 200 mg q2w administrations, respectively, for a typical male patient, as compared to a typical female patient of the same body weight.

It should be noted that since females generally have lower body weight compared to males, higher exposure is expected in females compared to males due to the impact of body weight on PK. As no dose adjustment is recommended based on body weight (see section 2.7.2.2 for details), dose adjustment based on sex is not warranted. For additional details see section 1.1.1 of PM review.

2.7.2.3 Elderly

Population PK analysis (Study POH0428) with data from patients (N=1770) with age ranging from 18 to 87 years (14% of patients in the data set were >65 years) did not identify age as a significant covariate influencing sarilumab PK.

2.7.2.4 Race/Ethnicity

Population PK analysis (Study POH0428) with sarilumab serum concentration data from 1554 Caucasian (88% of the population PK data set), 105 Asian (6%), 60 Black (3%), and 51 other race (3%) patients with RA did not identify race (Caucasian versus non-Caucasian) as a significant covariate influencing functional sarilumab PK.

A single SC dose of 50 to 200 mg sarilumab administered to Japanese patients with RA (Study TDU13402) resulted in higher functional sarilumab exposure in Japanese patients than in Caucasian patients when compared across studies. This difference may be linked to the difference in body weight between Japanese patients (mean = 56.5 kg) and Caucasian patients in the other studies (mean = 76.5 to 78.2 kg).

2.7.2.6 Renal Impairment

The impact of renal impairment was evaluated in population PK analysis that included patients with mild (N=52) and moderate renal impairment (N=277). No patients with severe renal impairment were included in the analysis as Phase 3 studies excluded patients with severe renal impairment. No dose adjustment is recommended for patients with mild or moderate renal impairment. The rationale for no dose adjustment is as follows:

a) The magnitude of the effects of renal impairment on PK are minimal: Based on the final model, a mild or moderate renal impairment patient with CRCL of 30–90 ml/min, will have ~2-21% lower Vmax (maximum target mediated clearance) compared to a typical patient with CRCL of 100 mL/min. [(90/100)^0.212 ; (30/100)^0.212]. CRCL does not affect the linear clearance. Therefore, the overall impact of renal impairment on clearance is not clinically significant.

b) Creatinine clearance is related to renal function. However, renal elimination pathways are not expected to contribute significantly to the clearance of sarilumab, given that it is a monoclonal antibody.

c) No trend of increase in adverse events was observed with regards to serious infection and ALT increase (ALT>3xULN) in patients with renal impairment compared to patients who have normal renal function (Table 13). Therefore no dose adjustments are recommended for patients with mild or moderate renal impairment.

It should however be noted that in a categorical analysis by renal impairment category, individual post hoc predicted sarilumab exposures (AUC0-14 days) after repeated 150 and 200 mg q2w SC doses were greater by 39% to 43% in patients with mild renal impairment (CLcr of 60 to 90 mL/min) and by 62% to 99% in moderate renal impairment (CLcr of 30 to 60 mL/min), as compared to patients with normal renal function (Table 14). The effect of creatinine clearance is not considered meaningful for the following reasons

The distributions of two covariates impacting sarilumab exposure, body weight and sex, were different among renal function categories. Patients with mild and moderate renal impairment had lower median body weights (66 and 61 kg, respectively) than patients with normal renal function (79 kg), and more patients were female (86% and 90%, respectively) in the renal impairment group compared to patients with normal renal function (80%). Thus, the greater differences in exposure in patients with mild and moderate renal impairment exposures from the post hoc univariate analysis are most likely explained by the indirect effects of two confounding factors, body weight and sex, and are unlikely to reflect a direct effect of renal function on sarilumab PK.

Additionally as explained above, the impact of creatinine clearance was minimal after accounting for body weight in a typical patient.

Importantly no trend of increase in adverse events was observed with regards to serious infection and ALT increase (ALT>3xULN) in patients with renal impairment compared to patients who have normal renal function.

Table 13. Summary of AEs by Renal status (pool 1)

	Renal function Group	Placebo	150 mg q2w Sarilumab	200 mg q2w Sarilumab
Serious Infection	Normal (≥90 ml/min)	4/478 (0.84%)	7/468 (1.5%)	13/457 (2.84%)
	Mild (60 to 90 ml/min)	7/136 (5.15%)	4/150 (2.67%)	5/151 (3.31%)
	Moderate (30 to 60 ml/min)	0/20 (0%)	1/25 (4.0%)	1/31 (3.23%)
	Renal function Group	Placebo	150 mg q2w Sarilumab	200 mg q2w Sarilumab
ALT>3xULN	Normal (≥90 ml/min)	8/478 (1.67%)	38/468 (8.12%)	33/457 (7.22%)
	Mild (60 to 90 ml/min)	3/136 (2.21%)	9/150 (6 %)	9/151 (5.96%)
	Moderate (30 to 60 ml/min)	0/20 (0%)	1/25 (4%)	1/31 (3.23%)

(Source: Reviewer's analysis)

Table 14. Functional sarilumab steady state exposures by renal function category in patients with rheumatoid arthritis in Phase 3 studies (Study POH0428)

Level of renal impairment	150 mg q2w				200 mg q2w			
	N	C_{max} (mg/L)	$AUC_{0\text{-}14\ days}$ (mg•day/L)	C_{trough} (mg/L)	N	C_{max} (mg/L)	$AUC_{0\text{-}14\ days}$ (mg•day/L)	C_{trough} (mg/L)
Normal (≥90 mL/min)	393	18.1 (7.88) [16.0]	176 (99.6) [142]	4.78 (5.97) [1.89]	434	32.5 (13.6) [30.5]	352 (182) [313]	13.8 (12.2) [10.3]
Mild (60 to 90 mL/min)	130	23.4 (9.68) [22.9]	252 (130) [234]	9.48 (8.90) [7.16]	147	42.3 (15.1) [41.0]	488 (209) [452]	22.3 (14.7) [19.6]
Moderate (30 to 60 mL/min)	24	31.2 (13.0) [28.0]	350 (169) [315]	15.0 (11.1) [11.8]	28	48.0 (21.5) [41.2]	569 (302) [479]	28.2 (21.1) [20.5]

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

$AUC_{0\text{-}14\ days}$: area under the serum concentration versus time curve at steady state; C_{max}: maximum serum concentration; C_{trough}: serum concentration observed before drug administration during repeated dose administration; q2w: every 2 weeks

(Source: Table 13, summary of clin pharm)

2.7.2.7 Hepatic Impairment

Since sarilumab is an antibody, it is not expected to be cleared through the liver. The effect of hepatic impairment was not evaluated.

2.7.2.8 What pregnancy and lactation use information is available?

Adequate and well-controlled trials with sarilumab have not been conducted in pregnant women.

2.7.3 Does genetic variation impact exposure and/or response?

No analysis was conducted on impact of genetic variation on exposure and/or response.

2.7.4 Immunogenicity

2.7.4.1 What is the incidence of the formation of the ADA, including the rate of pre-existing antibodies, the rate of ADA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

ADA incidence is higher in the lower dose group (150 mg q2w) compared to higher dose (200 mg q2w) in general. Patients who received sarilumab and concomitant MTX had a lower incidence of antibodies to sarilumab than patients who received sarilumab without MTX.

As shown in Table 15, the incidences of positive ADA response in the placebo and sarilumab 150 and 200 mg q2w treatment groups across placebo-controlled studies (Pool 1) were 3.5% (21 of 608), 19.3% (117 of 607), and 14.0% (85 of 607) respectively. Most of these responses were transient, with 2.0%, 5.6%, and 4.0% having a persistent treatment-emergent positive ADA response in the placebo and sarilumab 150 and 200 mg q2w treatment groups, respectively. The majority of the ADA positive patients exhibited low titers (≤60). Among the persistent treatment-emergent positive ADA responses, only 0.2%, 1.6%, and 1.0% in the placebo, and 150 and 200 mg q2w treatment groups, respectively, exhibited anti-sarilumab NAbs.

The ADA incidence did not increase over time in the sarilumab treated patients. As shown in Table 16, in the sarilumab with DMARD long term safety population (Pool 2), the overall rate of ADA positivity in any dose group was 16.3%, with a median titer of 30. Most of patients had transient responses (11.7%), with 4.5% having a persistent treatment-emergent positive response. Among the persistent treatment-emergent positive ADA responses, only 1.2% exhibited NAbs.

Patients who received sarilumab and concomitant MTX had a lower incidence of antibodies to sarilumab than patients who received sarilumab without MTX. In the sarilumab monotherapy population (Pool 3, Table 17), incidences of positive ADA status for the treatment groups of 150 and 200 mg q2w and the pool of both sarilumab doses (any dose) were 24.6%, 18.2%, and 21.4%, respectively. Incidences of persistent positive ADA status were 12.3%, 6.1%, and 9.2% respectively. Among patients with persistent treatment-emergent positive ADA responses, 10.8%, 3.0% and 6.9% exhibited NAbs, respectively.

Table 15. Overview of antidrug antibodies assay response during the entire treatment-emergent adverse event period: the placebo-controlled immunogenicity population (Pool 1)

Number of patients	Placebo and DMARD (N=608)	Sarilumab and DMARD	
		Sarilumab 150 mg q2w (N=607)	Sarilumab 200 mg q2w (N=609)
ADA assay results available	608/608 (100%)	607/607 (100%)	607/609 (99.7%)
Negative ADA sample at baseline	597/606 (98.5%)	585/599 (97.7%)	589/599 (98.3%)
Positive ADA sample at baseline	9/606 (1.5%)	14/599 (2.3%)	10/599 (1.7%)
ADA negative during the TEAE period	587/608 (96.5%)	490/607 (80.7%)	522/607 (86.0%)
ADA positive during the TEAE period[a]	21/608 (3.5%)	117/607 (19.3%)	85/607 (14.0%)
Neutralizing[b]	1/608 (0.2%)	20/607 (3.3%)	11/607 (1.8%)
Non-neutralizing	20/608 (3.3%)	97/607 (16.0%)	74/607 (12.2%)
Treatment-boosted	0/608 (0%)	1/607 (0.2%)	1/607 (0.2%)
Treatment-emergent	21/608 (3.5%)	116/607 (19.1%)	84/607 (13.8%)
Peak titer			
Median	60.00	60.00	60.00
Q1 : Q3	30.00 : 60.00	30.00 : 120.00	30.00 : 120.00
Minimum : maximum	30.0 : 120.0	30.0 : 3840.0	30.0 : 7680.0
Persistent positive[c]	12/608 (2.0%)	34/607 (5.6%)	24/607 (4.0%)
Neutralizing[b]	1/608 (0.2%)	10/607 (1.6%)	6/607 (1.0%)
Non-neutralizing	11/608 (1.8%)	24/607 (4.0%)	18/607 (3.0%)
Transient positive[d]	9/608 (1.5%)	82/607 (13.5%)	60/607 (9.9%)
Neutralizing[b]	0/608 (0.0%)	9/607 (1.5%)	5/607 (0.8%)
Non-neutralizing	9/608 (1.5%)	73/607 (12.0%)	55/607 (9.1%)

a No positive assay response at baseline but with a positive assay response during the TEAE period or with a positive ADA assay response at baseline and at least a 4-fold increase in titer during the TEAE period

b At least one postbaseline measurement classified as neutralizing positive

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

d Any positive ADA assay response not considered persistent

ADA: antidrug antibody; DMARD: disease modifying antirheumatic drug; Q1: quartile 1; q2w: every 2 weeks; Q3: quartile 3; TEAE: treatment-emergent adverse event

The DMARD in Study EFC11072 Part B was methotrexate; DMARDs in Study EFC10832 were methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine. A treatment-emergent ADA positive patient is defined as a patient with negative or missing ADA response at baseline, but with a positive assay response during the TEAE period. A treatment-boosted ADA positive patient is defined as a patient with a positive ADA assay response at baseline who has at least a 4-fold increase in titer compared to baseline during the TEAE period.

(Source: Table 14, summary of clinical pharmacology)

Table 16. Overview of antidrug antibody assay response during the entire treatment-emergent adverse event period: sarilumab with disease-modifying antirheumatic drug immunogenicity population (Pool 2)

	Sarilumab and DMARD		
Numbers of patients	Sarilumab 150 mg q2w Initial dose N = 1099	Sarilumab 200 mg q2w Initial dose N = 1248	Sarilumab Any dose N = 2559
ADA assay results available	1099/1099 (100%)	1244/1248 (99.7%)	2555/2559 (99.8%)
Negative ADA sample at baseline	1063/1082 (98.2%)	1216/1236 (98.4%)	2386/2426 (98.4%)
Positive ADA sample at baseline	19/1082 (1.8%)	20/1236 (1.6%)	40/2426 (1.6%)
ADA negative during the TEAE period	862/1099 (78.4%)	1096/1244 (88.1%)	2138/2555 (83.7%)
ADA positive during the TEAE period[a]	237/1099 (21.6%)	148/1244 (11.9%)	417/2555 (16.3%)
Neutralizing[b]	30/1099 (2.7%)	17/1244 (1.4%)	52/2555 (2.0%)
Non-neutralizing	207/1099 (18.8%)	131/1244 (10.5%)	365/2555 (14.3%)
Treatment-boosted	1/1099 (<0.1%)	1/1244 (<0.1%)	3/2555 (0.1%)
Treatment-emergent	236/1099 (21.5%)	147/1244 (11.8%)	414/2555 (16.2%)
Peak titer			
Median	30.00	60.00	30.00
Q1 : Q3	30.00 : 120.00	30.00 : 120.00	30.00 : 120.00
Minimum : maximum	30.0 : 3840.0	30.0 : 7680.0	30.0 : 15360.0
Persistent positive[c]	77/1099 (7.0%)	40/1244 (3.2%)	114/2555 (4.5%)
Neutralizing[b]	18/1099 (1.6%)	8/1244 (0.6%)	31/2555 (1.2%)
Non-neutralizing	59/1099 (5.4%)	32/1244 (2.6%)	83/2555 (3.2%)
Transient positive[d]	159/1099 (14.5%)	107/1244 (8.6%)	300/2555 (11.7%)
Neutralizing[b]	11/1099 (1.0%)	9/1244 (0.7%)	20/2555 (0.8%)
Non-neutralizing	148/1099 (13.5%)	98/1244 (7.9%)	280/2555 (11.0%)

a No positive assay response at baseline but with a positive assay response during the TEAE period or with a positive ADA assay response at baseline and at least a 4-fold increase in titer during the TEAE period

b At least one postbaseline measurement classified as neutralizing positive

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

d Any positive ADA assay response not considered persistent

ADA: antisarilumab antibody; DMARD: disease modifying antirheumatic drug; q2w: every 2 weeks; TEAE: treatment-emergent adverse event

(Source: Table 15 on page 91/112 of summary of clinical pharmacology)

Table 17. Overview of ADA assay response during the entire TEAE period – Sarilumab monotherapy immunogenicity population (Pool 3)

	Sarilumab		
	150 mg q2w Initial Dose (N=65)	200 mg q2w Initial Dose (N=66)	Any Dose (N=131)
Number of patients with ADA assay results available	65/65 (100%)	66/66 (100%)	131/131 (100%)
Patients with an ADA positive sample at baseline	1/65 (1.5%)	2/66 (3.0%)	3/131 (2.3%)
ADA positive patients[a] during the TEAE period	16/65 (24.6%)	12/66 (18.2%)	28/131 (21.4%)
Neutralizing[b]	7/65 (10.8%)	2/66 (3.0%)	9/131 (6.9%)
Non-Neutralizing	9/65 (13.8%)	10/66 (15.2%)	19/131 (14.5%)
Treatment-boosted ADA positive patients	0/65	0/66	0/131
Treatment-emergent ADA positive patients	16/65 (24.6%)	12/66 (18.2%)	28/131 (21.4%)
Patients with a persistent[c] positive response	8/65 (12.3%)	4/66 (6.1%)	12/131 (9.2%)
Neutralizing[b]	7/65 (10.8%)	2/66 (3.0%)	9/131 (6.9%)
Non-Neutralizing	1/65 (1.5%)	2/66 (3.0%)	3/131 (2.3%)
Patients with a transient[d] positive response	8/65 (12.3%)	8/66 (12.1%)	16/131 (12.2%)
Neutralizing[b]	0/65	0/66	0/131
Non-Neutralizing	8/65 (12.3%)	8/66 (12.1%)	16/131 (12.2%)
Peak titers for treatment-emergent ADA positive patients			
Median	30.00	30.00	30.00
Q1 : Q3	30.00 : 120.00	30.00 : 45.00	30.00 : 60.00
Min : Max	30.0 : 240.0	30.0 : 120.0	30.0 : 240.0

Percentages based on number of patients with ADA assay results available. No imputation is used for missing ADA results.

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

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

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

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

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

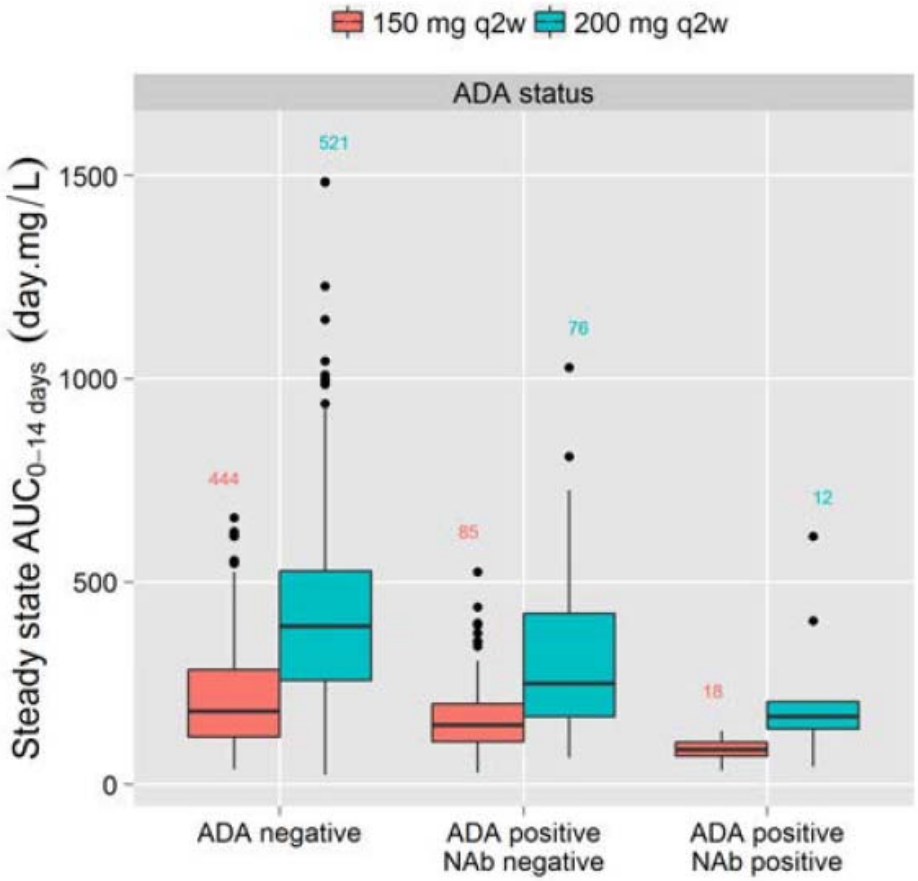
PGM=PRODOPS/SAR153191/OVERALL/CSS/REPORT/PGM/pk_ada_s_t.sas OUT=REPORT/OUTPUT/pk_ada_s_t_p3_i.rtf (28JUN2015 - 17:04)

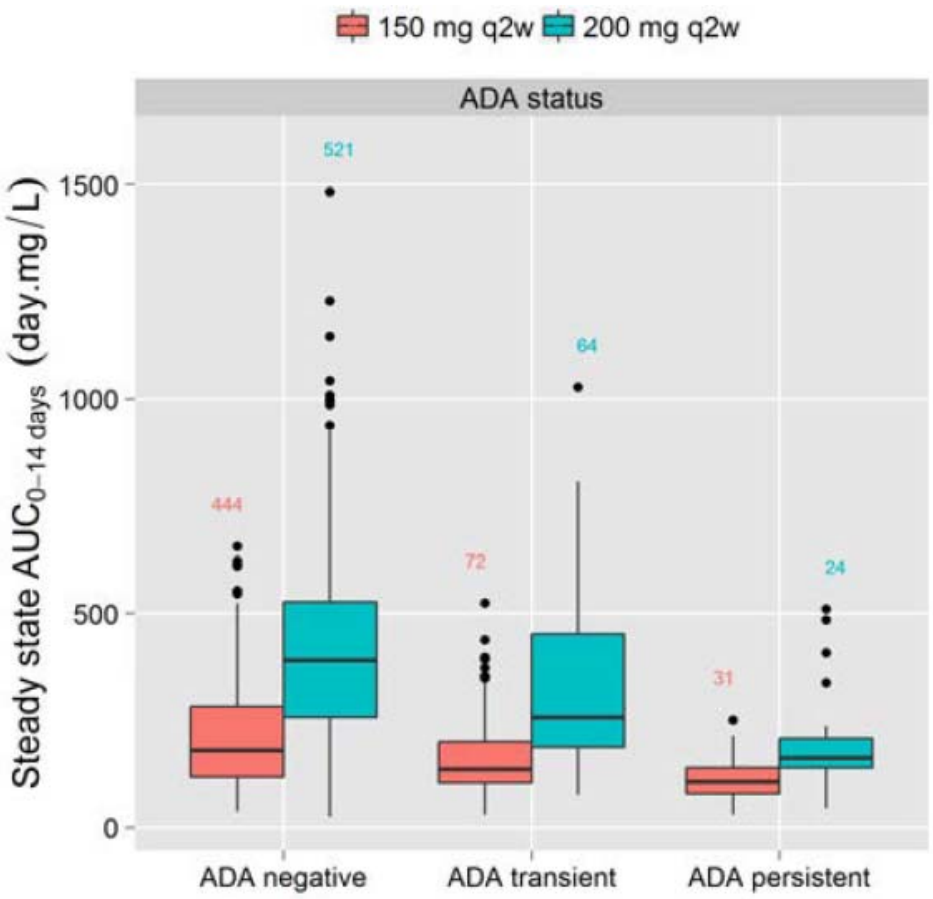
(Source: Table 69, summary of clinical safety)

2.7.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

Positive ADA status has an impact on PK (a 24% to 28% lower exposure when compared to ADA
negative patients), with concentrations in patients with persistent response being lower (by 32% to
41%) than in patients with transient response. Persistent ADA response was observed in 2.0%, 5.6%, and 4.0% of patients in the placebo and sarilumab 150 and 200 mg q2w treatment groups across the placebo controlled immunogenicity population (Pool 1), with 0.2%, 1.6%, and 1.0% of
patients also exhibiting NAbs. Sarilumab concentrations in this small number of NAb positive patients appeared to be lower than in NAb negative patients (by 49% to 59%).

After adjusting for PK, the ADA status does not have additional impact on exposure-response analysis for efficacy endpoints such as DAS 28, or safety endpoints such as ANC, ALT, or LDL (See Pharmacometrics review). While sarilumab exposure in ADA positive patients was lower than in ADA negative patients, this did not lead to discontinuations due to lack or loss of efficacy (See section 2.7.4.4).





ADA: antidrug antibody; NAb, neutralizing antidrug antibody; q2w: every 2 weeks
Descriptive statistics for individual post hoc predicted pharmacokinetic parameters for Studies EFC11072 Part B and EFC10832 from population pharmacokinetic analysis. Boundaries of boxes indicate the 25th and the 75th percentiles. Lines within boxes mark the median. Whiskers indicate minimum and maximum values. Outlier data points are plotted individually. Numbers inside the plot panels indicate numbers of patients within covariate categories

Figure 17. Functional sarilumab steady state exposure ($AUC_{0\text{-}14\ days}$) as a function of antidrug antibody status in patients with rheumatoid arthritis in Phase 3 studies (Study POH0428)
(Source: Figure 26, clin pharm summary)

2.7.4.3 Does the ADA have neutralizing activity?

Among patients with the persistent treatment-emergent positive ADA responses, about 1-10.8% exhibited neutralizing activity. See section 2.7.4.1 for details.

2.7.4.4 What is the impact of ADA on clinical efficacy?

In general, the persistent ADA incidence is low (See section 2.7.4.1). The sponsor indicated that the incidence of patients who discontinued due to loss or lack of efficacy was similar in patients

who were positive for ADA and those who were ADA negative as depicted in the table below. No patients with NAb responses discontinued due to loss or lack of efficacy.

Table 18. Number (%) of patients who discontinued due to lack of efficacy or loss of efficacy by ADA status during the entire TEAE period - Sarilumab+DMARD immunogenicity population (Pool 2)

		ADA positive[a]		
n(%)	ADA negative (N=2138)	Neutralizing (N=52)	Non-neutralizing (N=365)	All (N=417)
Lack of efficacy[b]	60(2.8%)	0	14(3.8%)	14(3.4%)
Loss of efficacy[c]	26(1.2%)	0	7(1.9%)	7(1.7%)

(Source: Table 59 on page 182/302 of summary of clinical safety)

2.7.4.5 What is the impact of ADA on clinical safety?

The sponsor indicates that the incidence of a reported hypersensitivity reaction during the treatment period, systemic or local (at the injection site), was 5.3% in those patients who were ADA positive, compared to 8.5% in patients who were ADA negative. Of the 22 ADA positive patients with hypersensitivity reaction, 5 had an injection site reaction described as a rash at the injection site. Of the 27 patients who discontinued due to a hypersensitivity reaction, only 2 were positive for ADA (injection site reaction and generalized rash) and for these 2 patients titers were low (30-60), further supporting a lack of clinical relevance from the presence of ADA.

2.8 Extrinsic Factors

2.8.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Elevated interleukin-6 (IL-6) concentration may down-regulate CYP activity such as in patients with RA and hence increase drug levels of CYP substrates compared to subjects without RA. Blockade of IL-6 signaling by IL-6Rα antagonists such as sarilumab might reverse the inhibitory effect of IL-6 and restore CYP activity, leading to reduced drug concentrations. See 2.8.2 for DDI results with simvastatin, a CYP3A4 substrate.

2.8.2 What are the drug-drug interactions?

Administration of concomitant MTX, the most commonly prescribed DMARD for patients with RA, did not impact sarilumab clearance, as assessed by population PK analyses. Prior use of biologics (for RA treatment), had no appreciable impact on sarilumab PK based on graphical exploration of the post-hoc predicted exposure data.

A DDI study evaluating effect of sarilumab on simvastatin, a sensitive CYP3A4 substrate, showed that in 17 patients with RA, exposure of simvastatin and simvastatin acid decreased by 45% and 36%, respectively, following a single 40 mg oral dose of simvastatin one week after a

single SC dose of sarilumab 200 mg. The following labeling recommendation related to this DDI is proposed by the sponsor:

'The modulation of IL-6 effect on CYP enzymes by sarilumab may be clinically relevant for CYP substrates with a narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of sarilumab, in patients being treated with CYP substrate medicinal products, (b) (4) .'

2.8.3 Does the label specify co-administration of another drug?

The label indicates that sarilumab may be used as monotherapy or in combination with methotrexate (MTX) or other (b) (4) DMARDs (b) (4).

2.8.4 What other co-medications are likely to be administered to the target population?

Patients evaluated in the two Phase 3 Studies received either concomitant MTX or concomitant (b) (4) DMARDs as suggested in the labeling.

2.9 General Biopharmaceutics

2.9.1 How is the proposed to-be-marketed formulation/device linked to the clinical development formulation/device?

The planned-to-be-marketed drug product is identical to the drug product used in Phase 3 studies. The drug product presentation was a vial in early Phase 1 and 2 clinical studies, later changed to a PFS introduced during the pivotal Phase 3 studies. The Phase 2 ((b) (4)F2) and Phase 3 ((b) (4)F3) products are linked through two relative bioavailability studies in healthy subjects and RA patients that indicated that there were no meaningful differences in functional sarilumab exposure or immunogenicity (ADA) when the 2 products were administered.

An overview of the sarilumab drug product development and the studies conducted to compare drug products used in the clinical studies program is provided in the figure below:

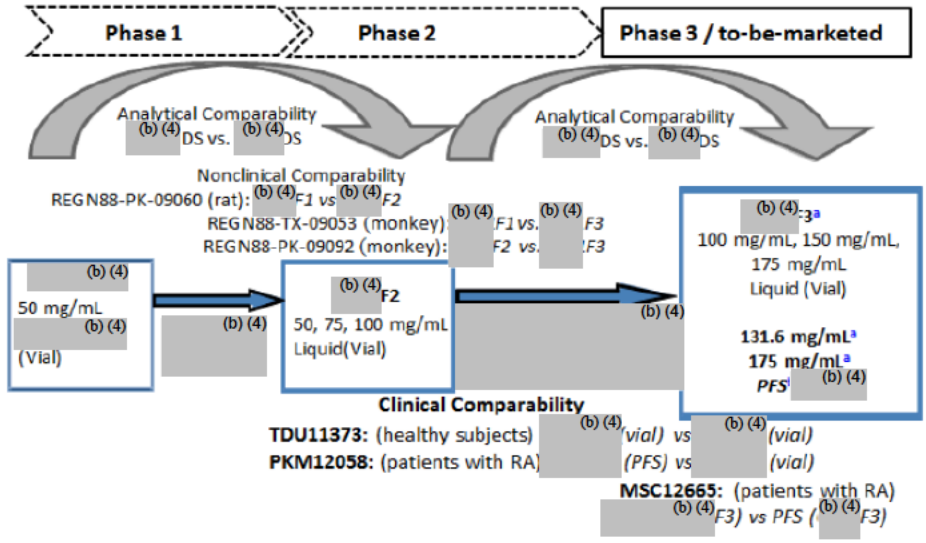


Figure 18. Overview of the Studies Conducted to Assess the Comparability of Sarilumab Drug Products or Devices Used in Clinical Studies

(Source: Figure 1, summary of biopharmaceutics)

The differences in the 3 product formulations, i.e., [(b) (4)] are shown in the table below:

Table 19. Differences between Three Sarilumab Drug Products Used in Clinical Studies

Current Nomenclature used in Submission		Drug Product Formulation
Drug Substance	Drug Product[a]	
[(b) (4)]	[(b) (4)] F1 F2 F3 F3 (used in Phase 3 studies) (planned-to-be-marketed)	[(b) (4)] 21 mM histidine[b], 45 mM arginine[c], 5% sucrose, 0.2% polysorbate 20, pH 6.0

(Source: Table 1, summary of biopharmaceutics)

In healthy male subjects, after a single 100 mg dose of sarilumab [(b) (4)] F3 or [(b) (4)] F2 drug products, similar functional sarilumab exposure (Cmax or AUClast) was observed (Study TDU11373 , **Table 20**). Comparable trough concentrations of functional sarilumab were observed after SC administration of 150 mg or 200 mg q2w of the [(b) (4)] F2 drug product used in Phase 2 (Study EFC11072, Part A) and [(b) (4)] F3 drug product used in Phase 3 (Study EFC11072, Part B).

Table 20. Mean (± SD) Cmax and AUClast for Functional Sarilumab after Administration of a 100 mg Sarilumab SC Dose using Different Drug Products (Study TDU11373, Part 2)

Drug Product	[(b) (4)]F3[a]	[(b) (4)]F2[b]
Parameters (unit)	100 mg in vial (N=14)	100 mg in vial (N=14)
C_{max} (mg/L)		
Mean ± SD	7.77 ± 3.65	7.88 ± 3.27
Geometric Mean (%CV)	6.45 (47.0)	7.06 (41.5)
AUC_{last} (mg•day/L)		
Mean ± SD	45.0 ± 22.7	47.5 ± 23.5
Geometric Mean (%CV)	33.8 (50.1)	36.9 (49.7)

AUC_{last} = area under the concentration versus time curve from time zero to the last quantifiable serum concentration, C_{max} = maximum serum concentration, CV = coefficient of variation; SD= standard deviation

a. The [(b) (4)]F3 drug product was used in the Phase 3 studies. It is the planned-to-be-marketed drug product.

b. The [(b) (4)]F2 drug product used in the Phase 2 dose-ranging study (EFC11072, Part A) was the reference drug product.

Note: The C_{max} values presented as ng/mL and the AUC_{last} values presented as ng•hour/mL in the TDU11373 report were converted to mg/L and mg•day/L, respectively, for presentation in the table.

(Source: Table 31, study report IDU11373)

Table 21. Comparison of Functional Sarilumab Ctrough in Serum on Day 28 Observed in Study EFC11072, Part A (Phase 2; [(b) (4)]F2) and Part B (Phase 3 [(b) (4)]F3)

		150 mg q2w		200 mg q2w	
PK Parameter(mg/mL)	Day	[(b) (4)]F2 (N=52)	[(b) (4)]F3 (N=401)	[(b) (4)]F2 (N=51)	[(b) (4)]F3 (N=396)
Mean C_{trough} ±SD[a] (n)	28[b]	2.71 ± 3.50 (47)	3.35 ± 4.88 (366)	7.06 ± 6.53 (43)	9.63 ± 9.42 (360)

C_{trough} = serum concentration observed before drug administration during repeat-dose administration; n = number of patients for Day 28 values; PK= pharmacokinetic; SD = standard deviation; q2w = every 2 weeks

[a] The C_{trough} values presented as ng/mL the EFC11072 Part B table were converted to mg/L for presentation in the table.

[b] The Week 4 values are presented in the table.

(Source: Table 13, summary of biopharmaceutics)

2.9.2 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

The subcutaneous administration route is not expected to be affected by food and no food-effect studies have been conducted.

2.10 Analytical Section

2.10.1 What bioanalytical methods were used to assess sarilumab plasma concentrations?

Three assays were developed and validated by the sponsor to determine the concentrations of functional and bound forms of sarilumab in human serum: 2 validated versions of an assay to measure functional sarilumab, and 1 validated assay to measure bound sarilumab. The functional assay provides information about the amount of drug that is pharmacologically active (e.g., 1 or 2 binding sites available to bind target) and the bound assay provides information about target engagement and saturation (e.g., 1 or 2 binding sites bound to target). The functional and bound assays both measure a sarilumab form that is bound to a single IL-6Rα molecule (i.e., has only 1 binding site occupied with IL-6Rα and the other binding site free). This overlap in the singly

bound sarilumab form between the 2 assays prevents the simple addition of functional concentration and bound concentration to derive a total concentration of sarilumab.

Since the PK of bound sarilumab were consistent and predictable across all studies in which it was measured, the Sponsor decided to discontinue measurement of bound sarilumab after completion of Study EFC11072, Part B. Systemic concentrations of functional sarilumab, which is a pharmacologically active drug, were measured for all studies conducted after EFC11072, Part B.

The initial enzyme-linked immunosorbent assay (ELISA) method for the determination of the concentration of functional sarilumab in human serum (REGN88-AV-07026-VA-01V2) was validated and used in early clinical studies. As the clinical program progressed, this ELISA method was optimized to increase robustness and sample throughput. Therefore, the new optimized method was validated (REGN88-AV-13131-VA- 01V2) and cross-validated with the initial method.

2.10.2 For all moieties measured, is free, bound, or total measured?

Functional sarilumab concentrations were measured in all studies where PK samples were collected. Functional sarilumab is assumed to represent the pharmacologically active drug.

The sponsor also measured bound sarilumab in earlier studies. The data of bound sarilumab concentration is not stated in the label or used in the exposure-response analysis. Therefore, this review did not assess the concentration of bound sarilumab.

2.10.3 What is the range of the standard curve? What is the limit of quantitation? What are the accuracy, precision, and selectivity at these limits? What is the sample stability under conditions used in the study?

A summary of the bioanalytical methods is provided in the table below:

Table 22. Summary of Analytical Methods

Study (method)	Analyte	Matrix (MRD)	Calibration Curve (ng/mL)	LLOQ[a] Sensitivity (ng/mL)	Accuracy (%AR)	Within-run Precision (CV%)	Between-run Precision (CV%)	Long Term Stability at -80°C	Clinical Studies	Study Report Location
[REGN88-AV-07026-VA-01V2] SOP PCL2356	functional sarilumab	human serum (1:50)	5.88 – 200	294	84 – 101	≤13	≤15	at least 24 months	TDU10808/ 6R88-RA-0703 TDU10809/ 6R88-RA-0801 ACT10804/ 6R88-RA-0803 TDU10805/ 6R88-RA-0802 TDU11373 TDU13402 ACT11575 PKM12058 EFC11072A EFC11072B LTS11210	5.3.1.4
[REGN88-AV-13131-VA-01V1] SOP PCL3576[b]	functional sarilumab	human serum (1:50)	6.25 – 400	313	94-107	≤3	≤8	at least 21months	6R88-RA-1309 LTS11210 EFC10832 INT12684 SFY13370 EFC13752 MSC12665	5.3.1.4
[REGN88-AV-08010-VA-01V2] SOP PCL3060[c]	bound sarilumab	human serum (1:100)	6.62 – 225	662	96 - 101	≤12	≤12	at least 24 months	LTS11210 EFC11072 B TDU13402	5.3.1.4
[REGN88-AV-08010-VA-01V2] SOP PCL2381[c]	bound sarilumab	human serum (1:100)	6.62 – 225	662	96 - 118	≤12	≤12	at least 24 months	TDU10808/ 6R88-RA-0703 TDU10809/ 6R88-RA-0801 ACT10804/ 6R88-RA-0803 TDU10805/ 6R88-RA-0802 TDU11373 ACT11575 PKM12058 LTS11210 EFC11072A	5.3.1.4
Non-Validated Method SOP PCL2386	anti-sarilumab antibodies	human serum (1:30)	NA	NA	NA	NA	NA	NA	TDU10808/ 6R88-RA-0703 TDU10809/ 6R88-RA-0801 ACT10804/ 6R88-RA-0803 TDU10805/ 6R88-RA-0802	NA
[REGN88-AV-10017-VA-01V2] SOP PCL2649[d]	anti-sarilumab antibodies	human serum (1:30)	NA	63.5	NA	NA	NA	at least 24 months	TDU11373 TDU13402 ACT11575 PKM12058 EFC11072A EFC11072B	5.3.1.4
[REGN88-AV-10017-VA-01V2] SOP PCL2649[e]	anti-sarilumab antibodies	human serum (1:30)	NA	116.3	NA	NA	NA	at least 24 months	EFC11072B LTS11210	5.3.1.4

[REGN88-AV-10017-VA-01V2] SOP PCL2649[f]	anti-sarilumab antibodies	human serum (1:30)	NA	75.6	NA	NA	NA	at least 24 months	LTS11210[5] MSC12665 EFC10832 EFC11574 INT12684 SFY13370 6R88-RA-1309	5.3.1.4
[REGN88-AV-10017-VA-01V2] SOP PCL2649[h]	anti-sarilumab antibodies	human serum (1:30)	NA	99.2	NA	NA	NA	at least 24 months	EFC13752 LTS11210	5.3.1.4
[REGN88-AV-12055-VA-01V3] SOP PCL3081	neutralizing anti-sarilumab antibodies	human serum (1:20)	NA	150	NA	NA	NA	at least 24 months	EFC11072B EFC10832 SFY13370 LTS11210 EFC13752 EFC11574 MSC12665	5.3.1.4
[DOH1012]	free sIL-6Rα	human serum	0.0781 – 10.0	0.781	≤25	12.3-14.9	0-8.20	at least 3 months	ACT11575 EFC11072A	5.3.1.4
[DOH1007]	total sIL-6Rα	human serum	0.0781 – 100.0	0.781	≤25	13.6-17.4	0-7.25	at least 3 months	ACT11575 PKM12058 TDU11373 EFC11072A	5.3.1.4
[DOH1163]	total sIL-6Rα	human serum	15-1000	15	80-120	3.7-6.4	12.1-15.8	at least 12 months	EFC11072B 6R88-RA-1309	5.3.1.4

MRD: minimal required dilution; LLOQ = lower limit of quantitation; AR: analyte recovery; CV: coefficient of variation.

[a] in undiluted serum matrix

(Source: Table 15, summary of biopharm)

2.10.4 What bioanalytical methods are used to assess therapeutic protein concentrations?

An ELISA ([REGN88-AV-07026-VA-01V2]) was validated for the determination of the concentration of functional sarilumab (i.e., sarilumab with ≥1 free binding sites for IL-6Rα and capable of target binding) in human serum. Functional sarilumab was captured on plates coated with the IL-6Rα ligand and detected using a biotinylated goat anti-kappa light chain specific polyclonal antibody, followed by NeutrAvidin conjugated to horseradish peroxidase (HRP). A luminol-based substrate specific for peroxidase was then added to achieve a signal intensity that was proportional to the concentration of functional sarilumab. The assay provided a quantitative measurement of the concentrations of free sIL-6R. The assay provided a quantitative measurement of the concentrations of functional sarilumab.

The validated ELISA method, REGN88-AV-07026-VA-01V1, was optimized to increase robustness and sample throughput. The revisions to the method involved utilization of a more specific detection reagent and a change from triplicate sample analysis (in the original assay) to duplicate sample analysis. The new revised method was then validated. Functional sarilumab was captured on plates coated with the IL-6Rα ligand and detected using a biotinylated mouse anti-sarilumab monoclonal antibody, followed by NeutrAvidin conjugated to HRP. A luminol-based substrate specific for peroxidase was then added to achieve a signal intensity that is proportional to the concentration of functional sarilumab. The assay provided a quantitative measurement of the concentrations of functional sarilumab.

2.10.5 What bioanalytical methods are used to assess the formation of the anti-drug antibodies?

Two assays were developed by the sponsor to assess the immunogenicity of sarilumab: 1 assay to detect ADA, and 1 assay to detect NAbs. Antidrug antibodies were assessed in human serum using a validated electrochemiluminescence-based bridging immunoassay (REGN88-AV-10017-VA-01V2) that employed a 3-tiered approach for evaluating immunogenicity; screening, confirmation, and titer. Samples from the Phase 3 studies that were positive in the ADA assay were further assessed for neutralizing activity using a validated competitive ligand binding assay (REGN88-AV-12055-VA-01V3). See details in the OBP review.

3. DETAILED LABELING RECOMMENDATIONS

The revised labeling language based on the preliminary review is as below. Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font. At the time of this review, cross-discipline labeling review is ongoing and these label revisions may differ from the final label recommendations.

7 DRUG INTERACTIONS

7.1 Use with Other Drugs for Treatment of Rheumatoid Arthritis

(b) (4)

Population pharmacokinetic analyses did not detect any effect of methotrexate (MTX) on sarilumab clearance. (b) (4) has not been investigated in combination with JAK inhibitors or biological DMARDs such as TNF antagonists *[see Dosage and Administration (2.2)]*.

7.2 Interactions with CYP450 Substrates

Various *in vitro* and limited *in vivo* human studies have shown that cytokines and cytokine modulators can influence the expression and activity of specific cytochrome P450 (CYP) enzymes and therefore have the potential to alter the pharmacokinetics of concomitantly administered drugs that are substrates of these enzymes. Elevated interleukin-6 (IL-6) concentration may down-regulate CYP activity such as in patients with RA and hence increase drug levels compared to subjects without RA. Blockade of IL-6 signaling by IL-6Rα antagonists such as sarilumab might reverse the inhibitory effect of IL-6 and restore CYP activity, leading to altered drug concentrations.

The modulation of IL-6 effect on CYP enzymes by sarilumab may be clinically relevant for CYP substrates with a narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of (b) (4) in patients being treated with CYP substrate medicinal products, perform therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., theophylline) and adjust the individual dose of the medicinal product as needed.

(b) (4)

-Exercise caution when coadministering (b) (4) with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc. The effect of sarilumab on CYP450 enzyme activity may persist for several weeks after stopping therapy *[see Clinical Pharmacology (12.3)]*.

7.3 Live Vaccines

Avoid concurrent use of live vaccines during treatment with (b) (4) *[see Warnings and Precautions (5.6)]*.

8 USE IN SPECIFIC POPULATIONS

8.6 Hepatic Impairment

The safety and efficacy of (b) (4) have not been studied in patients with hepatic impairment, including patients with positive HBV or HCV serology *[see Warnings and Precautions (5.5)]*.

8.7 Renal Impairment

No dose adjustment is required in patients with mild to moderate renal impairment. (b) (4) has not been studied in patients with severe renal impairment *[see Clinical Pharmacology (12.3)]*.

12.2 Pharmacodynamics

Following single-dose subcutaneous administration of sarilumab 200-mg and 150-mg in patients with RA, rapid reduction of CRP levels was observed. Levels were reduced to normal (b) (4) after treatment initiation. Following single-dose sarilumab administration, in patients with RA, absolute neutrophil counts decreased to the nadir between 3 to 4 days and thereafter

recovered towards baseline *[see Warnings and Precautions (5.2)]*. Treatment with sarilumab resulted in decreases in fibrinogen and serum amyloid A, and increases in hemoglobin and serum albumin.

12.3 Pharmacokinetics

Absorption

The pharmacokinetics of sarilumab were characterized in 1770 patients with rheumatoid arthritis (RA) treated with sarilumab which included 631 patients treated with 150 mg and 682 patients treated with 200 mg doses every two weeks for up to 52 weeks. The median t_{max} was observed in 2 to 4 days.

At steady state, exposure over the dosing interval measured by area under curve (AUC) increased 2-fold with an increase in dose from 150 to 200 mg every two weeks. Steady state was reached in 14 to 16 weeks with a 2- to 3-fold accumulation compared to single dose exposure.

For the 150-mg every two weeks dose regimen, the estimated mean (± SD) steady-state AUC, C_{min} and C_{max} of sarilumab were 202 ± 120 mg.day/L, 6.35 ± 7.54 mg/L, and 20.0 ± 9.20 mg/L, respectively.

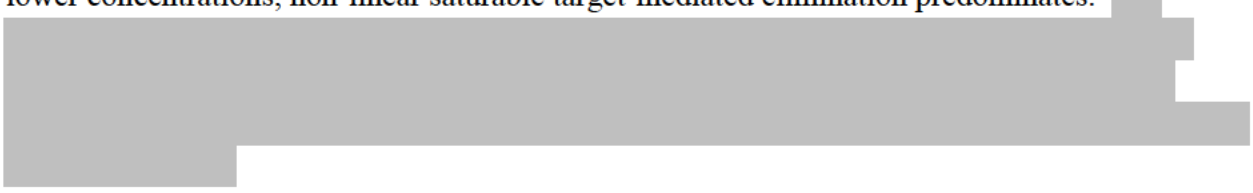
For the 200-mg every two weeks dose regimen, the estimated mean (± SD) steady-state AUC, C_{min} and C_{max} of sarilumab were 395 ± 207 mg.day/L, 16.5 ± 14.1 mg/L, and 35.6 ± 15.2 mg/L, respectively.

Distribution

In patients with RA, the apparent volume of distribution at steady state was 7.3 L.

Elimination

Sarilumab is eliminated by parallel linear and non-linear pathways. At higher concentrations, the elimination is predominantly through the linear, non-saturable proteolytic pathway, while at lower concentrations, non-linear saturable target-mediated elimination predominates. (b) (4)



After the last steady state dose of 150 mg and 200 mg sarilumab, the median times to non-detectable concentration are 28 and 43 days, respectively.

Metabolism

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

Excretion

Monoclonal antibodies are not eliminated via renal or hepatic pathways.

(b) (4) *Specific Populations*

Population pharmacokinetic analyses in adult patients with rheumatoid arthritis showed that age, gender and race did not meaningfully influence the pharmacokinetics of sarilumab. Although body weight influenced the pharmacokinetics of sarilumab, no dose adjustments are recommended for any of these demographics.

Hepatic Impairment

No formal study of the effect of hepatic impairment on the pharmacokinetics of sarilumab was conducted.

Renal Impairment

No formal study of the effect of renal impairment on the pharmacokinetics of sarilumab was conducted. (b) (4)
Based on population pharmacokinetic analysis of data from 1770 patients with RA, including patients with mild (CrCl: 60 to 90 mL/min; N= (b) (4) at baseline) or moderate (CrCl: 30 to 60 mL/min; N= (b) (4) at baseline) renal impairment, CRCL was correlated with sarilumab exposure. However, the effect of CRCL on exposure is not sufficient to warrant a dose adjustment. (b) (4) Patients with severe renal impairment were not studied.

Drug-Drug Interactions

CYP450 Substrates

Simvastatin is a CYP3A4 substrate. In 17 patients with RA, one week following a single 200-mg SC administration of sarilumab, exposure of simvastatin and simvastatin acid decreased by 45% and 36%, respectively *[see Drug Interactions (7.2)]*.

4. APPENDIX

4.1 Pharmacometrics review

1. SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 What are the covariates contributing to the inter-subject PK variability of sarilumab based on population PK analyses? Is dose adjustment warranted with respect to these covariates?

The effect of covariates on PK parameters can be visualized in Figure 19. Body weight, ADA-status, drug product, albumin, sex, creatinine clearance and baseline CRP were identified as significant covariates influencing sarilumab PK. The final PK model retained the effects of weight, ADA, drug product (b) (4) F2 and sex on CL (linear clearance); weight, albumin, BSA-normalized creatinine clearance (CLCRN), baseline CRP (BLCRP) on Vmax (non-linear clearance); and drug product (b) (4) F2 effect on ka.

No dose adjustment was recommended for the starting dose with respect to any of the covariates. Figure 20 and Table 23 summarizes the predicted individual sarilumab steady state exposure (post-hoc analysis, exposure after the last dose) in two Phase 3 studies (EFC11072-Part B and EFC10832) by covariates included in the final PopPK model as well as some other covariates of general interest (i.e., age and concomitant methotrexate). The post-hoc analysis showed that age, sex, race, albumin, baseline CRP and concomitant methotrexate did not meaningfully influence the pharmacokinetics of sarilumab. Compared to ADA negative patients, ADA positive status decreased the steady state AUC0-14, Cmax, and Ctrough by 24%, 18%, and 48% respectively for the 150 mg q2w dose, and 28%, 22%, and 43% respectively for the 200 mg q2w dose. Although body weight and creatinine clearance influenced the pharmacokinetics of sarilumab, no dose adjustments are recommended for any of these demographics, as discussed below.

Renal function (CRCL)

In a categorical analysis by renal impairment category, individual post hoc predicted sarilumab exposures (AUC0-14 days) after repeated 150 and 200 mg, q2w, SC doses were greater by 39% to 43% in patients with mild renal impairment (CLcr of 60 to 90 mL/min) and by 62% to 99% in moderate renal impairment (CLcr of 30 to 60 mL/min), as compared to patients with normal renal function (Figure 20 and Table 23). The effect of creatinine clearance is not considered meaningful for the following reasons:

(a) Creatinine clearance is related to renal function. However, renal elimination pathways are not expected to contribute significantly to the clearance of sarilumab.

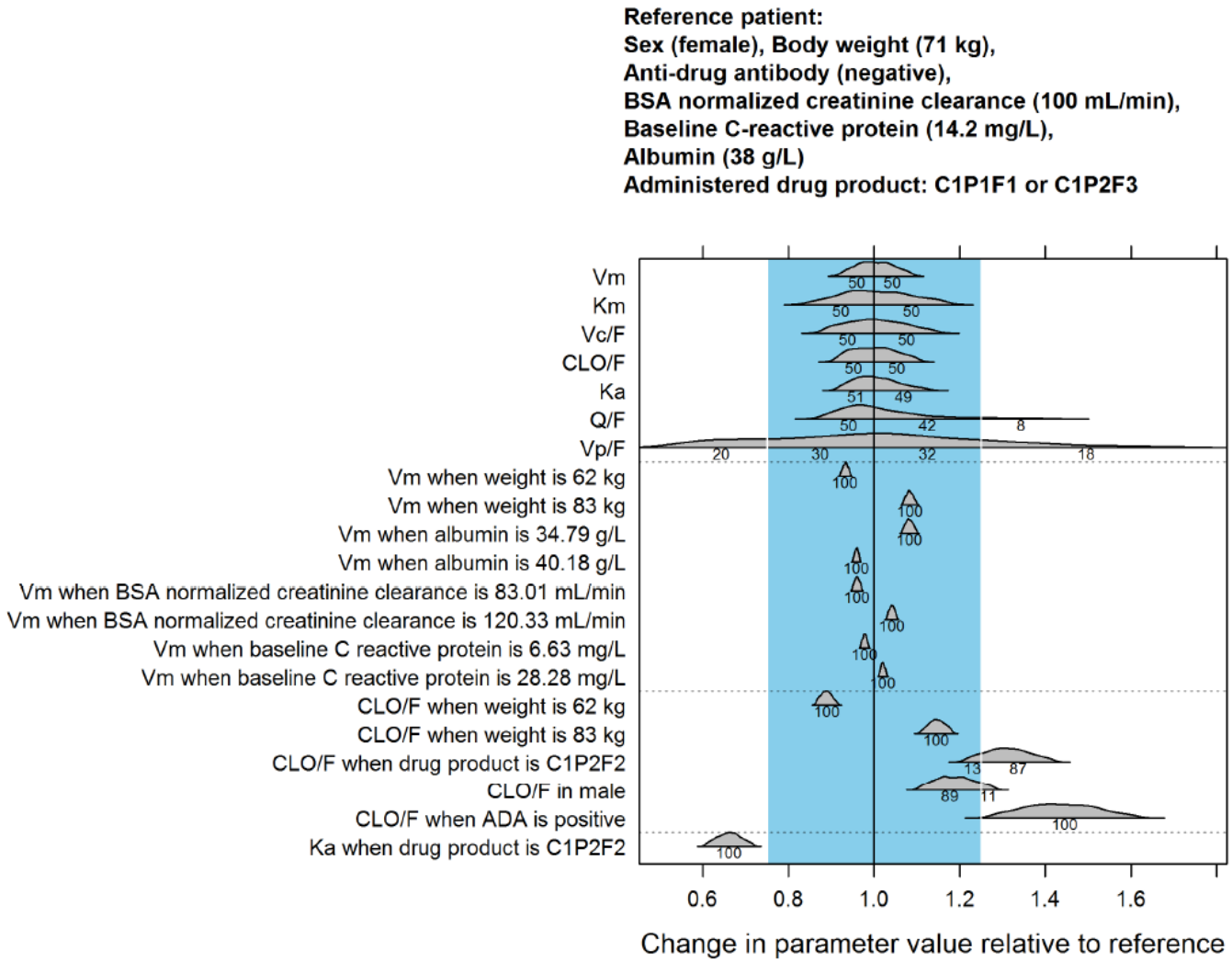
(b) The distributions of 2 covariates impacting sarilumab exposure, body weight and sex, were different among renal function categories. Patients with mild and moderate renal impairment had lower median body weights (66 and 61 kg, respectively) than patients with normal renal function (79 kg), and more patients were female (86% and 90%, respectively) in the renal impairment group compared to patients with normal renal function (80%). Thus, the greater differences in exposure in patients with mild and moderate renal impairment exposures from the post hoc univariate analysis are most likely explained by the indirect effects of 2 confounding factors, body weight and sex, and are unlikely to reflect a direct effect of renal function on sarilumab PK.

(c) The magnitude of the effects of renal impairment on PK are minimal: Based on the final model, a renal patient with CRCL of 30–90 ml/min, will have ~2-21% lower Vmax (maximum target mediated clearance) compared to a typical patient with CRCL of 100 mL/min. [(90/100)^0.212 ; (30/100)^0.212]. CRCL does not affect the linear clearance. Therefore, the overall impact of renal impairment on clearance is not clinically significant and does not require dose adjustment.

(d) Finally, similar safety profiles were observed across the different renal categories (see medical review for details). Therefore no dose adjustments are recommended for patients with mild or moderate renal impairment.

Body weight

See section 1.1.5 of Pharmacometrics review.



*The comparison of PK parameters change was made for each continuous covariate's 25th and 75th percentile versus reference value. A cluster of fold- or percentage-changes at each comparison level (i.e., 5th to 95th percentile, or 90% CI of 1000 bootstraps' values at each comparison level) was represented as kernel smooth density plot. The percentage for this cluster of fold- or percentage-change values falling in different regions with cutoff lines as 1 ± 0.25 was also annotated.

Figure 19. Impact of covariates on PK parameters displayed as ratio- or percentage with 90% CI comparing to a reference patient

(Source: Figure 31, Study report POH0428)

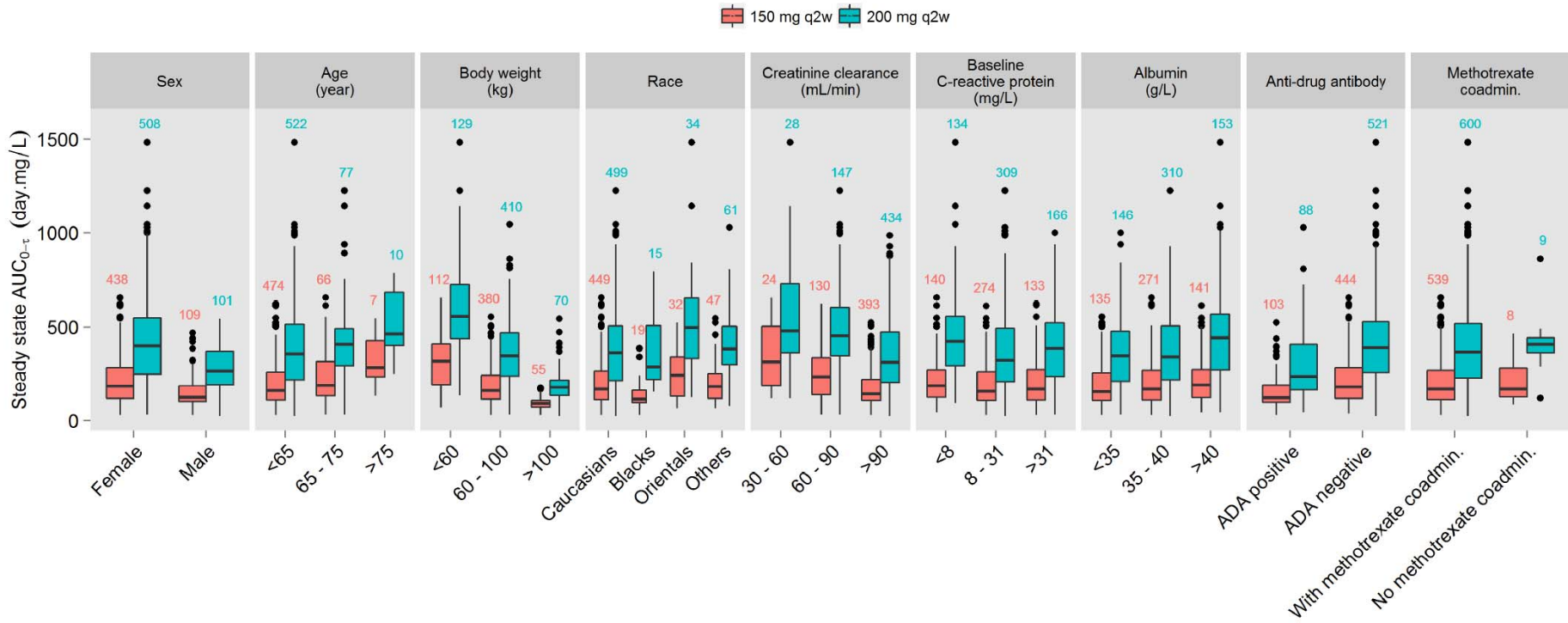


Figure 20. Boxplot of sarilumab AUCtau post repeated dosing in RA patients by covariates included in the final PopPK model and other covariates of general interest (numbers inside plot panel indicate the counts of observed PK parameters in each bin of the specific covariate)

(Source: Figure 26, Study report POH0428)

Table 23. Mean (SD) predicted individual steady state exposure of sarilumab in RA patients in Phase 3 studies(EFC11072-Part B and EFC10832) -150 and 200 mg q2w sarilumab

Covariate [a]		N		$AUC_{0\text{-}14\ day}$ (day.mg/L)		C_{max} (mg/L)		C_{trough} (mg/L)	
		150 mg q2w	200 mg q2w	150 mg q2w	200 mg q2w	150 mg q2w	200 mg q2w	150 mg q2w	200 mg q2w
All		547	609	202 (120)	395 (207)	20 (9.2)	35.6 (15.2)	6.35 (7.54)	16.5 (14.1)
Age (yr)	<65	474	522	195 (113)	388 (205)	19.5 (8.72)	35.1 (15.1)	5.92 (7.14)	16 (13.9)
	65 to 75	66	77	239 (147)	425 (220)	22.4 (11.1)	37.4 (16)	8.78 (9.34)	18.9 (14.9)
	≥75	7	10	327 (146)	516 (186)	30.3 (13.2)	44.1 (13)	12.5 (9.31)	23.9 (14.6)
Weight (kg)	<60	112	129	314 (142)	590 (226)	28.4 (10.3)	49.6 (15.8)	12.8 (10.3)	29.2 (16.5)
	60 to 100	380	410	185 (93.7)	368 (164)	18.8 (7.44)	33.7 (12.4)	5.21 (5.77)	14.5 (11.2)
	≥100	55	70	90.3 (31)	196 (96.4)	11.1 (3.3)	20.8 (8.23)	1.11 (0.83)	4.69 (5.61)
Sex	Male	109	101	151 (86.5)	279 (115)	16.4 (7.52)	27.2 (8.6)	3.51 (4.7)	9.02 (7.34)
	Female	438	508	214 (124)	418 (214)	20.9 (9.37)	37.3 (15.7)	7.05 (7.94)	18 (14.6)
Albumin (g/L)	<35	135	146	195 (124)	364 (191)	19.4 (9.86)	33.3 (14.1)	6.04 (7.4)	14.5 (13)
	35 to 40	271	310	199 (118)	379 (196)	19.8 (9.04)	34.3 (14.3)	6.23 (7.48)	15.7 (13.1)
	≥40	141	153	212 (120)	455 (233)	20.8 (8.86)	40.3 (17.1)	6.86 (7.83)	20.1 (16.2)
CLCR (mL/min)	30 to 60	24	28	350 (169)	569 (302)	31.2 (13)	48 (21.5)	15 (11.1)	28.2 (21.1)
	60 to 90	130	147	252 (130)	488 (209)	23.4 (9.68)	42.3 (15.1)	9.48 (8.9)	22.3 (14.7)
	≥90	393	434	176 (99.6)	352 (182)	18.1 (7.88)	32.5 (13.6)	4.78 (5.97)	13.8 (12.2)
Baseline CRP (mg/L)	<8	140	134	213 (121)	451 (223)	20.7 (9.1)	39.6 (16)	7 (7.67)	20.1 (15.3)
	8 to 31	274	309	193 (113)	371 (204)	19.3 (8.79)	34 (15.4)	5.73 (7.08)	14.9 (13.7)
	≥31	133	166	209 (131)	394 (194)	20.5 (10.1)	35.3 (13.9)	6.93 (8.26)	16.5 (13.3)
ADA	Negative	444	521	213 (123)	412 (206)	20.8 (9.34)	36.8 (15.1)	6.96 (7.86)	17.5 (14.1)
	Positive	103	88	154 (93.3)	295 (185)	16.4 (7.65)	28.1 (13.8)	3.68 (5.23)	10.4 (12.1)
Concomitant methotrexate	Without	8	9	218 (139)	423 (198)	20.1 (10.6)	40.7 (23.8)	7.89 (9.55)	14.7 (8.4)
	With	539	600	201 (120)	395 (208)	20 (9.19)	35.5 (15.1)	6.32 (7.52)	16.5 (14.1)

[a], Includes covariates retained in the final PopPK model (weight, sex, albumin, CLCR, baseline CRP, ADA) as well as covariates of general interest (age, concomitant methotrexate).

(Source: Table 3, summary, study report POH0428)

1.1.2 What are the characteristics of the dose/exposure-response relationship for effectiveness?

Following every week (100 and 150 mg qw) and every other week (100, 150, and 200 mg q2w) dose regimens in the Phase 2 dose-ranging study (EFC11072 Part A), the efficacy (ACR20, ACR50, and ACR70 scores and the DAS28 CRP) was apparent only at concentrations achieved with doses of 150 mg q2w or above (Figure 1, Figure 2). Furthermore, a plateau was reached for all efficacy endpoints at e sarilumab concentrations achieved at the 200 mg q2w dose, with further increase in exposure by as much 2.7-fold (150 mg qw) providing only marginal change in

the responses. Thus, 150 mg q2w and 200 mg q2w doses were considered appropriate for the Phase 3 program.

Table 24. ACR response rates in EFC11072 Part B, Cohort 2 and EFC10832

	EFC11072 Part B, Cohort 2			EFC10832		
	Placebo +MTX (N=398)	**Sarilumab 150 mg q2w + MTX (N=400)**	**Sarilumab 200 mg q2w + MTX (N=399)**	**Placebo +DMARD (N=181)**	**Sarilumab 150 mg q2w + DMARD (N=181)**	**Sarilumab 200 mg q2w + DMARD (N=181)**
ACR 20 at Week 24	33.4%	58.0%	66.4%	33.7%	55.8%	60.9%
ACR 50 at Week 24	16.6%	37.0%	45.6%	18.2%	37.0%	40.8%
ACR 70 at Week 24	7.3%	19.8%	24.8%	7.2%	19.9%	16.3%

(Source: Table 4, clinical overview)

A dose response relationship also was observed for ACR20, ACR50, and ACR70 over the dose range of 150 to 200 mg q2w in the Phase 3 studies (Table 3). Consistent with the dose-response, increased efficacy with respect to ACR20, ACR50, ACR70, CDAI, and DAS28 was observed with increasing exposure (Ctrough) in Phase 3 studies at the within the concentration range observed at 150 mg q2w and 200 mg q2w doses (Figure 3, Figure 4, similar results also shown for study EFC10832, see Pharmacometrics review).

In the Phase 3 studies, the effect at the median serum trough concentration of 200 mg q2w was better than at the median trough concentration of 150 mg q2w for all endpoints (ACR20, ACR50, and ACR70 scores, the HAQ-DI, mTSS, CDAI, and DAS28-CRP) except for the HAQ-DI, where there was a minimal difference. For details see Pharmacometrics review section 2.2.

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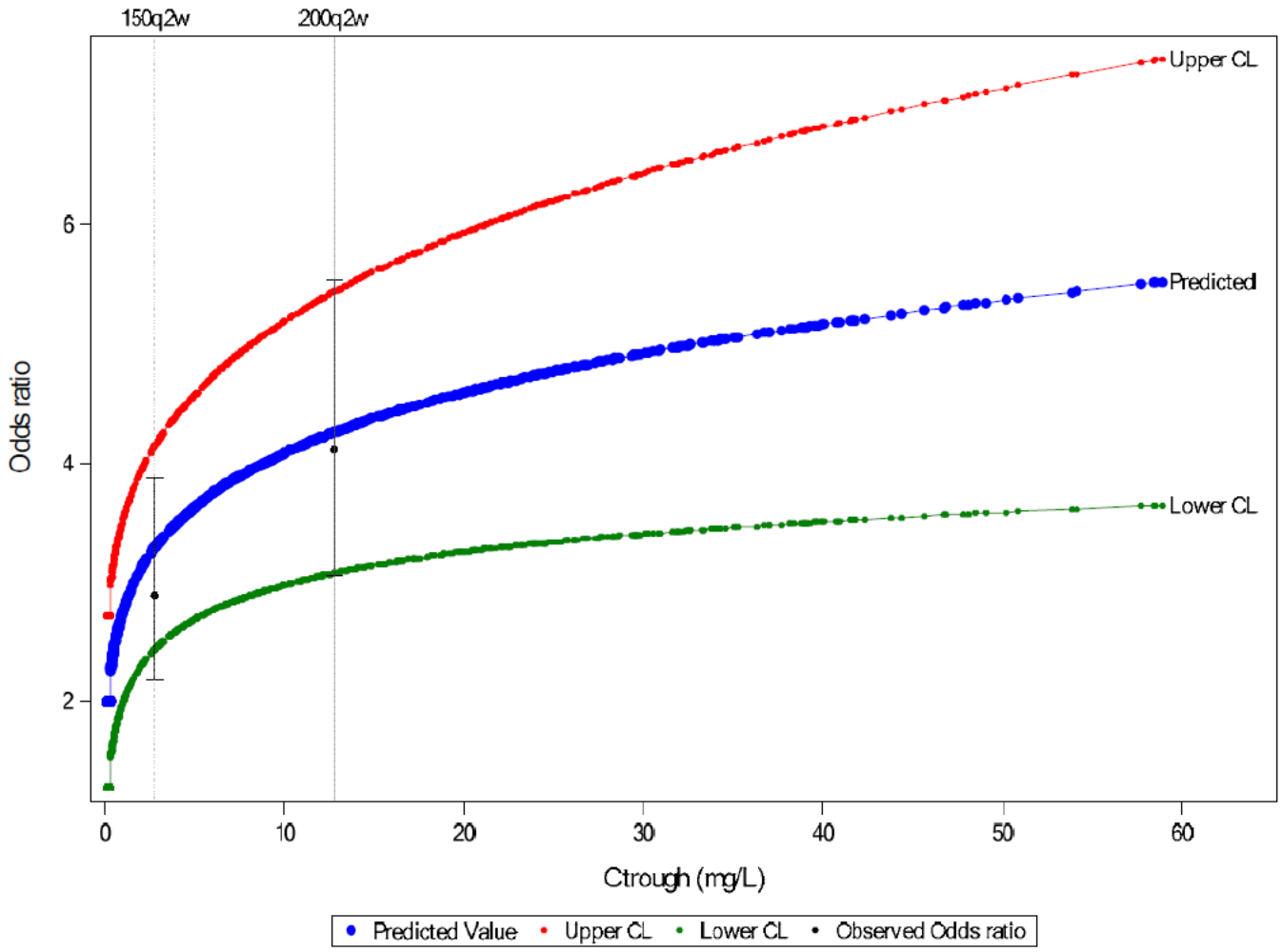

Figure 21. ACR20 responder at Week 24: PK/PD model predicted odds ratio (95% CI) from placebo versus trough concentration of functional sarilumab overlaying with observed treatment odds ratio (95% CI) (EFC11072 Part B Cohort 2)

(Source: Figure 1, study report poh0455)

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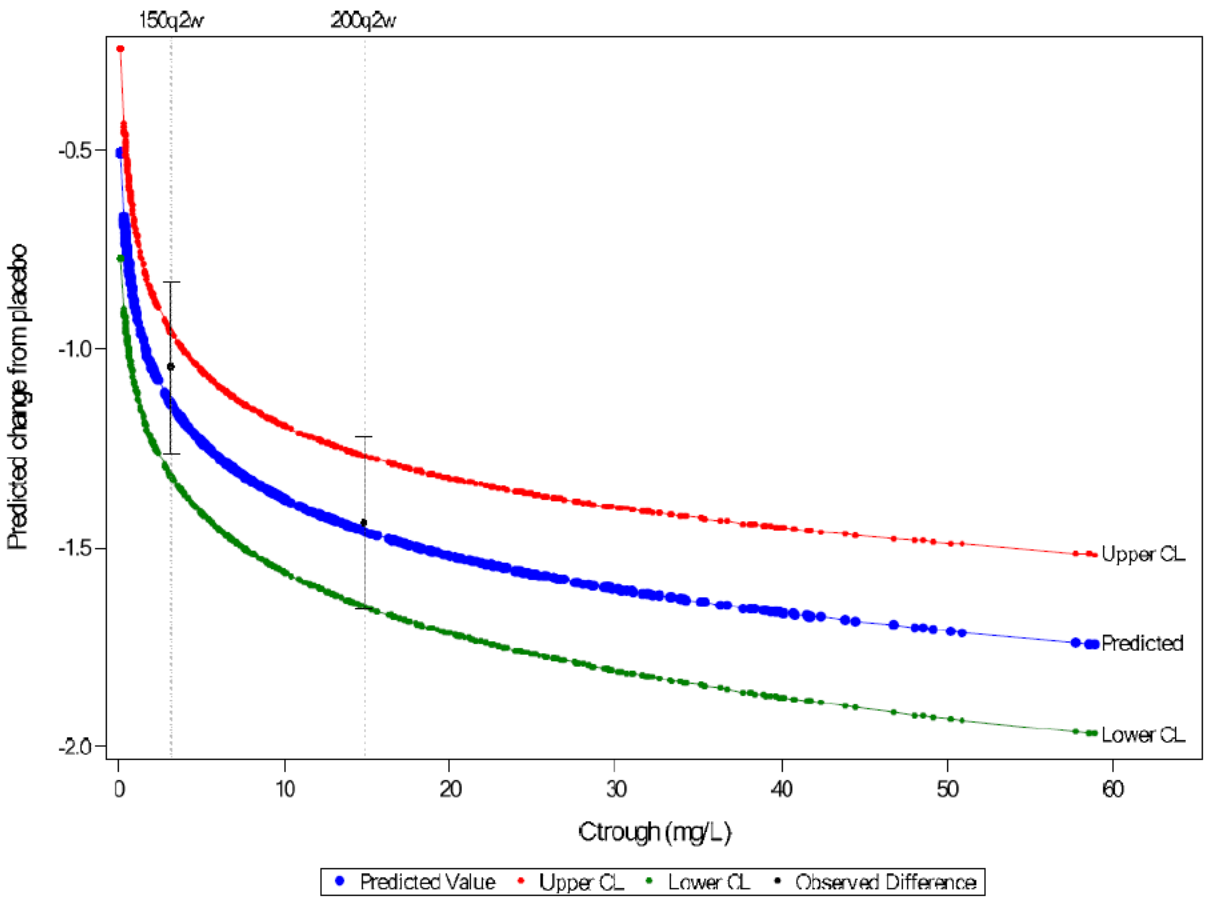

Figure 22. DAS28-CRP change from baseline at Week 24: PK/PD model predicted difference (95% CI) from placebo versus trough concentration of functional sarilumab overlaying with observed treatment difference (95% CI) (EFC11072 Part B Cohort 2)
(Source: Figure 12, study report poh0455)

1.1.3 What are the characteristics of the dose/exposure-response relationship for safety?

There was a slight increase in the incidence of AEs with the 200 mg q2w dose compared to the 150 mg q2w dosing regimen of sarilumab (See medical review). These differences were generally attributable to differences in the incidence of neutropenia (Table 4), which is anticipated based on the pharmacodynamic effects of IL-6 blockade on the peripheral neutrophil count. Consistent with the dose-response, the change from baseline in ANC was related to sarilumab concentration (Figure 5, Figure 6) within the concentration range observed in the Phase 2 and 3 studies at the studied dose regimens (100 and 150 mg qw; 100, 150, and 200 mg q2w). Based on the pharmacodynamics of the changes in ANC (Figure 7), laboratory results should be obtained at the end of the dosing interval when considering dose modification.

The change from baseline in ALT was related to sarilumab concentration (Figure 8). The exposure –response relationship is consistent with the dose-response relationship observed in

Phase 3 studies (150 mg and 200 mg q2w, **Table 4**). Based on the exposure/dose- response relationship for ANC and ALT, dose modification is an appropriate management strategy in the event of laboratory abnormalities that persist at the end of the dosing interval.

Table 25. Overview of lab abnormality TEAEs: number (%) of patients - Placebo-controlled safety population (Pool 1)

		Sarilumab	
	Placebo + DMARD	**150 mg q2w + DMARD**	**200 mg q2w + DMARD**
Total number of patients	**661**	**660**	**661**
Total treatment duration in pt-yrs	**382.3**	**440.7**	**441.4**
Neutropenia	3 (0.5%)	65 (9.8%)	94 (14.2%)
ALT			
> 1 - 1.5 ULN	127/661 (19.2%)	163/659 (24.7%)	178/657 (27.1%)
> 1.5 - 3 ULN	70/661 (10.6%)	124/659 (18.8%)	162/657 (24.7%)
> 3 and ≤ 5 ULN	10/661 (1.5%)	36/659 (5.5%)	31/657 (4.7%)
> 5 and ≤ 10 ULN	1/661 (0.2%)	9/659 (1.4%)	10/657 (1.5%)
> 10 and ≤ 20 ULN	0/661	4/659 (0.6%)	1/657 (0.2%)
> 20 ULN	0/661	0/659	1/657 (0.2%)
Total patients with ≥ 1 Thrombocytopenia (%)	0	6 (0.9%)	11 (1.7%)

(Source: Table 37, 40, 41, summary of clin safety)

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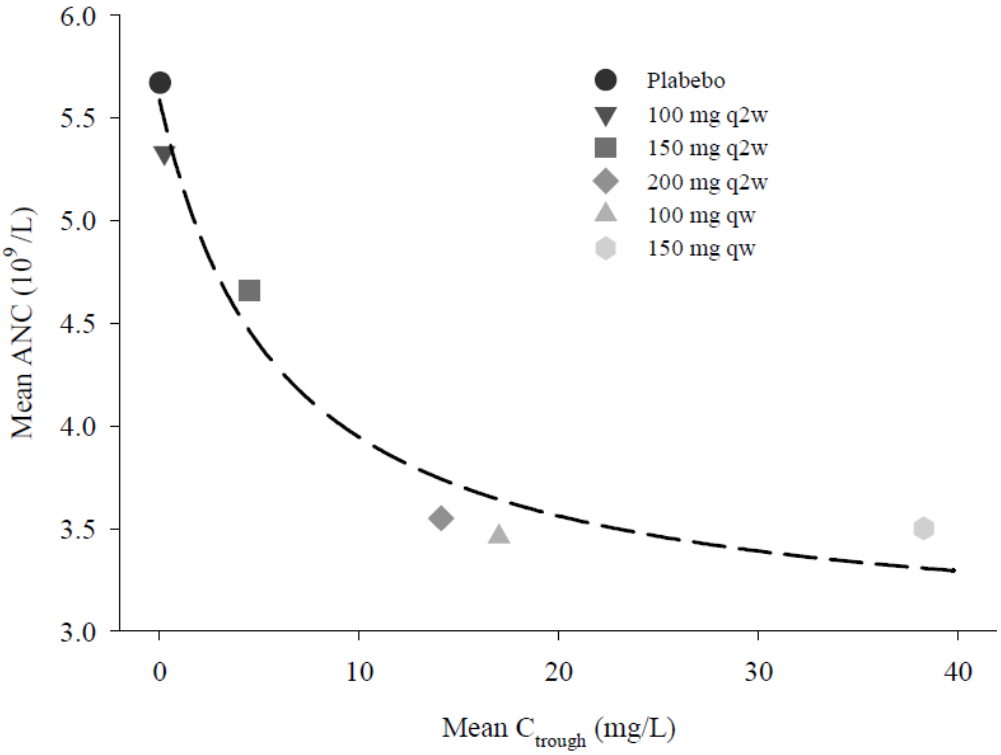

Figure 23. Absolute neutrophil count versus serum trough concentration of functional sarilumab at Week 12 in patients with rheumatoid arthritis (Study EFC11072 Part A)
(Source: Figure 22, summary of clin pharm)

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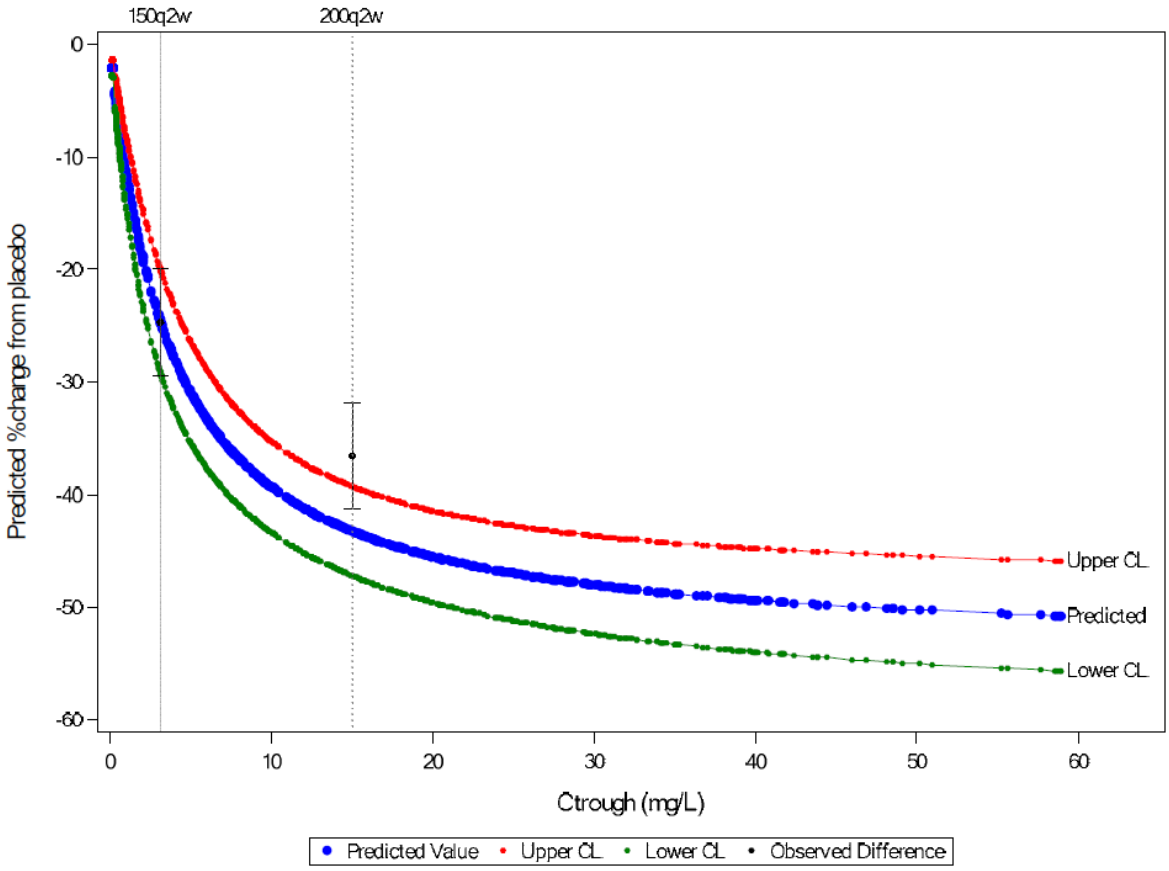

Figure 24. ANC %change from baseline at Week 24: PK/PD model predicted difference (95% CI) from placebo versus trough concentration of functional sarilumab overlaying with observed treatment difference (95% CI) (Safety Pool)
(Source: Figure 15, Study report POH0455)

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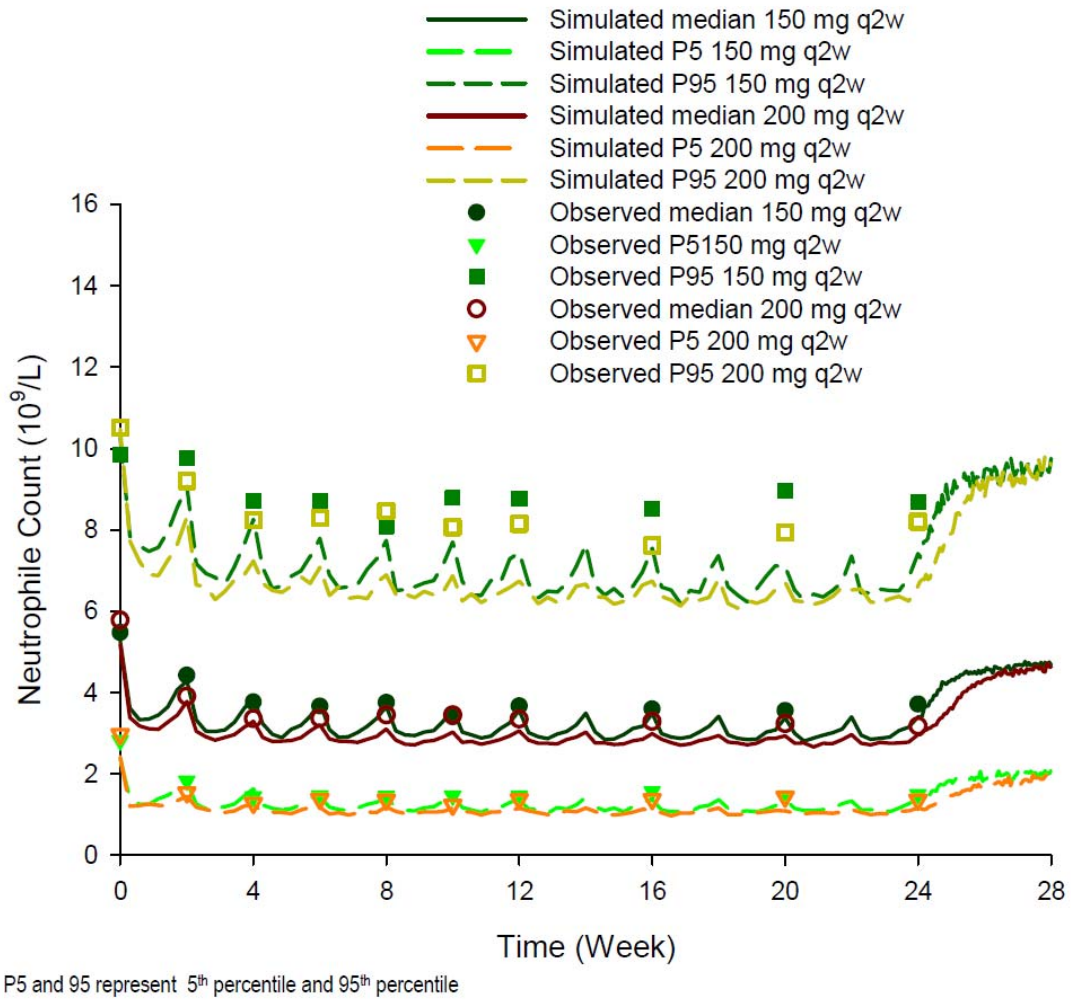

Figure 25. ANC level-time profiles (observed vs model predicted median, 5th and 95th percentiles)
(source: Figure 9, study report POH0429)

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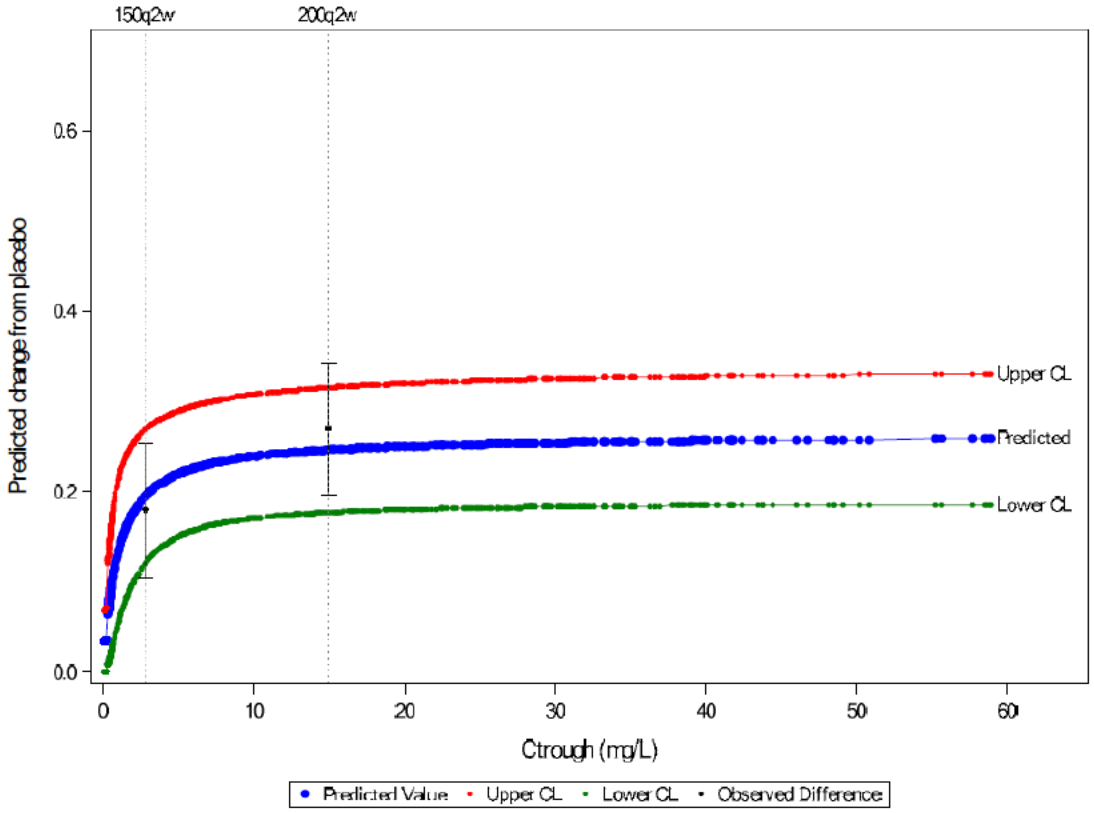

Figure 26. ALT (ULN) change from baseline at Week 24: PK/PD model predicted difference (95% CI) from placebo versus trough concentration of functional sarilumab overlaying with observed treatment difference (95% CI) (Safety Pool)
(Source: Figure 18, Study report POH0455)

1.1.4 Does the dose/exposure-response relationship for effectiveness and safety endpoints support the proposed dose and dose modification scheme?

The proposed dosing regimen for sarilumab seems reasonable. The proposed dosing recommendation is to initiate dosing with sarilumab 200 mg q2w and to decrease the dose to 150 mg q2w for laboratory abnormalities. The proposed dose was supported by a dose ranging study (EFC11072 Part A) and two pivotal phase 3 studies (EFC11072 Part B and EFC10832). There is increased efficacy for the 200 mg q2w compared to a dose of 150 mg q2w and lower in phase 2 and 3 studies (see section 1.1.2). Similar trend was observed in the exposure-response analysis where increased sarilumab exposure is associated with increased efficacy in the observed Phase 3 150 mg q2w and 200 mg q2w concentration range.

For safety, there was a slight increase in the incidence of AEs with the 200 mg q2w dose compared to the 150 mg q2w dosing regimen of sarilumab. Per medical review, the risk/benefit assessment supports the starting dose of 200mg q2w for the proposed indication. Additionally, increased lab abnormalities with increasing dose supports sponsor's dose reduction scheme. Higher proportion of subjects with greater than 3xULN increase in AST, ALT or GGT;

2) thrombocytopenia; 3) neutropenia was observed in the 200 mg q2w dose group compared to the 150 mg q2w dose group. Thus sponsor's dose modification based on lab abnormalities is reasonable.

1.1.5 Based upon what is known about E-R relationships in the target population and their variability, is dosage regimen adjustments required in lower/higher weight group?

The main source of intrinsic PK variability identified in the population PK analysis was body weight, with decreasing body weight resulting in an increase in sarilumab exposure (**Table 26**); however, the effect of body weight on exposure is not sufficient to warrant a dose adjustment.

Table 26. Mean (SD) predicted individual steady state exposure of sarilumab in RA patients in Phase 3 studies(EFC11072-Part B and EFC10832) -150 and 200 mg q2w sarilumab

Covariate [a]		N		$AUC_{0\text{-}14\ day}$ (day.mg/L)		C_{max} (mg/L)		C_{trough} (mg/L)	
		150 mg q2w	200 mg q2w	150 mg q2w	200 mg q2w	150 mg q2w	200 mg q2w	150 mg q2w	200 mg q2w
All		547	609	202 (120)	395 (207)	20 (9.2)	35.6 (15.2)	6.35 (7.54)	16.5 (14.1)
Weight (kg)	<60	112	129	314 (142)	590 (226)	28.4 (10.3)	49.6 (15.8)	12.8 (10.3)	29.2 (16.5)
	60 to 100	380	410	185 (93.7)	368 (164)	18.8 (7.44)	33.7 (12.4)	5.21 (5.77)	14.5 (11.2)
	≥100	55	70	90.3 (31)	196 (96.4)	11.1 (3.3)	20.8 (8.23)	1.11 (0.83)	4.69 (5.61)

(Source: Table 3, summary, study report POH0428)

As 200 mg q2w is the highest dosing regimen assessed in phase 3 studies, and it is efficacious in the higher weight patients (≥100 kg), there is no need for dose adjustment/increase for higher weight patients.

Similar safety profiles were observed across the different weight groups in general (see medical review), so there is no need for dose adjustment/decrease for lower weight patients. In the subgroup analysis of safety, a numerically higher incidence of ANC <1.0 Giga/L was observed in patients with weight <60 kg (17.6%) compared to higher weight patients. However, there is no increase of serious infection in the lower weight group (2.2%). Also, a lower starting dose at 150 mg q2w does not significantly lower the risk of neutropenia (14.1%). Therefore, dose adjustment is not required for the starting dose in patients with weight <60kg.

Also, in the long-term extension study11210, ~20% lower weight patients (<60kg) required a dose reduction from 200 mg q2w to 150 mg q2w due to AE. This is similar to the percentage (~18%) of patients who had dose reduction due to AE in the higher body weight group (60-100kg). This observation confirms that dosage regimen adjustment is not required in the lower weight group.

Table 27. Summary of AE of interest by subgroups during the entire TEAE period - Sarilumab+DMARD long-term safety population (Pool 2)

		Placebo + DMARD (N=661)	Sarilumab 150 mg q2w + DMARD (N=660)	Sarilumab 200 mg q2w + DMARD (N=661)
Serious infection	Weight			
	<60 kg	2/135 (1.5%)	2/128 (1.6%)	3/136 (2.2%)
	≥60 and <100 kg	9/454 (2.0%)	8/467 (1.7%)	11/451 (2.4%)
	≥100 kg	1/72 (1.4%)	2/65 (3.1%)	5/74 (6.8%)
ANC<1G/L	Weight			
	<60 kg	1/135 (0.7%)	18/128 (14.1%)	24/136 (17.6%)
	≥60 and <100 kg	0/454 (0.0%)	20/467 (4.3%)	32/451 (7.1%)
	≥100 kg	0/72 (0.0%)	2/65 (3.1%)	5/74 (6.8%)
ALT>3XULN	Weight			
	<60 kg	2/135 (1.5%)	7/128 (5.5%)	9/136 (6.6%)
	≥60 and <100 kg	7/454 (1.5%)	38/467 (8.1%)	33/451 (7.3%)
	≥100 kg	2/72 (2.8%)	4/65 (6.2%)	1/74 (1.4%)

(source: Table 80, 82, 84, summary of Clin safety)

Table 28. Patients who had dose reduction due to AE by weight group (study 11210)

WT GRP (kg)	Total patients	Patients who had dose reduction due to AE	% Dose reduction patients
<60	353	72	20.40%
>=60 - 100	1437	256	17.81%
>=100	215	25	11.63%

(source: reviewer summary based on dataset:

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1.2 Recommendations

The Division of Pharmacometrics in Office of Clinical Pharmacology has reviewed the information contained in BLA 761037. This BLA is considered acceptable from a Pharmacometrics perspective.

1.3 Label Statements

Please refer to Section 3 - Detailed Labeling Recommendations in clinical pharmacology review.

2. RESULTS OF SPONSOR'S ANALYSIS

2.1 Population PK analysis

Primary objective of sponsor's population PK analysis were:
1. Develop and qualify a population pharmacokinetic (PopPK) model for sarilumab, and describe the PK of sarilumab in RA patients
2. Assess the variability in sarilumab PK and to identify covariates (intrinsic and extrinsic factors) that are potential sources of variability in exposure.
3. Predict individual patient sarilumab exposure to be used in PK-PD analyses for efficacy and safety endpoints.

2.1.1 Methods

Data

Data from 7 Phase1 studies (TDU10809, ACT10804, TDR10805, PKM12058, TDU13402, 6R88-RA-1309 and INT12684), 1 Phase 2 study (EFC11072-Part A), and 4 Phase 3 studies (EFC11072-Part B, SFY13370, MSC12665 and EFC13752) were combined for this population PK analysis. Sarilumab was administered as a single subcutaneous (SC) dose of 50 to 200 mg in rheumatoid arthritis (RA) patient (studies TDU10809, ACT10804, PKM12058, TDU13402, 6R88-RA-1309, and INT12684) or as SC doses every week (qw) and every two weeks (q2w) of 50 to 200 mg in RA patients (studies TDR10805, EFC11072, SFY13370, MSC12665 and EFC13752). Actual dosing data were used in the analysis.

The Initial Data Set available for PopPK analysis consisted of 1770 patients with 7692 observations after excluding the predose, BQL (below the lower limit of quantification, LLOQ) and placebo treatment samples.

The sampling scheme for the these studies is shown in Figure 27.

A. Distribution of sampling time points from first dose by study (n=1935 patients)

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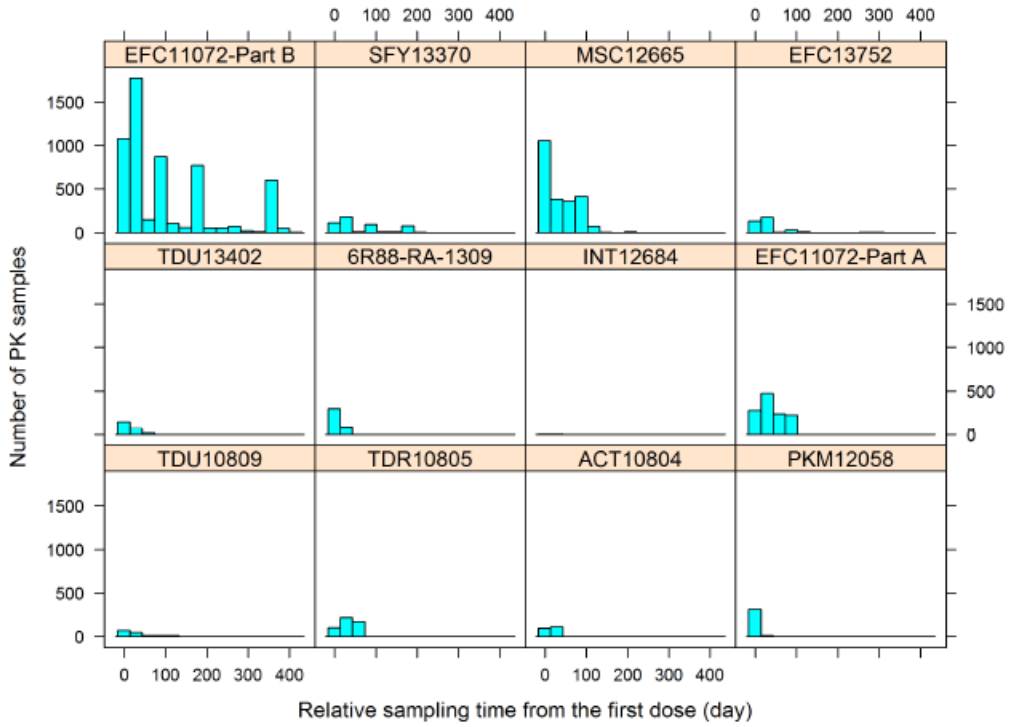

B. Distribution of sampling time points from last dose by study (n=1935 patients)

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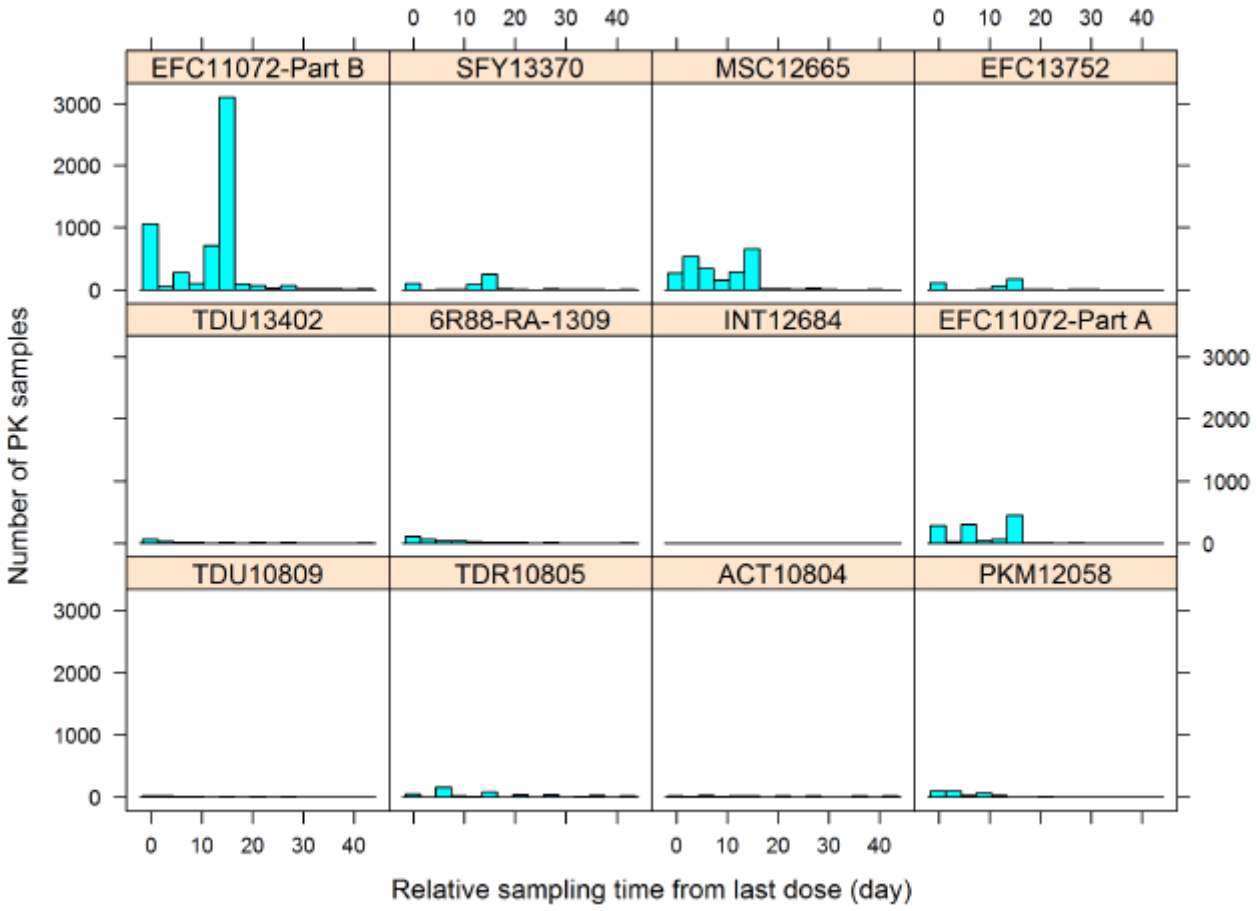

Figure 27. Sampling scheme by study
(Source: Figure 2 and 3 from study report POH0428)

Model Development

The model development was based on the PK analysis dataset and was separated into three steps: base model development, covariate model development and development of the final model.

The selection of structural PK model was driven by general knowledge of PK characteristics of drugs that are also monoclonal antibodies and have mechanism of action similar to sarilumab, goodness-of-fit (GOF) plots and stability of model. Different structural PK models (TMDD with M-M or QSS approximation) and different residual error models (proportional and combined) were evaluated. Models were fitted to the data using a log transform both sides (LTBS) approach, and the base model of sarilumab was established.

The relationship between the individual estimates and the below covariates was then investigated. The continuous covariates assessed were time-varying except baseline DAS28-CRP and baseline CRP. The only time-varying categorical covariate was immunogenicity.

- Demographic characteristics: age, sex, weight (WT), body mass index (BMI) and race.
- Renal function: serum creatinine and body surface area (BSA) normalized creatinine clearance as calculated by Cockraft- Gault formula (CLCRN).
- Liver function/injury parameters normalized to their respective upper limit of normal (ULN): aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (ALB) and total bilirubin.
- Disease status: baseline DAS28-CRP.
- Biomarker: baseline c-reactive protein (BLCRP)
- Prior and concomitant treatment: prior biologics treatment and methotrexate.
- Immunogenicity status: patient level and sample level (time-varying) for anti-drug antibody (ADA) and neutralizing antibody (NAb).
- Drug product: difference in cell line used to produce drug substance, manufacturing process in combination with different formulations, namely - (b) (4) F1 (used in Phase 1 studies only), (b) (4) F2 (used in some Phase 1 studies and the dose ranging Phase 2 study), or (b) (4) F3 (used in Phase 3 studies and planned to-be-marketed drug product).

Potential covariates were identified using a standard forward-addition and backward-deletion strategy. Briefly, these covariates were added individually (forward-addition) to the model and tested for statistical significance using a p-value of 0.01. Only covariates providing a significant decrease of the objective function value (OFV) were included in the full model and then tested in a backward-deletion step using a p-value of 0.001. The covariates that were associated with an increase in OFV of ≥ 10.8 ($p<0.001$) when deleted were retained in the final model. The population parameters were then re-estimated considering the relationship with the covariates.

The validation of the final PopPK model was performed using different approaches (bootstrap method and visual predictive check [VPC]). Finally, individual sarilumab exposure up to the last dose was calculated using an empirical Bayesian estimation approach (maximum a posteriori probability [MAP] estimate) to support the sequential exposure response analysis for various studies, including EFC10832 that was not included in model building.

2.1.2 Results

The base PK model was a Michaelis-Menten (M-M) approximation of the TMDD model, specifically a two-compartment model with first order absorption from the depot (with absorption rate constant, Ka) to the central compartment and parallel linear and nonlinear (i.e., M-M) elimination from the central compartment with inter-individual variability (η) on apparent linear clearance from central compartment (CLO/F), apparent central volume of distribution (Vc/F), absorption rate constant (Ka) and maximum elimination rate (Vm).

The final PK model includes the covariates as listed below:
- Body weight (WT), albumin normalized to the upper limit of normal (ALBR), BSA-normalized creatinine clearance (CLCRN), baseline CRP (BLCRP) effect on Vm.

- WT, ADA (time-varying), drug product [(b) (4)] F2 and sex effect on CLO/F.
- [(b) (4)] F2 effect on Ka.

$$Vm = \theta_1 \cdot (\frac{WT}{71})^{\theta_{11}} \cdot (\frac{ALBR}{0.78})^{\theta_{12}} \cdot \left(\frac{1.73 \cdot \frac{CLCR}{BSA}}{100} \right)^{\theta_{13}} \cdot (\frac{BLCRP}{14.2})^{\theta_{18}} \exp(\eta_1)$$

$$Km = \theta_2$$

$$\frac{Vc}{F} = \theta_3 \cdot \exp(\eta_3)$$

$$\frac{CLO}{F} = \theta_4 \cdot (\frac{WT}{71})^{\theta_{10}} \cdot (\theta_{15})^{ADA} \cdot (\theta_{16})^{C1P2F2} \cdot (\theta_{17})^{SEX} \exp(\eta_2)$$

$$Ka = \theta_5 \cdot (\theta_{14})^{C1P2F2} \cdot \exp(\eta_4)$$

$$\frac{Q}{F} = \theta_6$$

$$\frac{Vp}{F} = \theta_7$$

where 71, 0.78, 100 and 14.2 are the median values in the Final Dataset for WT (kg), ALBR, CLCRN (mL/min) and baseline CRP (mg/L), respectively.

Figure 28. Final pop PK model
(Source: Page 6, study report POH0428)

The PK of sarilumab in RA patients was adequately described by a two-compartment model with first order absorption from the depot (site of SC administration) to the central compartment and parallel linear and nonlinear elimination from the central compartment. Inter-individual variability was estimated for maximum elimination rate (Vm), linear clearance (CLO/F), volume of central compartment (Vc/F), and absorption rate constant (Ka), together with an additive residual error for Log-transformed sarilumab concentration. The parameter estimates from the final model are shown in Table 29. The goodness of fit plots for the model is shown in Figure 29.

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Table 29. Sarilumab population pharmacokinetic model for the Final Data Set (n = 1770 RA patients)

Parameter	Estimate	RSE (%)	Median [95%CI] from bootstrap	Shrinkage (%)
θ_1 (Vm, mg/day)	8.06	1.96	8.10 [7.34; 8.95]	n/a
θ_2 (Km, mg/L)	0.939	4.38	0.925 [0.751; 1.12]	n/a
θ_3 (Vc/F, L)	2.08	3.20	2.12 [1.81; 2.48]	n/a
θ_4 (CLO/F, L/day)	0.260	5.36	0.259 [0.230; 0.290]	n/a
θ_5 (Ka, day^{-1})	0.136	2.53	0.137 [0.123; 0.160]	n/a
θ_6 (Q/F, L/day)	0.156	3.87	0.160 [0.138; 0.252]	n/a
θ_7 (Vp/F, L)	5.23	5.98	5.13 [2.60; 10.1]	n/a
θ_{10} (WT effect on CLO/F)	0.885	12.0	0.876 [0.604; 1.12]	n/a
θ_{11} (WT effect on Vm)	0.516	9.45	0.510 [0.407; 0.643]	n/a
θ_{12} (ALBR effect on Vm)	-0.844	5.49	-0.839 [-1.05; -0.653]	n/a
θ_{13} (CLCRN effect on Vm)	0.212	9.59	0.219 [0.149; 0.290]	n/a
θ_{14} ([(b) (4)]F2 effect on Ka)	0.663	4.38	0.662 [0.594; 0.730]	n/a
θ_{15} (ADA effect on CLO/F) [a]	1.43	3.05	1.43 [1.25; 1.67]	n/a
θ_{16} ([(b) (4)]F2 effect on CLO/F)	1.30	4.48	1.31 [1.19; 1.45]	n/a
θ_{17} (SEX effect on CLO/F)	0.846	4.74	0.841 [0.770; 0.915]	n/a
θ_{18} (BLCRP effect on Vm)	0.0299	23.0	0.0293 [0.0146; 0.0454]	n/a
Interindividual variability (CV %)				
Vm [b]	32.4	6.07	31.8 [27.2; 35.2]	29.8
CLO/F [b]	55.3	6.21	54.2 [44.0; 65.6]	42.8
Vc/F [b]	37.3	16.7	37.9 [27.0; 51.4]	64.2
Ka [b]	32.1	9.52	32.5 [27.1; 43.2]	49.6
Block Vm- CLO/F [c]	-0.566	10.8	-0.557 [-0.668; -0.405]	n/a
Residual variability				
σ^2 (studies other than EFC11072) [d]	0.395	0.811	0.393 [0.366, 0.421]	n/a
σ^2 (study EFC11072) [d]	0.554	0.743	0.553 [0.519, 0.591]	n/a

Vm: maximum elimination rate from central compartment; Km: Michaelis-Menten constant; Vc/F: apparent volume of central compartment; CLO/F: apparent linear clearance from central compartment; Ka: absorption rate constant; Q/F: apparent inter-compartmental clearance; Vp/F: apparent peripheral volume of distribution; WT: body weight; ALBR: albumin normalized to upper limit of normal; CLCRN: BSA normalized creatinine clearance; [(b) (4)]F2: drug product; ADA: anti-drug antibody; BLCRP: baseline c-reactive protein; RSE: Percentage of Relative Standard Error (100 x SE / Estimate); 95%CI: 95% confidence interval (i.e., 2.5th and 97.5th percentile); n/a: Not applicable.

[a], ADA was time-varying.

[b], inter-individual variability are expressed as coefficient of variation (CV %).

[c], estimate of covariance between two variances is expressed as correlation coefficient.

[d], Variance of residual error is based on the Log-transformed dependent variable (i.e., sarilumab concentration).

(Source: Table 2, study report POH0428)

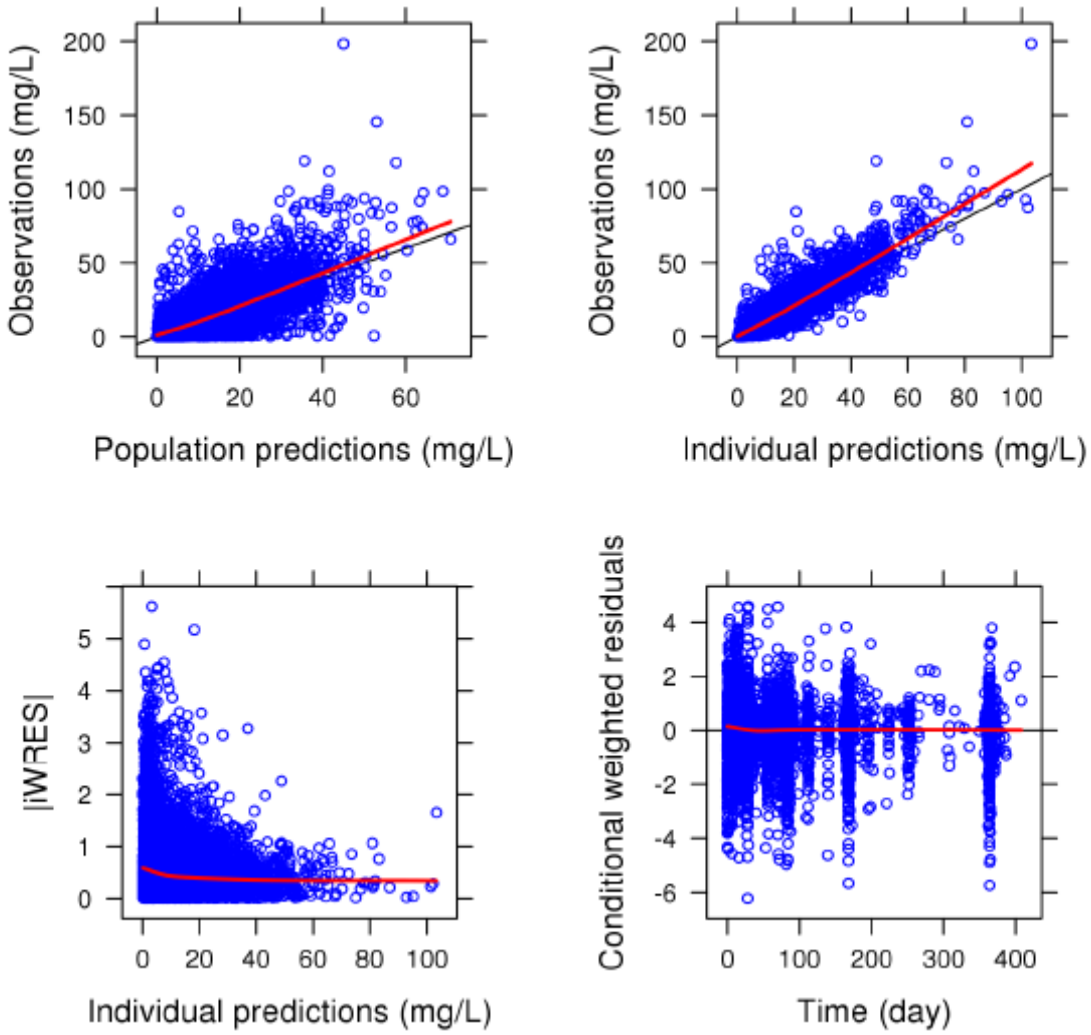


Figure 29: goodness-of-fit plot with Lowess Smooth (red lines) from final model

(Source: Figure 16, Study report POH0428)

The absolute bioavailability for sarilumab

The bioavailability for sarilumab SC injection was calculated using the Final Data Set in combination with the PK data in RA patients post single intravenous injection of sarilumab (study TDU10808). There are 6 patients using IV injection in the dataset. Four patients (2 males and 2 females) received 0.6 mg/kg and 2 female patients received 2.0 mg/kg of sarilumab. The absolute bioavailability for sarilumab SC injection was estimated to be ~80% for the to-be-marketed product ([(b) (4)]F3) based on the final pop-PK model (cross study comparison).

The effect of covariates on PK parameters

See section 1.1.1.

Steady state and accumulation ratio

The time to steady state in a typical patient, estimated from population PK analysis, was 14 to 16 weeks for AUC0-14 days and 18 to 20 weeks for Ctrough. The accumulation ratios, based on post hoc individual predicted PK parameters, were determined to be 2.3 and 2.5 for AUC0-14 days and 2.6 and 3.0 for Ctrough after sarilumab 150 and 200 mg q2w dosing regimens, respectively. This is consistent with the observed Ctrough data, with steady state reached between week 12 to week 24, with ~ 3-4 fold accumulation.

Summary of findings based on population PK analysis:

1. The PK of sarilumab in RA patients was adequately described by a two-compartment model with first order absorption from the depot (site of SC administration) to the central compartment and parallel linear and nonlinear elimination from the central compartment.
2. Body weight, ADA-status, drug product, albumin, sex, creatinine clearance and baseline CRP were identified as significant covariates influencing sarilumab PK, although none were deemed clinically significant. No dose adjustments are necessary with respect to these covariates (See section 1.1.1).
3. The absolute bioavailability of the to-be-marketed sarilumab product ((b) (4) F3) via SC route was estimated to be ~80%.
4. Sarilumab showed approximately three-fold accumulation (accumulation ratio was calculated as the ratio of individual predicted Ctrough at steady state divided by the Ctrough at Week 2 predose) and steady-state was achieved by Week 20 following dosing every two weeks.

Reviewer's Comments:

1. *A rigorous analysis assessing the of the covariate effects on sarilumab exposure was performed using population PK methodology. Residual diagnostics based on the sponsor's analyses showed that the model fitted the data reasonably well. With regard to the covariates chosen, the reviewer's analysis of sarilumab resulted in similar results with similar parameter estimates. Therefore, the reviewer concludes the analysis, and the corresponding conclusions and interpretations, presented by the sponsor is reasonable.*

2. *It is expected that body weight is a covariate for the PK of sarilumab as monoclonal antibody is degraded by proteolysis throughout the body. Sarilumab shows conventional allometric scaling typically seen for protein drugs.*

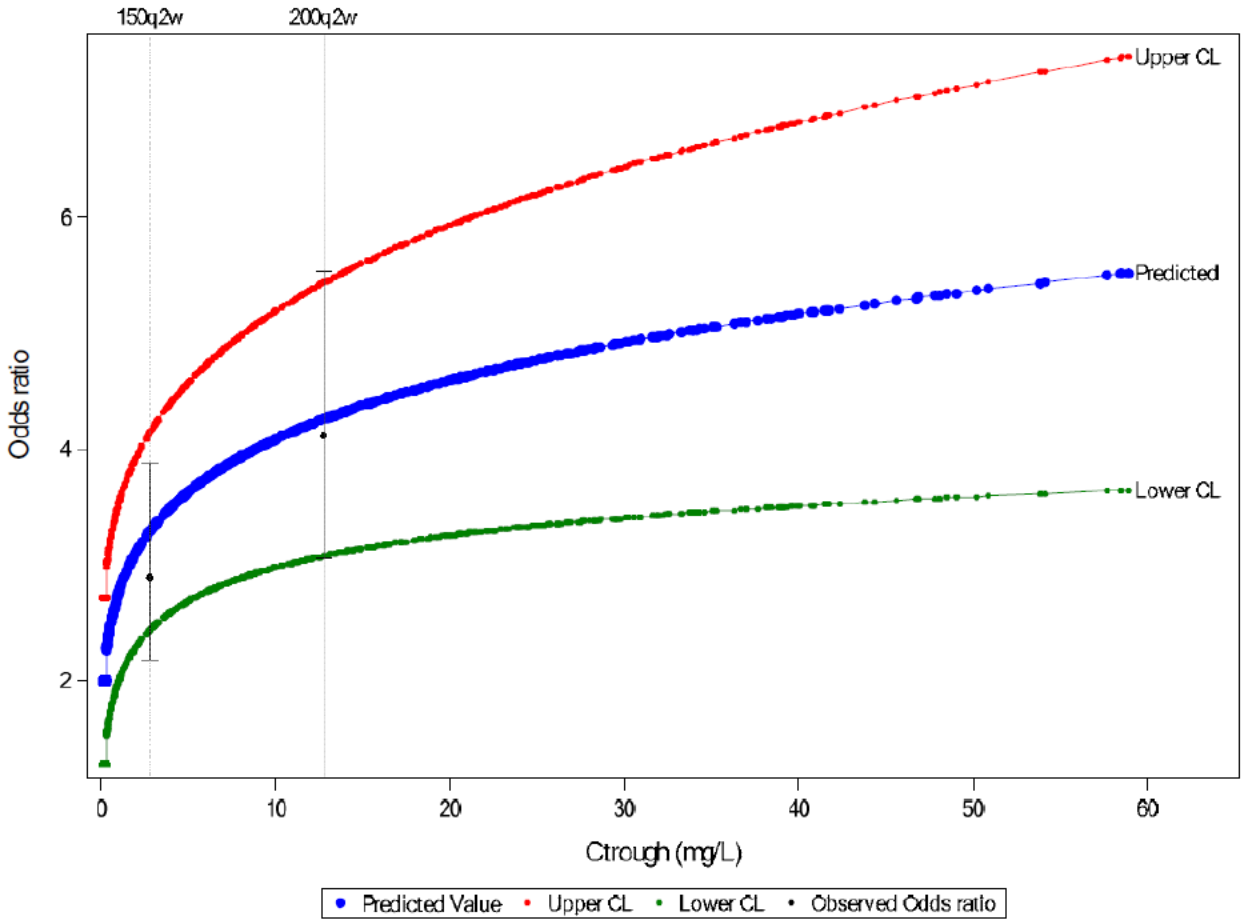
3. *The data from IV injection is limited. Also, the IV doses were different from the SC doses in the cross-study comparison. As sarilumab PK is non-linear, it is reasonable to derive absolute bioavailability based on pop PK analysis.*

2.2 E-R analysis for efficacy

2.2.1 E-R analysis for ACR 20, 50 70 at week 24

A log-linear model well described the exposure-response relationships between efficacy endpoints ACRn and functional sarilumab trough concentration in RA patients. The model was fit for data from study EFC11072 Part B and study EFC10832 separately. For both studies, there was a trend for a greater ACR20 response as the trough concentration increased in the observed concentration range (Figure 30 and Figure 31). The PK/PD model predicted mean treatment differences from placebo of 150 mg q2w and 200 mg q2w doses (predicted at the median trough concentration) , which consistent in trend with observed differences from placebo of 150 mg q2w and 200 mg q2w. Baseline DAS28-CRP was identified and included in the model. Sarilumab-treated patients had higher probability to become responders when they had higher baseline DAS28-CRP.

Similar analysis done for ACR50 and 70 also indicated a trend of increasing efficacy for these endpoints with increased concentration in the observed Phase 3 150 mg q2w and 200 mg q2w concentration range (data not shown).

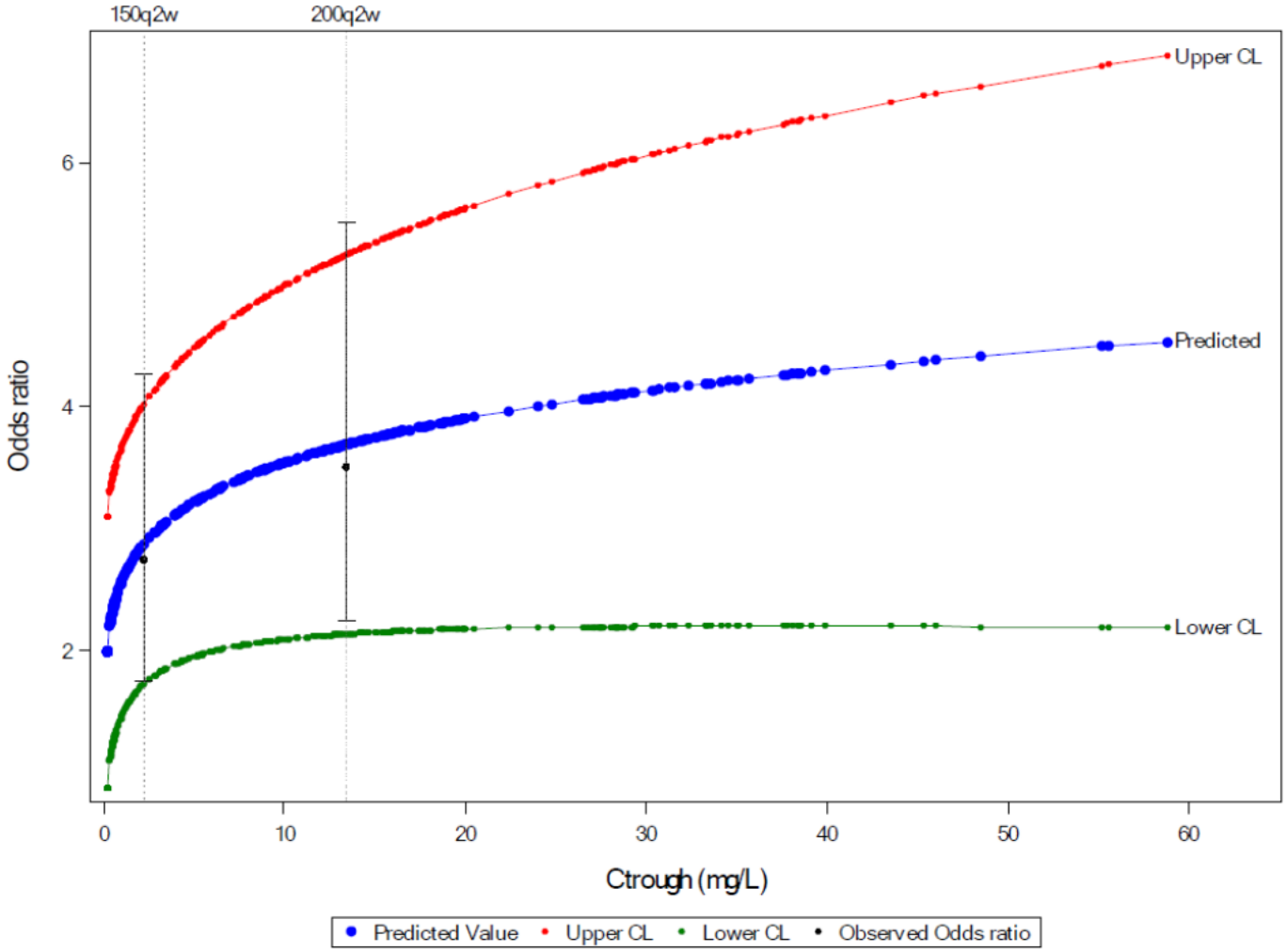


Dose	Observed Odds ratio	PK/PD Predicted Odds ratio	Median C_{trough} (mg/L)
150mg q2w	2.898 (2.167 , 3.876)	3.299 (2.444 , 4.154)	2.8300
200mg q2w	4.113 (3.055 , 5.536)	4.26 (3.08 , 5.44)	12.8000

Patients with both efficacy and PK data were included in the analysis, which is a subset of ITT population. # of patients at week 24: placebo=397,150mg q2w=397, 200mg q2w=393. Observed treatment odds ratios are based on a logistic regression model with biological use, region and treatment. PK/PD model predicted odds ratios are based on a logistic regression PK/PD model with biological use, region, age, RA class, placebo effect and C_{trough} in natural log scale.

Figure 30. ACR20 responder at Week 24: PK/PD model predicted odds ratio (95% CI) from placebo versus trough concentration of functional sarilumab overlaying with observed treatment odds ratio (95% CI) (EFC11072 Part B Cohort 2)

(Source: Figure 1, study report poh0455)



Dose	Observed Odds ratio	PK/PD Predicted Odds ratio	Median C_{trough} (mg/L)
150mg q2w	2.74 (1.757 , 4.273)	2.876 (1.73 , 4.023)	2.2400
200mg q2w	3.512 (2.241 , 5.504)	3.691 (2.135 , 5.247)	13.4492

Patients with both efficacy and PK data were included in the analysis, which is a subset of ITT population. # of patients at week 24: placebo=181,150mg q2w=179,200mg q2w=180. Observed treatment odds ratios are based on a logistic regression model with biological use, region and treatment. PK/PD model predicted odds ratios are based on a logistic regression PK/PD model with biological use, region, baseline DAS28-CRP, placebo effect, C_{trough} in natural log scale and an interaction of baseline DAS28-CRP and C_{trough} in natural log scale.

Figure 31. ACR20 responder at Week 24: PK/PD model predicted odds ratio (95% CI) from placebo versus trough concentration of functional sarilumab overlaying with observed treatment odds ratio (95% CI) (EFC10832)

(Source: Figure 4, study report poh0455)

2.2.2 E-R analysis for DAS28

DAS28-CRP is a continuous measure allowing for measurement of absolute change in disease burden and percentage improvement. It is a composite score that includes 4 variables:

- tender joints count (based on 28 joints)
- swollen joints count (based on 28 joints)
- general health assessment (GH) by the patient assessed from the ACR RA core set questionnaire (patient global assessment)
- marker of inflammation assessed by the hs-CRP (mg/L)

The DAS28-CRP can be calculated using the following formula:

$$\text{DAS28-CRP} = 0.56 \times \sqrt{28TJC} + 0.28 \times \sqrt{28SJC} + 0.36 \times \text{Log}(\text{CRP}+1) + 0.014 \times \text{GH} + 0.96$$

The DAS28-CRP provides a number indicating the current activity of the RA. A DAS28-CRP above 5.1 means high disease activity, whereas a DAS28-CRP below 3.2 indicates low disease activity and a DAS28-CRP below 2.6 means disease remission.

2.2.2.1 Methods

Analysis Dataset

The dataset for exposure-response analysis contained DAS28 measurements from a total of 2082 subjects (17229 DAS28 observations, **Table 30**). The individual PK parameters from final pop PK analysis (POH0428) were used in this two-step PopPK/PD analysis. Only the DAS28-CRP levels were used as dependent variable in the analysis.

Table 30. Description of studies included in DAS28 analysis

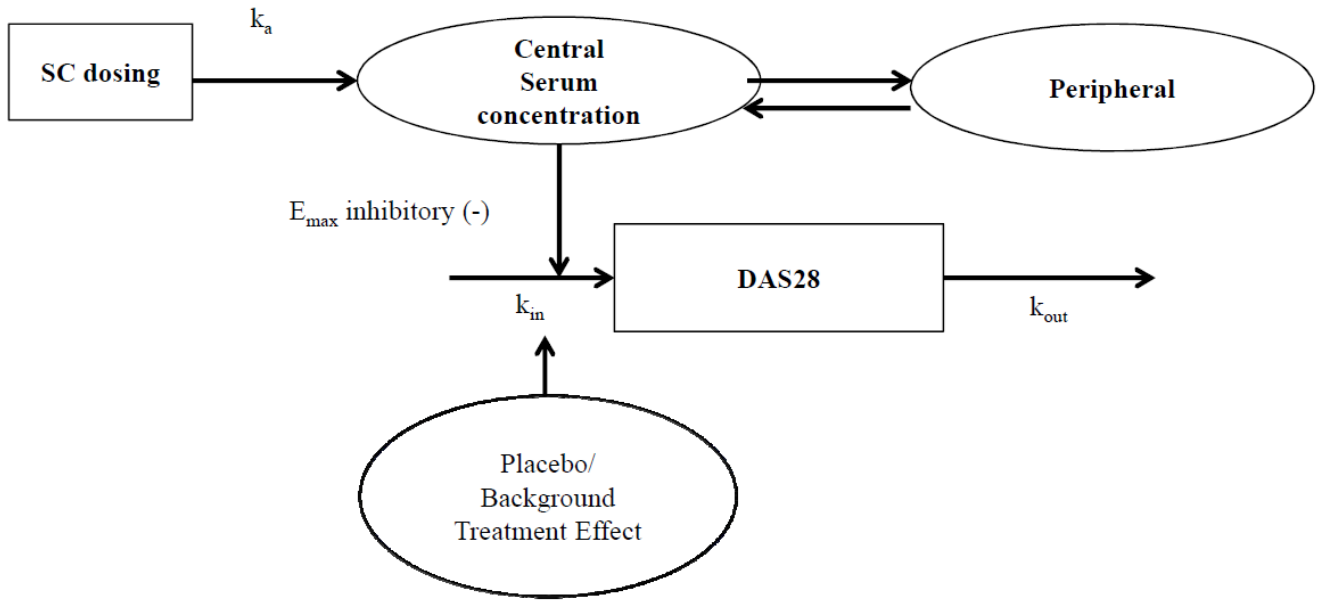
Study	Dose and Regimen	Population	N	PK and PD Sampling	No. of Patients in the PopPK/PD analysis
EFC11072 (MOBILITY)-Part A (Phase 2)	Placebo, 100 mg SC qw, 150 mg SC qw, 100 mg SC q2w, 150 mg SC q2w and 200 mg SC q2w, 12 weeks treatment duration	RA patients with MTX-IR	≈ 50 patients / arm	Sparse sampling	254
EFC11072 (MOBILITY)-Part B (Phase 3)	Placebo, 150 mg SC q2w, 200 mg SC q2w, 52 weeks treatment duration	RA patients with MTX-IR	≈ 350 patients / arm	Sparse sampling	1284
EFC10832 (TARGET) (Phase 3)	Placebo, 150 mg SC q2w, 200 mg SC q2w, 24 weeks treatment duration	RA patients with anti-TNF-IR	≈174 patients / arm	Sparse sampling	544

IR= inadequate response, MTX= methotrexate, TNF= tumor necrosis factor

(source: Table 1. Study report POH0446)

Model building

Based on an exploratory PopPK/PD analysis, the time-course of DAS28 was described by an indirect-response model with inhibition of production rate (Kin) driven by serum sarilumab concentrations. Sarilumab was assumed to inhibit 'production' of DAS28 via an Emax function (Figure 32).



$$d(DAS28\text{-}CRP)/dt = kin\ (1 - Eff(C)) - kout \times DAS28\text{-}CRP$$

$$Eff(C) = Emax \times (C+PLB)^{\gamma} / (IC50^{\gamma} + (C+PLB)^{\gamma})$$

E_{max} was modeled using LEmax, a log transformed parameter for Emax:

$$E_{max} = EXP(Emax) / (1+EXP(Emax))$$

Where, C = concentration, Emax = maximum drug inhibition effect, γ = hill coefficient for sigmoidicity, IC50 = concentration at 50% of Emax, kin = first order rate constant of DAS28-CRP production rate, kout = first order rate constant for loss of DAS28-CRP response, PLB = placebo/background treatment effect of concomitant DMARDs in sarilumab concentration units.

Figure 32. Model structure for exposure response analysis of DAS28-CRP
(Source: Page 31, study report PPOH0446)

Full model with backward elimination was used to identify the final covariate model. The full and/or final model development was assisted by the additional graphical exploration of the measured covariate values vs estimates of individual random effects from the full model. During backward elimination, (1) precisely estimated covariates with clinically insignificant effects and (2) covariates with effects close to null value and/or with high relative standard error and/or with the 95% confidence intervals that included the null value were excluded from the final model. Only the

covariates associated with a significant change of the objective function with a p value < 0.001 were retained in the final model. Increase of objective function value by less than 10.83 at a single covariate elimination was used as a criterion to exclude covariates.

The following covariates were screened for their effects on efficacy: age, weight, baseline Creactive protein (CRP) and IL6, baseline DAS28, baseline physicians global score of disease activity (PHYVAS), baseline values of health assessment questionnaire (HAQ), The rationale for exploring these covariates was based on clinical importance and mechanistic plausibility.

2.2.2.2 Results

The final PopPK/PD model included 4 covariates on baseline DAS28-CRP or BASE (baseline CRP or BLCRP, baseline PHYVAS or BLVAS, baseline HAQ-DI or BLHAQ, and body weight or WT), 1 covariate on Emax (baseline CRP or BLCRP), and 1 on kout (PRICORT) according to the following equations:

$$BASE = 6.06 * (BLCRP/15.7)^{**}0.0564 * (BLVAS/66)^{**}0.105 * (1+0.0779*(BLHAQ-1.75))) (WT/72.8)^{**}0.0522$$

$$LEmax = 0.237*(BLCRP/15.70)^{**}0.333$$

$$kout = 0.0264 * 1.26^{**} PRICORT$$

The Final PopPK/PD parameters are presented in **Table 31**.

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Table 31. PopPK/PD parameters in the Total Data Set (n=2082) after inclusion of covariates

Population Parameter			
Parameter	**Estimate**	**% RSE**	**[95%CI]**
BASE ($_1$)	6.06	0.32	[6.03, 6.10]
LEmax ($_2$)	0.237	19.8	[0.143;0.331]
IC50 ($_3$, mg/L)	2.32	17.6	[1.51,3.14]
kout ($_4$,day^{-1})	0.0264	4.61	[0.0239; 0.0289]
γ ($_5$)	1 (fixed)	NA	NA
PLB ($_6$, mg/L)	0.991	19.1	[0.612, 1.37]
BLCRP on BASE ($_7$)	0.0564	4.49	[0.0513, 0.0614]
BLPHYVAS on BASE ($_8$)	0.105	6.41	[0.0913, 0.118]
BLHAQ on BASE ($_9$)	0.0779	5.15	[0.0698, 0.0859]
WT on BASE ($_{10}$)	0.0522	20.2	[0.0311, 0.0733]
BLCRP on LEmax ($_{11}$)	0.333	34.5	[0.103, 0.562]
PRICORT on kout ( )	1.26	5.50	[1.12; 1.40]
Inter-individual variability (CV%)			
Parameter	**Estimate (CV%)**	**% RSE**	**[95%CI] (Shrinkage %)**
BASE	8.05	6.86	[7.47, 8.58] (31.3)
LEmax	71.2	8.26	[65.1, 76.9] (40.5)
IC50	158	13.4	[135, 178] (42.3)
kout	84.2	6.11	[78.9, 89.2] (31.9)
PLB	105	38.1	[51.2, 140] (75.8)
Residual variability			
Additive term (mg/L)	0.647	0.70	[0.642, 0.651] (11.0)

%RSE: Percentage of Relative Standard Error (100% * SE / Estimate); 95%CI: 95% confidence interval; BASE = baseline DAS28-CRP; BLCRP = baseline CRP; BLHAQ = baseline HAQ-DI; BLPHYVAS = baseline physician's global assessment of disease activity; CRP = C reactive protein; CV = coefficient of variation; Emax = maximum drug inhibition effect; γ = hill coefficient for sigmoidicity; IC50 = concentration at 50% of Emax; kin = first order rate constant of DAS28-CRP production rate; kout = first order rate constant for loss of DAS28-CRP response; LEmax = log transformed parameter for Emax, NA=not applicable; PLB = placebo/background treatment effect of concomitant DMARDs in sarilumab concentration units; θ and ω are the PopPKPD parameters (θ) and the variance of their associated inter-individual variability (ω)

(source: Table 5, Study report POH0446)

Model evaluation

The developed models were extensively evaluated by basic graphical evaluations, ETA shrinkage, and predictive checks. Basic graphical evaluations included graphical plots checking Observed DAS28 values (DV) vs predicted concentrations (Population prediction (PRED), individual predictions (IPRED)) (Figure 33), residual plots (absolute conditional weighted residuals, individual weighted residuals (IWRES) vs predictions and time), histograms and quantile-quantile plots (conditional weighted residuals and individual random effects (IIV)),

plots for individual random effects (intercorrelations and relationship to covariates) and their distribution plots stratified by the categorical covariates.

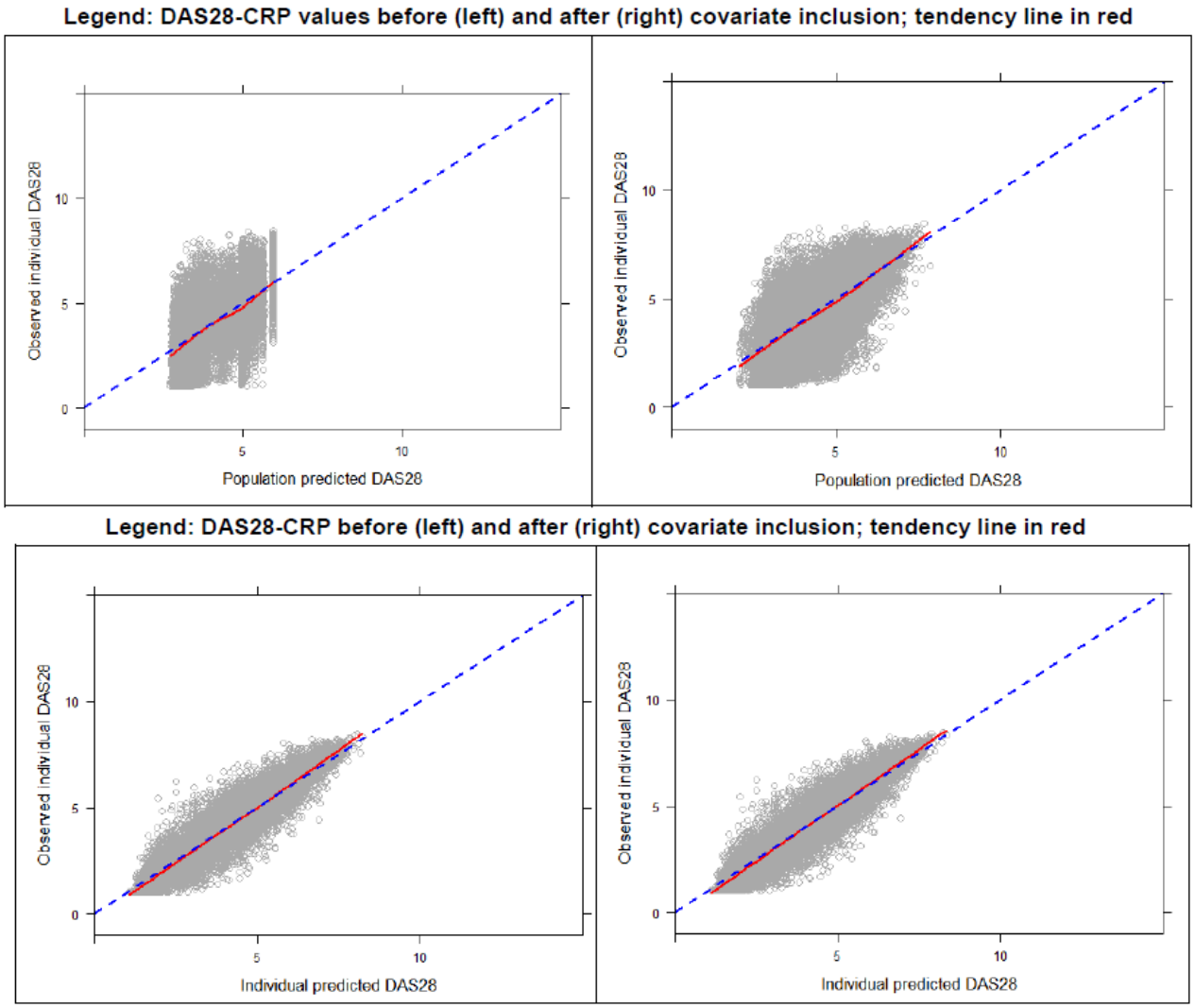


Figure 33. Relationship between population and individual predicted and observed concentrations of sarilumab in the Total Data Set before and after covariate inclusion – Linear scale
(Source: Figure 5, Figure 6, study report POH0446)

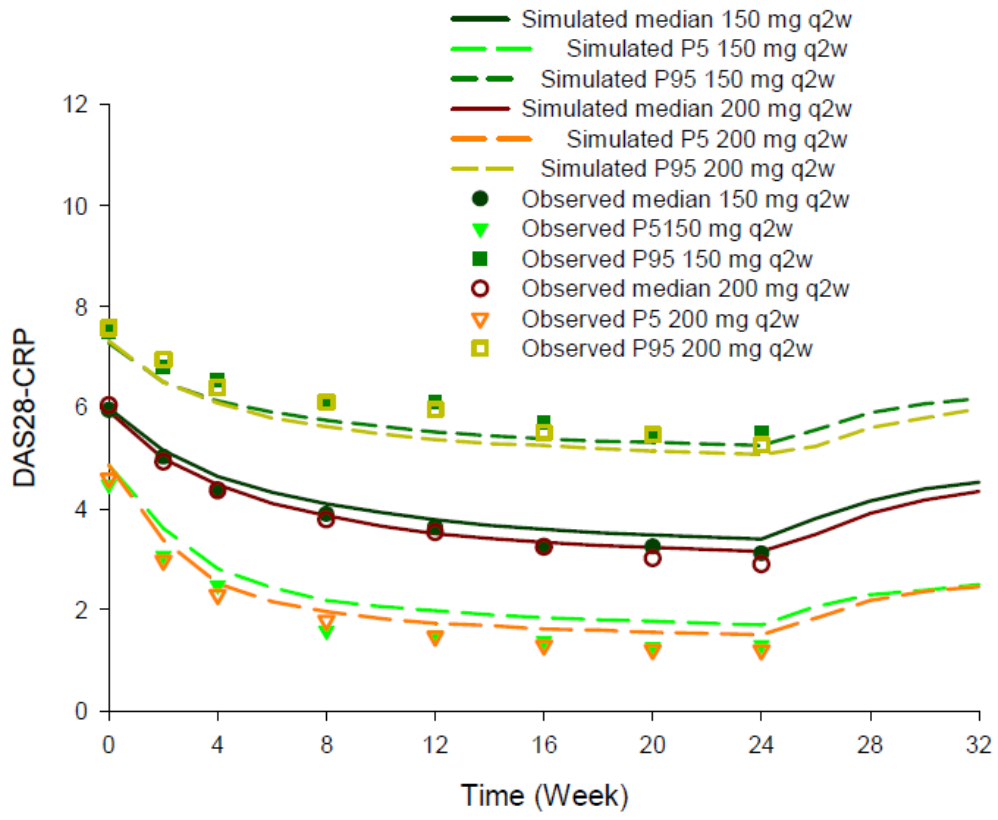
The indirect-response model with an inhibitory effect on DAS28 'production' rate by sarilumab serum concentrations was used to describe the magnitude and the time-course of DAS28 score reduction. Based on the final model, the population mean of the maximum effect of sarilumab corresponds to 55.9% reduction of DAS28 from baseline. with IC50 of 2.32 mg/L. Simulations were performed based on the final model for the DAS28 time-course for a 24 week treatment schedule. The real data observations were then compared, in the same figure (Figure 34). The population PD model well described the DAS28-CRP levels observed in patients (Table 32 and Figure 34). It showed that DAS28 scores steadily decrease after a rapid drop during the first 8

weeks. The effect of sarilumab on DAS28-CRP was lower for the 150 mg q2w (46.5% reduction from baseline) regimen than for the 200 mg q2w (50.3% reduction from baseline).

Table 32. Descriptive statistics of DAS28-CRP in the RA patients (Phase 3 studies EFC11072 Part B and EFC10832) on Week 24

	Model Estimated DAS28-CRP									Observed		
Dose	N	Mean	CV	SD	Min	P5	Median	P95	Max	N	Mean	SD
150 mg q2w	422	3.19	33.0%	1.05	0	1.67	3.11	5.03	6.28	422	3.24	1.30
200 mg q2w	470	3.01	33.7%	1.02	1.13	1.50	2.95	4.81	6.27	470	3.01	1.25

(Source: Table 8, study report POH0446)



P5 and 95 represent 5th percentile and 95th percentile

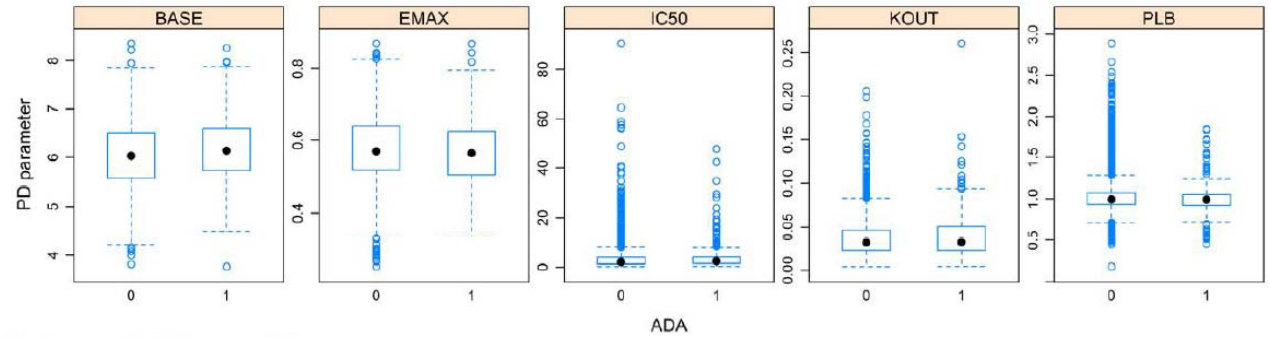
Figure 34. DAS28-CRP level-time (observed vs model predicted median, 5th and 95th percentiles)
(Source: Figure 9, study report POH0446)

The effect of covariates

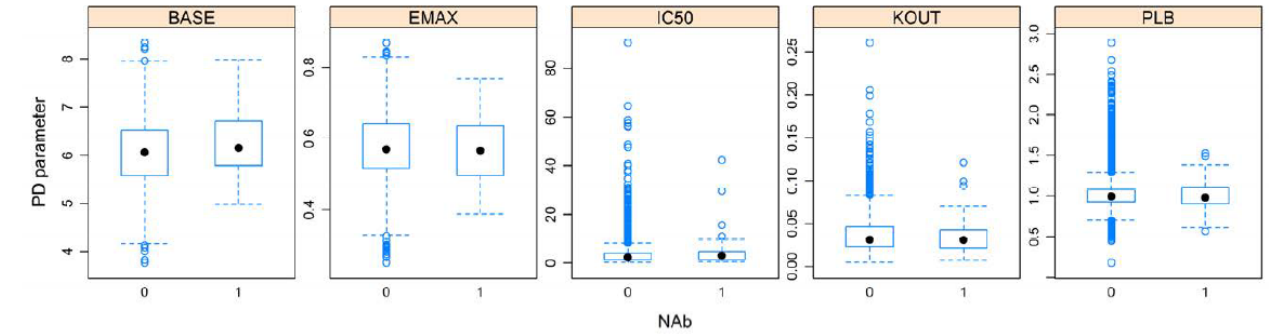
No covariate was found to have a clinical impact on the effect of sarilumab on DAS28. The covariates that remained in the final model are as follows: baseline values of CRP, HAQ, PHYVAS, and bodyweight for DAS28 values at baseline (BASE parameter) with positive relationships, which

is in line with the fact that many of these covariates are markers of RA disease activity; baseline CRP for the maximum effect of sarilumab (Emax) with higher Emax in patients with higher BLCRP; PRICORT on kout (DAS28 elimination rate) with higher kout in patients with higher PRICORT. The final model passed the model evaluation assessment as described in previous section.

The relationship between sarilumab concentration and DAS28 is independent of Gender, age, race, baseline RF, baseline Anti-CCP status, prior biologics treatment, concomitant methotrexate, or patient population (MTX-IR or TNF-IR). Additionally, a post-hoc analysis showed that baseline IL-6, ADA status and NAb status had no appreciable impact on sarilumab PD parameters (Figure 35).



ADA=0, negative ADA; ADA=1: positive ADA



NAb=0, negative NAb; NAb=1: positive ADA;

Figure 35. Comparison of PD parameters across ADA and NAb status
(Source: Figure 10, 11, study report POH0446)

2.3 E-R analysis for safety

2.3.1 E-R analysis for Neutrophils

2.3.1.1. Methods

Data

The dataset for exposure-safety response for population PK-neutrophil count analysis was pooled from 5 repeated dose studies for this analysis. The relevant characteristics of each clinical study are summarized in **Table 33**. The Total Data Set was composed of 1672 patients (17035 ANC concentration-time points).

Table 33. Description of studies included in POH0429

Study	Dose and Regimen	Population	N	PK and PD Sampling	No. of Patients in the PopPK/PD analysis
TDR10805 (6R88–RA–0802) (Phase 1)	Placebo, 50 mg every week (qw), 100 mg qw, 100 mg every other week (q2w), 150 mg qw, 150 mg q2w and 200 mg q2w SC for 5 weeks	RA patients	7-8 patients / cohort	Sparse sampling	42
EFC11072 (MOBILITY)-Part A (Phase 2)	Placebo, 100 mg SC qw, 150 mg SC qw, 100 mg SC q2w, 150 mg SC q2w and 200 mg SC q2w, 12 weeks treatment duration	RA patients with MTX-IR	≈ 50 patients / arm	Sparse sampling	203
EFC11072 (MOBILITY)-Part B (Phase 3)	Placebo, 150 mg SC q2w, 200 mg SC q2w, 52 weeks treatment duration	RA patients with MTX-IR	≈ 350 patients / arm	Sparse sampling	968
EFC10832 (TARGET) (Phase 3)	Placebo, 150 mg SC q2w, 200 mg SC q2w, 24 weeks treatment duration	RA patients with anti-TNF-IR	≈174 patients / arm	Sparse sampling	364
SFY13370 (ASCERTAIN) (Phase 3)	150 and 200 mg SC q2w Tocilizumab starting of 4 mg/kg IV Q4W (every 4 weeks) and followed by an increase to 8 mg/kg if needed based on clinical response), 24 weeks treatment duration [a]	RA patients with anti-TNF-IR	Sarilumab ≈ 50 patients / arm Tocilizumab ≈ 100 patients	Sparse sampling	95

[a] Tocilizumab data was not included in the analysis
IR= inadequate response, MTX= methotrexate, TNF= tumor necrosis factor

(source: Table 1, study POH0429)

Model building

The time-course of neutrophil counts was described by an indirect response model (Figure 36). Hill coefficient was used to link the sarilumab concentrations with ANC, via the stimulation of elimination rate, kout.

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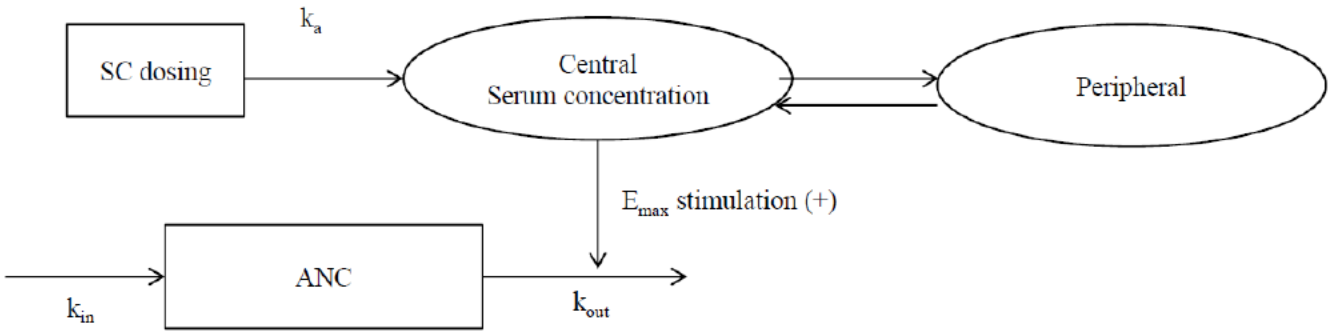

$$d(ANC)/dt = kin - kout \times (1 + Eff(C)) \times ANC$$

$$Eff(C) = Emax \times C^{\gamma} / (EC50^{\gamma} + C^{\gamma})$$

Where, C = concentration, Emax = maximum drug induced effect, γ = hill coefficient for sigmoidicity, EC50 = concentration at 50% of Emax, kin = first order rate constant of ANC production rate, kout = first order rate constant for ANC elimination rate.

Figure 36. Model structure for exposure response analysis of neutrophil
(Source: Page 29, study report POH0429)

Full model with backward elimination was used to identify the final covariate model. The full and/or final model development was assisted by the additional graphical exploration of the measured covariate values vs estimates of individual random effects from the full model. Each significant covariate was added sequentially and the new model was evaluated for its effect upon OFV and 95%CI of the corresponding parameter (covariate effect) estimates as well as for the decrease of the inter-individual variability of the parameter on which the covariate was added. During backward elimination, covariates with effects close to null value and/or with high relative standard error and/or with the 95% confidence intervals that included the null value were excluded from the final model. Only the covariates associated with a significant change of the objective function with a p value < 0.001 were retained in the final model. Increase of objective function value by less than 10.83 at a single covariate elimination was used as a criterion to exclude covariates.

The following covariates were screened for their effects on the PD parameters of Neutrophil PopPK/PD model:

- Demographics: Gender, age, race, body weight, smoking status
- Biomarker: Baseline CRP, baseline IL-6
- Disease status: Baseline rheumatoid arthritis factor (RF), baseline anti-cyclic citrullinated peptide status (Anti-CCP), baseline DAS28-CRP
- Medication: Prior corticosteroids treatment, prior biologics treatment, concomitant MTX
- Patient population: MTX-IR/DMARD-IR or TNF-IR

• ADA status (at patient level): ADA negative or positive depending on their ADA induction pattern during sarilumab treatment course (designated as ADA2 = 0 or 1, respectively).

• Neutralizing anti-drug-antibody (NAb) status: positive or negative

2.3.1.2. Results

The final POP PK/PD model included 1 covariate on baseline ANC (smoking status or SMK), 1 covariate on Emax (prior corticosteroids treatment or PRICORT), and 1 on kout (body weight or WT) according to the following equation:

$$BASE = 5.38 * 1.15^{**} SMK$$

$$Emax = 1.50 * 0.819^{**} PRICORT$$

$$kout = 2.17 * (WT/71)^{**0.875}$$

The Final PopPK/PD parameters are presented in **Table 34**.

Table 34. PopPK/PD parameters in the Total Data Set (n=1672) after inclusion of covariates

Population Parameter			
Parameter	**Estimate**	**% RSE**	**[95%CI]**
BASE (θ_1,10^9 /L)	5.38	1.05	[5.27, 5.50]
Emax (θ_2)	1.50	4.62	[1.36;1.64]
EC50 (θ_3, mg/L)	10.3	6.16	[9.00,11.5]
kout (θ_4,day^{-1})	2.17	35.3	[0.638, 3.71]
γ (θ_5)	0.862	4.55	[0.783, 0.940]
SMK on BASE (θ_7)	1.15	2.64	[1.09, 1.21]
Weight on kout (θ_8)	0.875	12.2	[0.662; 1.09]
PRICORT on Emax (θ_9)	0.819	4.63	[0.743; 0.895]
Inter-individual variability (CV%)			
Parameter	**Estimate (CV%)**	**% RSE**	**[95%CI] (Shrinkage %)**
BASE	32.1	4.61	[30.6, 33.5] (12.9)
EC50	36.9	28.0	[24.5, 46.1] (74.0)
Emax	61.9	6.83	[57.5, 66.0] (30.6)
kout	227	43.7	[80.5, 311] (79.3)
γ	80.4	8.89	[72.9, 87.2] (42.3)
Residual variability			
Proportional term (θ_6, %)	28.2	0.8	[28.0, 28.5] (7.14)

%RSE: Percentage of Relative Standard Error (100% * SE / Estimate); 95%CI: 95% confidence interval; BASE = baseline ANC; CV = coefficient of variation; Emax = maximum drug induced effect; γ = hill coefficient for sigmoidicity; EC50 = concentration at 50% of Emax; kin = first order rate constant of ANC production rate; kout = first order rate constant for ANC production rate; NA=not applicable; θ and ω are the PopPKPD parameters (θ) and the variance of their associated inter-individual variability (ω)

(Source: Table 6, study report POH0429)

Model evaluation

The developed models were extensively evaluated by basic graphical evaluations, ETA shrinkage, and predictive checks. Basic graphical evaluations included graphical plots checking Observed ANC values (DV) vs predicted concentrations (Population prediction (PRED), individual predictions (IPRED)) (Figure 37), residual plots (absolute conditional weighted residuals, individual weighted residuals (IWRES) vs predictions and time), histograms and quantile-quantile plots (conditional weighted residuals and individual random effects (IIV)), plots for individual random effects (intercorrelations and relationship to covariates) and their distribution plots stratified by the categorical covariates.

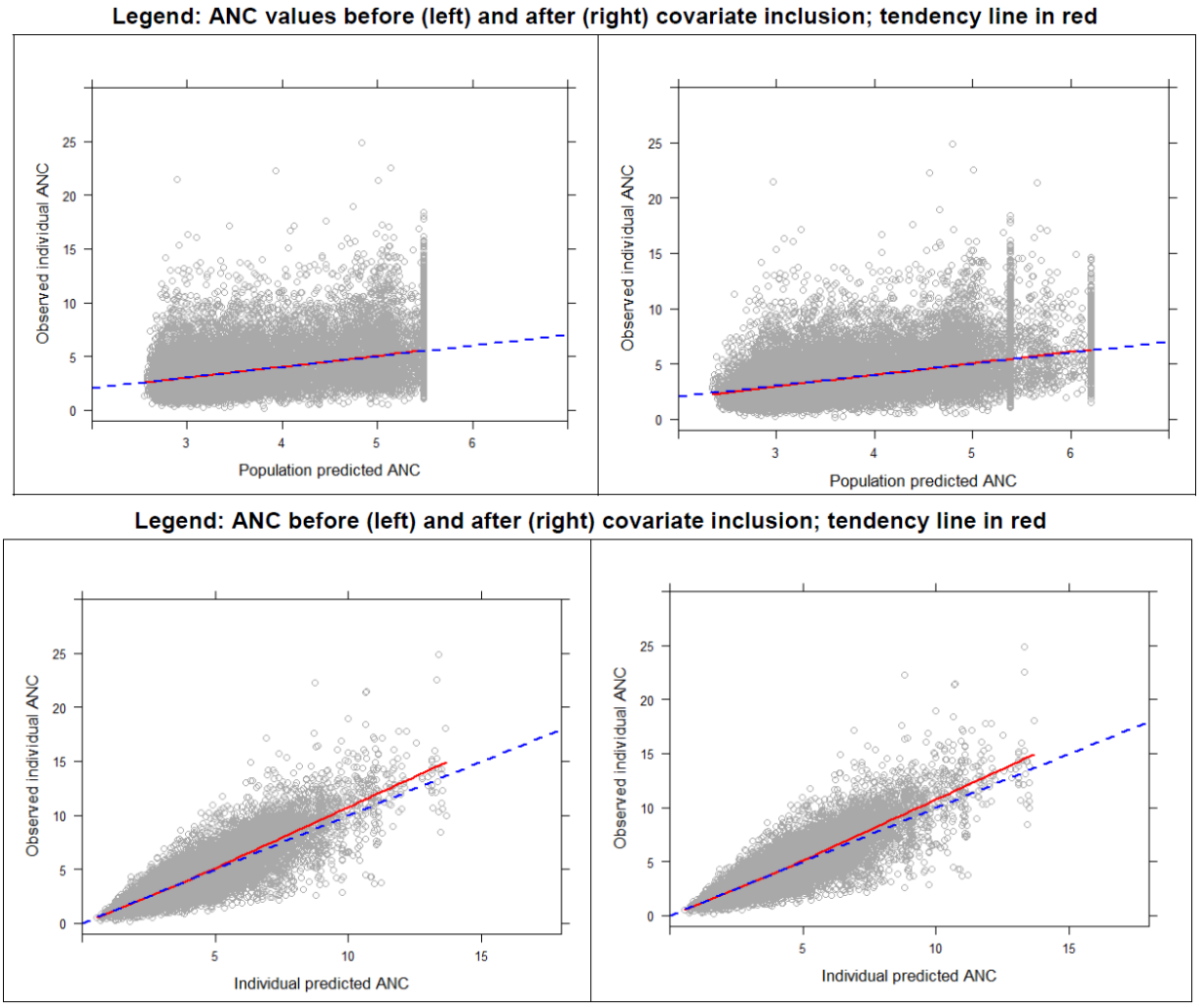

Figure 37. Relationship between population and individual predicted and observed concentrations of sarilumab in the Total Data Set before and after covariate inclusion
(Source: Figure 5, Figure 6, study report POH0429)

The ANC time-course following SC administration of sarilumab in patients with RA was described by an indirect response model, linking sarilumab concentrations with ANC via stimulation of ANC elimination rate. Based on the final model, the population mean of the maximum effect of sarilumab

corresponds to 60% maximal decrease of ANC from baseline with EC50 of 10.3 mg/L. Simulations were performed based on the final model for the ANC time-course for a 24 week treatment schedule. The real data observations were then compared, in the same figure (Figure 38). The population PD model well described the ANC levels observed in patients (Table 35 and Figure 38). It showed that ANC scores steadily decrease after a rapid drop during the first 2-4 weeks. The effect of sarilumab on ANC was smaller for the 150 mg q2w (31% reduction from baseline on week 24) regimen than for the 200 mg q2w (39% reduction from baseline on week 24). The model also described the ANC fluctuations within each dosing interval corresponding to the sarilumab concentration change after each dose (Figure 38). This is consistent with what has been observed in the PD studies (section 4.2, individual study review 6R88-RA-1309).

Table 35. Descriptive statistics of ANC in the RA patients (Phase 3 studies EFC11072 Part B EFC10832 and SFY13370) on Week 24

	Model Estimated ANC (10^9 L^{-1})									Observed ANC(10^9 L^{-1})		
Dose	N	Mean	CV	SD	Min	P5	Median	P95	Max	N	Mean	SD
150 mg q2w	461	4.10	47.2%	1.94	1.24	1.81	3.72	7.98	13.2	461	4.24	2.31
200 mg q2w	535	3.68	49.6%	1.83	0.913	1.53	3.29	7.03	13.4	535	3.79	2.19

P5:5th percentile, P95: 95th percentile.

(Source: Table 9, study report POH0429)

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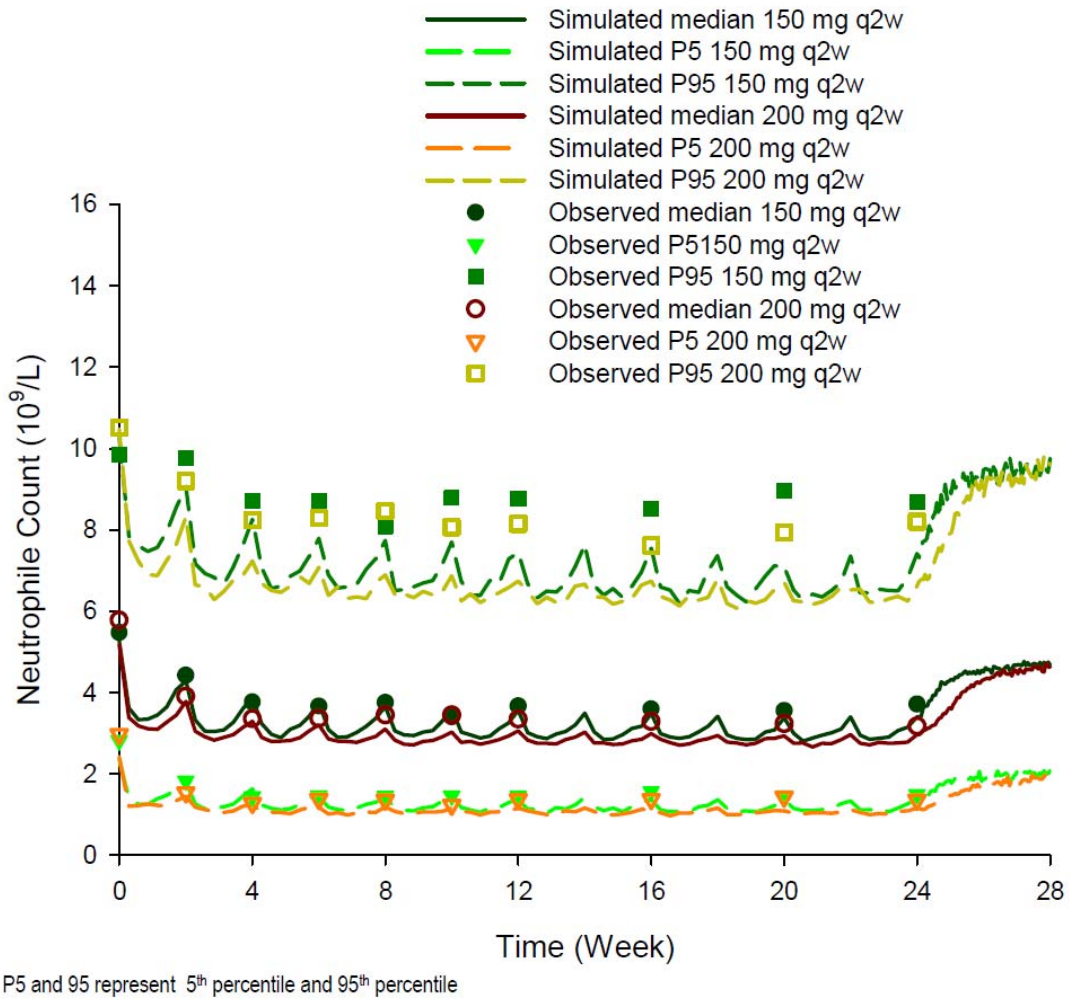


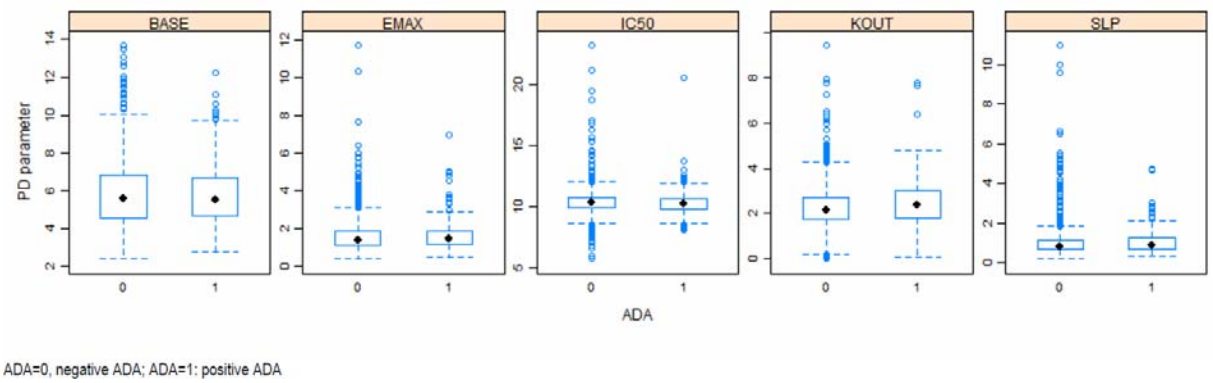
Figure 38. ANC level-time profiles (observed vs model predicted median, 5th and 95th percentiles)
(Source: Figure 9, study report POH0429)

The effect of covariates

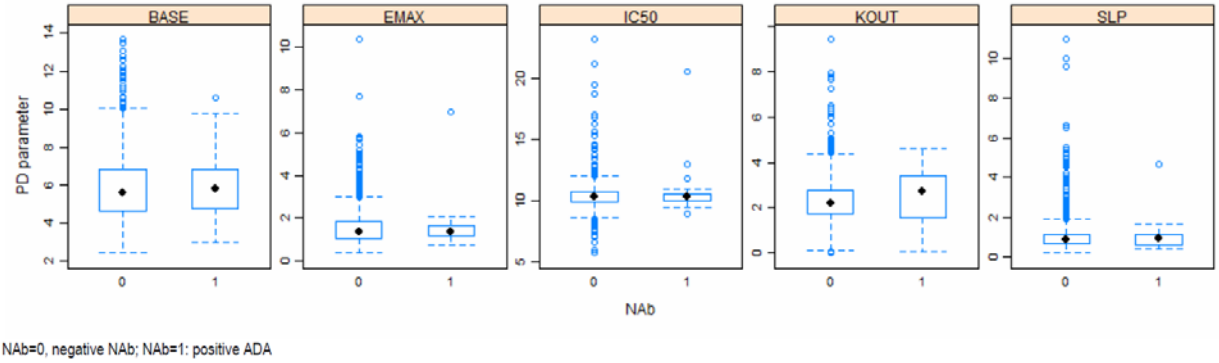
The magnitude of the covariate effects on model parameters is shown as in Table 34. The covariate effects on the neutrophil time course were also assessed using simulations. Overall, The effect of the above covariates on the PD parameters in the final popPK/PD model was small, with none of them having a clinically meaningful influence on the time course of ANC. The final POP PK/PD model included 1 covariate on baseline ANC (smoking status), 1 covariate on Emax (prior corticosteroids treatment), and 1 on kout (body weight). The maximal decrease of ANC in patients with prior corticosteroids treatment are 55% , compared to the 60% maximal decrease of ANC in patients without prior corticosteroids treatments. The effect of smoking and body weight is not related to sarilumab drug effect. The baseline ANC value was 15.1% higher in patients who were smokers than patients who were nonsmokers. Compared to patients with body weight of 71 kg (median), the kout value was 12.4% lower in patients with baseline body weight of 61.0 kg (25th percentile) and 15.7% higher in patients with body weight of 83.9 kg (75th percentile). However, this did not

translate to meaningful a meaningful ANC change (<1%) at Week 24. The final model passed the model evaluation assessment as described in previous section.

The relationship between sarilumab concentration and ANC is independent of Gender, age, race, baseline RF, baseline anti-CCP status, baseline DAS28-CRP, prior biologics treatment, concomitant methotrexate, or patient population (MTX-IR or TNF-IR). Additionally, a post-hoc analysis showed that baseline IL-6, ADA status and NAb status had no appreciable impact on sarilumab PD parameters (Figure 39).



ADA=0, negative ADA; ADA=1: positive ADA



NAb=0, negative NAb; NAb=1: positive ADA

Figure 39. Comparison of PD parameters across ADA and NAb status for ANC
(Source: Figure 10, 11, study report POH0429)

2.3.2 Graphical analysis of relationships between observed sarilumab concentrations and safety endpoints (ALT and LDL)

2.3.2.1. Methods

Data

The exposure-response relationship of selected safety endpoints (listed below) were modelled using the pooled safety data from the placebo-controlled Study EFC11072 Part A, Study EFC11072 Part B (Cohort 1 and Cohort 2) and Study EFC10832.

Model building

Graphical analyses were used to explore potential relationships between drug exposure (Ctrough) and safety endpoints. The following safety endpoints were evaluated: Continuous safety endpoints (%change from baseline in neutrophils, %change from baseline in LDL and change

from baseline in ALT in ULN) ; Time to event safety endpoints (time to first neutropenia and time to first ALT> 3xULN)

First, three base E/R relationship models, linear, log-linear and Emax, with appropriate and predetermined covariates, were compared to select the best fitted model by a goodness of fit criterion AICc (or AIC for logistic regression). Based on the best-fitted base model, each covariate was tested one at a time. To assess the E/R model fitting versus observed efficacy (or safety) dose effects, the observed efficacy (or safety) dose effects were compared to PK/PD model predicted mean effects of 150 mg q2w and 200 mg q2w doses.

2.3.2.2 E-R analysis for ALT

Emax E/R relationship well described the relationship of ALT (in ULN) change from baseline versus trough concentration. Sarilumab-treated patients with higher baseline ALT or higher BMI had greater ALT (in ULN) increase. Patients without prior use of biologics were associated with greater ALT increase regardless of treatment.

At Week 24, EC50 is 0.97 mg/L. The observed treatment differences from placebo of 150 mg q2w and 200 mg q2w doses were also plotted at its median concentration. In the median concentration range of 150mg q2w, there was a small increase of ALT change (ULN) as the concentration increased. The effect reached plateau in the median concentration range of 200mg q2w (Figure 40 and Table 36). The PK/PD model predications at Week 12 were similar to Week 24 results.

For ALT (ULN) change from baseline, there was no ADA status by concentration interaction effect identified on the endpoint.

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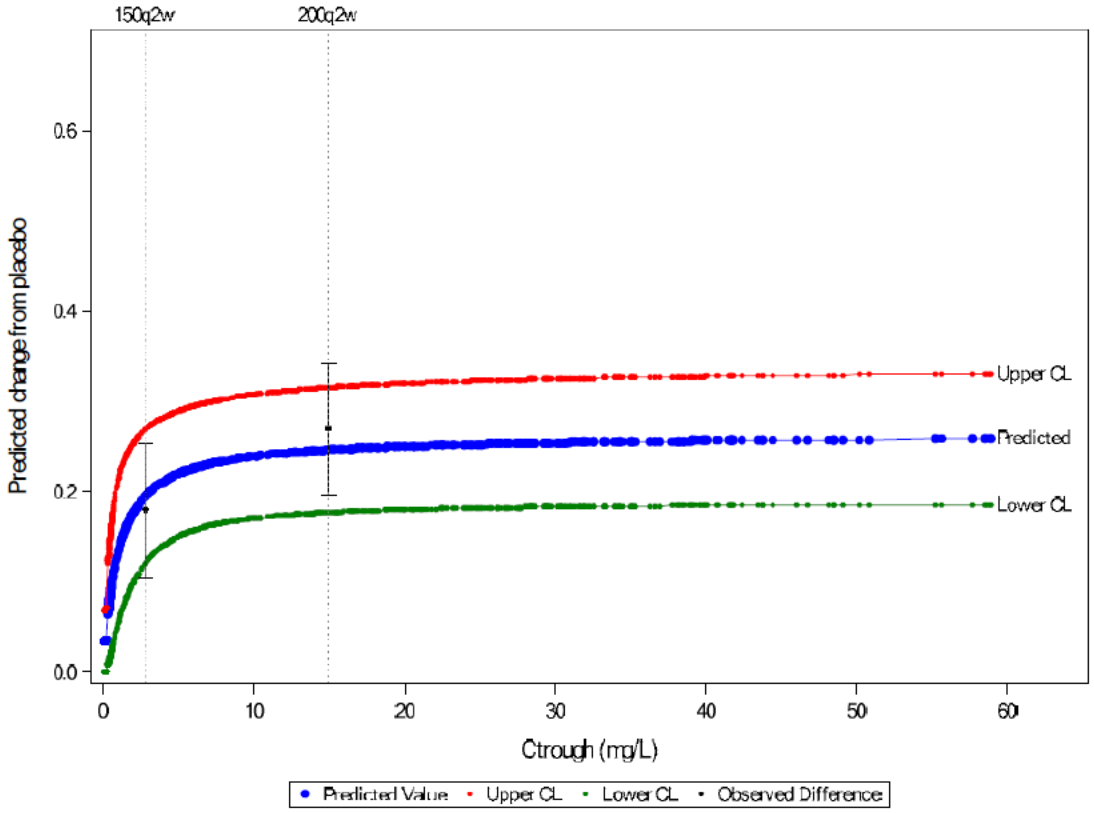

Figure 40. ALT (ULN) change from baseline at Week 24: PK/PD model predicted difference (95% CI) from placebo versus trough concentration of functional sarilumab overlaying with observed treatment difference (95% CI) (Safety Pool)

(Source: Figure 18, Study report POH0455)

Table 36. ALT (ULN) change from baseline at Week 24: Observed and PK/PD model predicted treatment difference (95% CI) from placebo (Safety Pool)

Dose	Observed difference	PK/PD Predicted difference	Median Ctrough (mg/L)
150mg q2w	0.18 (0.107 , 0.253)	0.195 (0.121 , 0.269)	2.81
200mg q2w	0.27 (0.196 , 0.343)	0.247 (0.178 , 0.316)	15.00

Model: change from baseline= b0+b1*(baseline ALT-median baseline ALT)+b2*(baseline BMI-median baseline BMI)+b3*(Without prior biological)+(Emax1+Emax2*(baseline ALT-median baseline ALT)+Emax3*(baseline BMI-median baseline BMI))*pk/(EC50+pk).
Observed difference based on a linear model with treatment and baseline ALT. Safety pool includes placebo-controlled EFC11072 B and EFC10832 at least 24 week long.
# of patients in PK/PD analysis at week 24: placebo=365, sarilumab=790.

(Source: Table 14, Study report POH0455)

Time to first ALT > 3xULN event was described well by a log-normal distribution. Based on the parametric survival model assuming a log-normal survival time, an Emax E/R relationship

provided the best fit to the data compared to a linear or log-linear model. **Figure 41** presented the model predicted hazard rate by mean trough concentration at selected time points, Week 12 and Week 24. Three vertical reference lines were also drawn at the median concentrations of 150 mg q2w, 200 mg q2w and 150 mg qw doses to indicate the concentration range of doses. Consistent with observed data, the PK/PD model predicted effects plateaued around the 200 mg q2w median concentration range.

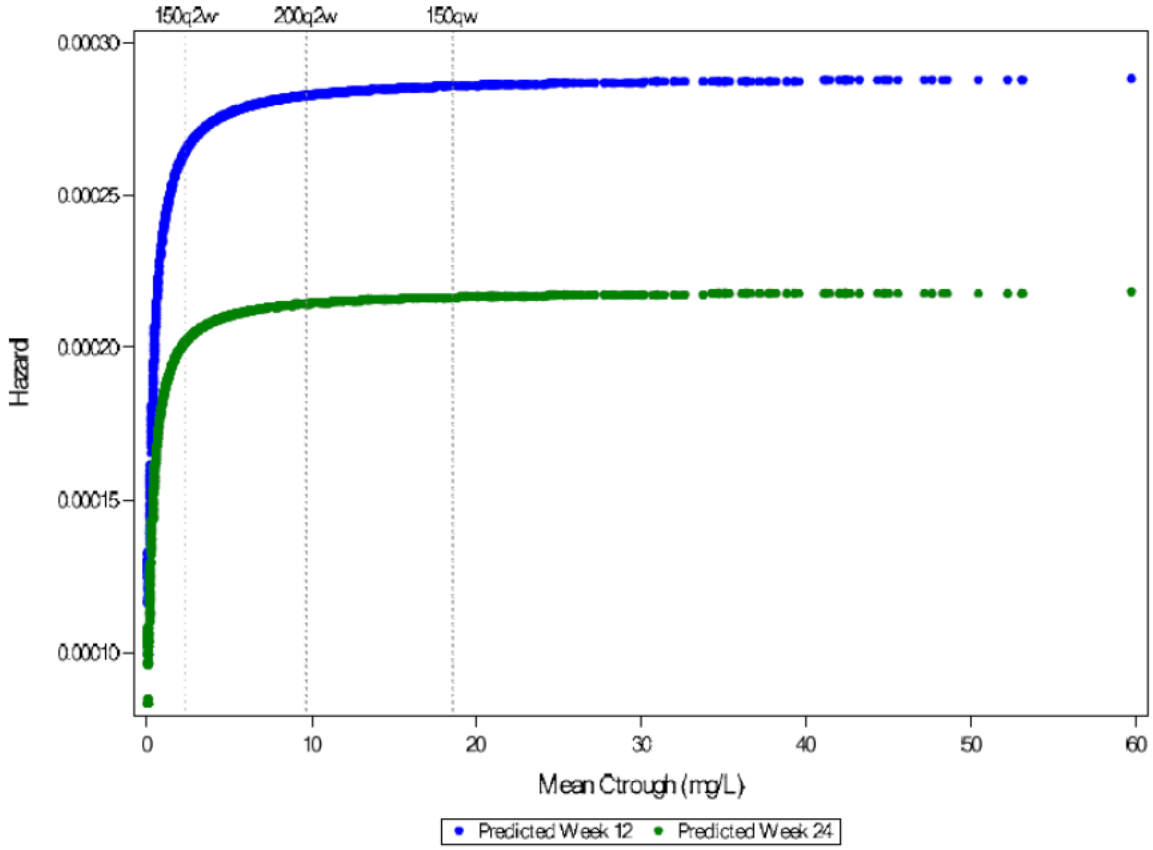

Figure 41. Time to first ALT>3ULN: PK/PD model predicted hazard at Week 12 and Week24 vs. mean C_{trough} assuming a lognormal survival time (Safety pool)

(Source: Figure 19, study report POH0455)

2.3.2.3 E-R analysis for LDL

Emax E/R relationship was used to describe the relationship of LDL change from baseline versus trough concentration. Sarilumab treated patients with higher baseline CRP or older patients had greater %increase in LDL change.

At Week 24, EC50 is 1.07 mg/L. The observed treatment differences from placebo of 150 mg q2w and 200 mg q2w doses were also plotted at its median concentration. The effect was reaching plateau around the median concentration range of 150mg q2w. The observed percentage of LDL change is similar between 150 mg q2w and 200 mg q2w.

For LDL (%) change from baseline, there was no ADA status by concentration interaction effect identified on the endpoint.

In the proposed dosing regimen, the sponsor did not propose dose modification based on lab abnormalities of LDL.

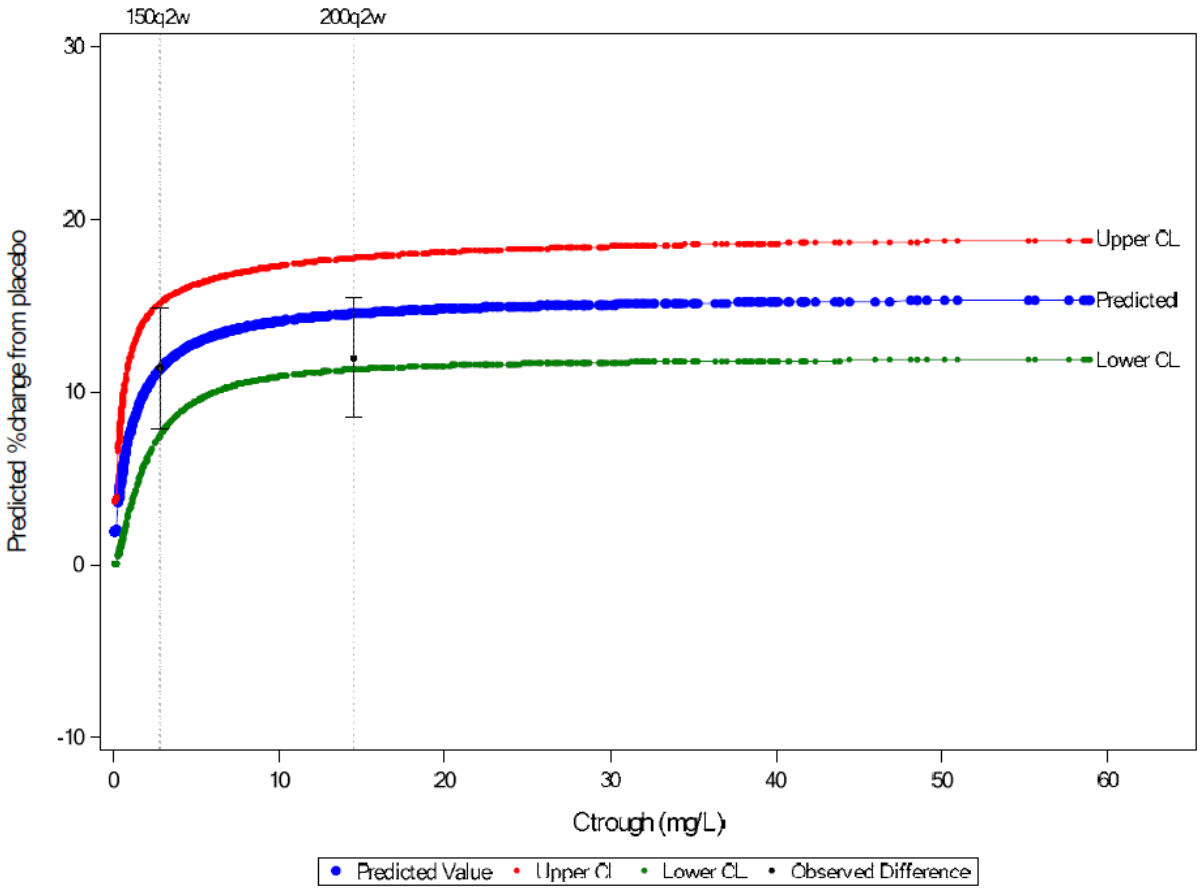

Figure 42. LDL % change from baseline at Week 24: PK/PD model predicted difference (95% CI) from placebo versus trough concentration of functional sarilumab overlaying with observed treatment difference (95% CI) (Safety Pool)
(Source: Figure 22, Study report POH0455)

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4.2 Appendix – Individual Study Review

Note –

In this review, early development name REGN88 or SAR153191 sometimes was used to refer to Sarilumab.

PHARMACOKINETICS

1. Single Ascending Dose IV

Trial # TDU10808

Study Type: Phase 1 single dose, IV, first in human
Study Dates: 27/Nov/2007– 15/Jul/2008
Drug Product: REGN88 is a lyophilized powder formulated with histidine, polysorbate 20 and sucrose at pH 6.0. Each vial of lyophilized REGN88 was reconstituted with 5.0 mL sterile water for injection under aseptic conditions to a final concentration of 50 mg/mL. Reconstituted REGN88 was diluted with 0.9% saline for IV infusion over a period of 2 hours.

Title: A Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Study of the Safety and Tolerability of REGN88 (IL6R-mAb) in Subjects with Rheumatoid Arthritis Receiving Concomitant Methotrexate

- **Objective:**
  - The primary objective of the study was to assess the safety and tolerability of a single dose of intravenously administered REGN88 in patients with RA who were concomitantly treated with MTX.
  - The secondary objectives of the study were to assess the pharmacokinetic (PK) profile and immunogenicity of a single intravenous (IV) dose of REGN88.

- **Study design:** This was a Phase 1, first-in-human, multi-centered, randomized, double blind, placebo controlled, single dose escalation study of the safety and tolerability of REGN88 in patients with RA who were concomitantly treated with MTX.

  Five cohorts of 5 patients were originally planned to be sequentially dosed IV with 0.6, 2, 4, 8, or 16 mg/kg REGN88 or placebo in a 4:1 ratio. After 2 patients were enrolled and dosed in the second cohort (2 mg/kg), one of these 2 patients experienced a transient, Common Terminology Criteria for Adverse Events (CTCAE) laboratory value of Grade 4 neutropenia within 24 hours after infusion of study treatment. Therefore, the study was terminated and a

total of 7 patients (5 patients at 0.6 mg/kg and 2 patients at 2 mg/kg) were enrolled in the study.

- **Sampling Schedule**

PK Sampling Schedule

On Day 1 (Visit 2), samples were collected at hour 0 (pre-dose) and then at hour 1, 4, 8 and 12 post dose. The timing of the post-dose pharmacokinetic draws was based on the end of the infusion. PK samples were subsequently collected on study days 2, 3, 4, 8, 15, 22, 29, 36, 43, 57, 73, 85, 99, and 113 (EOS).

PD Sampling Schedule

Blood samples for the analysis of hs-CRP and SAA were collected at baseline, day 3, 8, 15, 22, 29, 57, and 113 (EOS).

Immunogenicity Sampling Schedule

Serum samples were collected for analysis of antibodies to REGN88. These samples were collected prior to dosing on Day 1, 29, 57 and Day 113 (EOS).

Results:

Pharmacokinetic results

The observed noncompartmental PK parameters of functional REGN88 are summarized in Table 37. Nonlinear kinetics of functional REGN88 were observed. Visual examination of the semilogarithmic plots of functional REGN88 over time revealed 3 pharmacokinetic phases: 1) a distribution phase; 2) a linear elimination phase, and 3) a target-mediated elimination phase. The Cmax-to-dose ratio was very similar across the dose groups, and maximum concentration was reached at the end of IV infusion. The terminal half-life and mean residence time increased with dose, whereas the clearance decreased with dose. The terminal half-life was 1.73 and 4.49 days in the 0.6 mg/kg and 2.0 mg/kg dose groups, respectively.

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Table 37. Summary of Observed Noncompartmental Pharmacokinetic Parameters of Functional REGN88 by Dose

Parameter [unit]		Dose							
		0.6 mg/kg				2 mg/kg			
		N	Median	SE	CV%	N	Median	SE	CV%
$t_{1/2}$	[day]	3	1.73	0.491	47.2	2	4.49	0.582	18.3
CL	[L/day/kg]	3	0.0124	0.00142	20.3	2	0.00596	0.000139	3.30
V_z	[L/kg]	3	0.0359	0.00622	35.7	2	0.0385	0.00410	15.1
V_{ss}	[L/kg]	3	0.0325	0.00433	25.0	2	0.0359	0.00385	15.2
C_{max}	[mg/L]	4	19.3	0.433	4.48	2	58.7	5.55	13.4
C_{max}/Dose	[kg/L]	4	32.1	0.722	4.48	2	29.3	2.78	13.4
C_{last}	[mg/L]	4	0.315	1.27	167.	2	5.97	0.625	14.8
t_{last}	[day]	4	7.06	2.51	62.6	2	13.5	0.511	5.35
AUC_{last}	[day*mg/L]	4	41.1	7.44	34.5	2	296.	1.23	0.586
AUC_{all}	[day*mg/L]	4	44.0	6.23	26.8	2	317.	0.806	0.359
AUC_{inf}	[day*mg/L]	3	48.3	6.32	21.5	2	336.	7.82	3.30
AUC_{last}/AUC_{all}	N/A	3	0.980	0.102	19.9	2	0.884	0.0243	3.88
MRT_{inf}	[day]	3	2.49	0.485	33.0	2	6.05	0.787	18.4

N/A = not applicable

(Source – Table 9, TDU10808 CSR)

Pharmacodynamic results

At baseline, hs-CRP and SAA levels were within the normal range in 6 of the 7 patients enrolled. Some patients had an elevation in hs-CRP and SAA around day 22, and returned to within the normal range by end of the study. (Figure 43).

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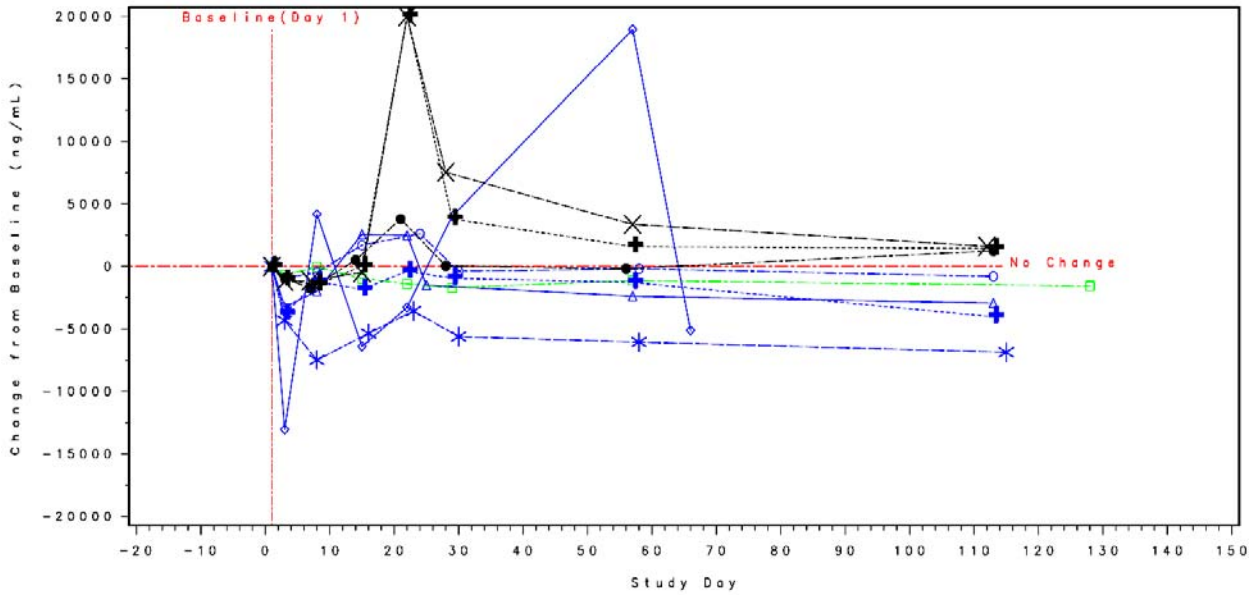
A. SAA



B. CRP

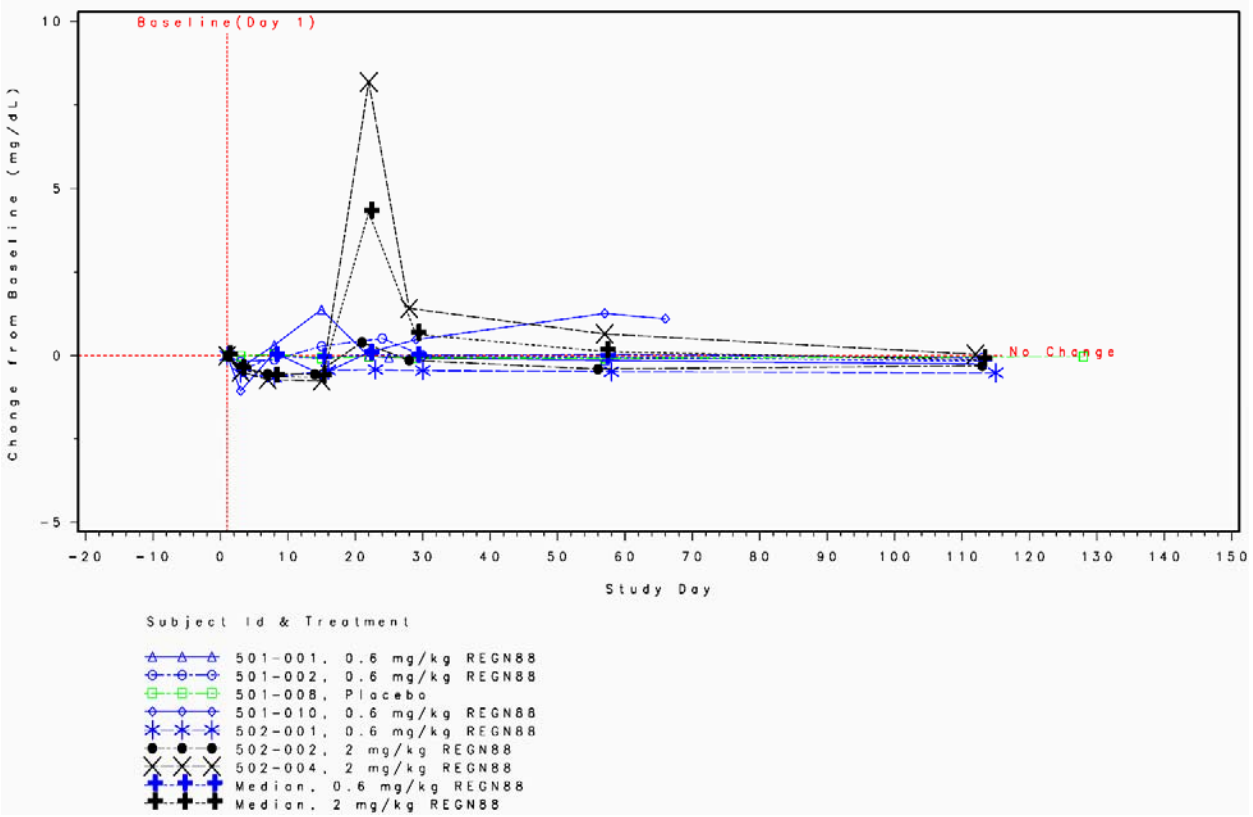


Figure 43. Percent change from baseline for Serum Amyloid A-RUO-(-70) (SAA) and C-Reactive Protein (hs-CRP) by subject and by study day

(Source: Figure 1.1, 2.1, TDU10808 CSR)

Immunogenicity results

All of the patients who tested negative for ANA and/or dsDNA at baseline remained negative when re-tested on study Day 113.

Conclusions:

Nonlinear kinetics of functional REGN88 were observed. The t1/2 increased with dose, whereas the CL decreased with dose. The Cmax-to-dose ratio was similar across the dose groups. Neither drug-specific antibodies to REGN88 nor autoantibodies were detected. As the formulation and administration route is different from the to-be-marketed product, the PK information collected in this study was not presented in the label for (b) (4)

2. Single Ascending Dose SC

Trial # TDU10809

Study Type: Phase 1 single ascending dose, SC

Study Dates: 5/Aug/2008– 24/Mar/2009

Drug Product: The REGN88 drug product used in this study was a lyophilized powder formulated with histidine, polysorbate 20, and sucrose at pH 6.0. Each vial of lyophilized REGN88 or placebo was reconstituted with 2.3 mL sterile water for injection under aseptic conditions to a final concentration of 100 mg/mL. Study doses of 50, 100, and 200 mg were administered via a single SC injection in the abdomen.

Title: A Randomized, Double-blind, Placebo-controlled, Single Ascending Dose Study of the Safety and Tolerability of Subcutaneously (SC) Administered REGN88 in Subjects with Rheumatoid Arthritis (RA) Receiving Concomitant Methotrexate (MTX)

- **Objective:**
  - The primary objective of the study was to assess the safety and tolerability of a single dose of subcutaneously administered REGN88 in patients with RA who were concomitantly treated with MTX.
  - The secondary objectives of the study were to assess the PK profile and immunogenicity of a single SC dose of REGN88.

- **Study design:** This was a phase 1, multi-centered, randomized, double blind, placebo-controlled, single dose escalation study of the safety and tolerability of SC administered REGN88 in patients with RA who were concomitantly treated with MTX. Three cohorts of 5 patients were planned to be sequentially dosed SC with 50, 100, or 200 mg REGN88 or placebo in a 4:1 ratio. Patients who completed the study participated in 14 study visits (16 weeks).

- **Sampling Schedule**

PK Sampling Schedule

Blood samples for REGN88 level (serum sample) were collected at Day 1 (Visit 3; pre-dose hour 0 and 8 hours post-dose), Day 3 (Visit 4), Day 5 (Visit 5), Day 8 (Visit 6), Day 11 (Visit 7), Day 15 (Visit 8), Day 22 (Visit 9), Day 29 (Visit 10), Day 43 (Visit 11), Day 57 (Visit 12), Day 85 (Visit 13), and Day 113 (Visit 14).

PD Sampling Schedule

Blood samples were collected at baseline (day 1), day 3, 8, 15, 22, 29, 57, 85 and 113 (EOS), for the analysis of PD markers such as IL-6, hs-CRP, SAA and ESR.

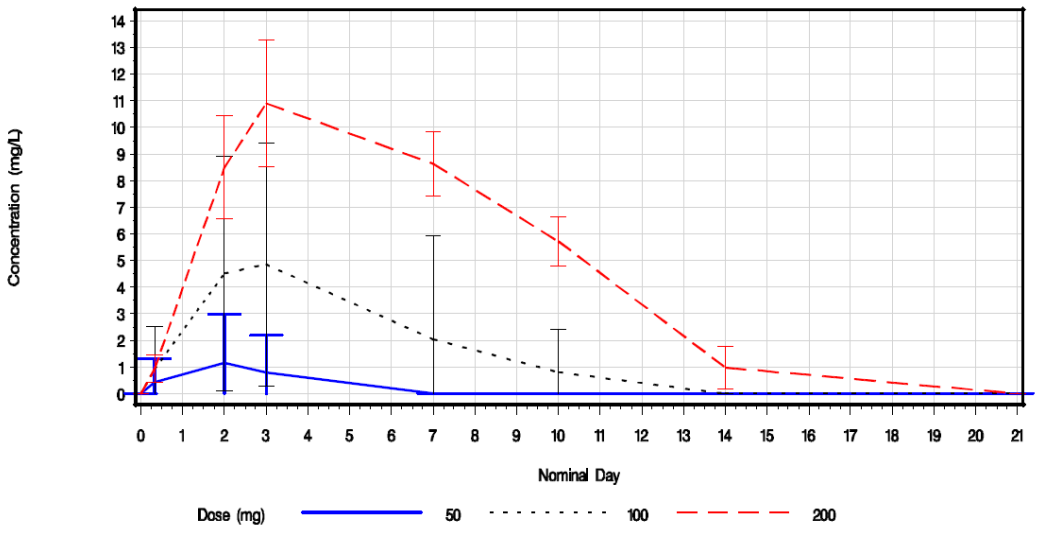
Immunogenicity Sampling Schedule

Blood samples for anti-REGN88 antibody (serum sample) were collected at Day 1 (Visit 3, pre-dose), Day 3 (Visit 4), Day 29 (Visit 10), Day 57 (Visit 12), and Day 113 (Visit 14).

Results:

Pharmacokinetic results

Mean concentrations of functional REGN88 are presented in Figure 44. The time to the first unquantifiable concentration of functional REGN88 increased with dose. By the end of the first week, all patients in the 50 mg treatment group had unquantifiable concentrations of functional REGN88, 2 out of 4 patients in the 100 mg treatment group had quantifiable concentrations, and all patients in the 200 mg treatment group had quantifiable concentrations.



Notes: a) One standard deviation around the mean is presented. b) Concentrations below the LLOQ are set to zero.

Figure 44. Mean (SD) Concentrations of Functional REGN88 vs. Nominal Day
(Source: Figure 5, TDU10809 CSR)

Nonlinear kinetics were observed, which was expected as the target is a cell-surface (mIL-6R) or soluble (sIL-6R) protein which can drive target-mediated clearance of the antibody. A

greater than dose proportional increase was observed in AUCall. The increase in Cmax was close to dose proportional.

The terminal half-life could not be determined for this study because the target-mediated elimination may not be exponential and the linear terminal phase may not exist. The MRTlast of functional REGN88 was 2.01, 3.00, and 5.59 days in the 50 mg, 100 mg, and 200 mg treatment groups, respectively. The estimate of MRTlast in the 50 mg treatment group can be biased because it was missing for 2 out of 4 patients who had concentrations of REGN88 below the LLOQ in all samples analyzed. AUCall was equal to 3.97, 29.1 and 93.3 mg.day/L in the 50 mg, 100 mg, and 200 mg treatment groups, respectively; Cmax was equal to 1.16, 4.89, and 10.9 mg/L in the 50 mg, 100 mg, and 200 mg treatment groups, respectively.

Table 38. Summary of Observed Noncompartmental Pharmacokinetic Parameters of Functional REGN88 by Dose

Dose/ Parameter		C_{max} (mg/L)	C_{max}/Dose (1/L)	T_{max} (day)	C_{last} (mg/L)	T_{last} (day)	AUC_{last} (day*mg/L)	AUC_{all} (day*mg/L)	AUC_{last}/Dose (day/L)	AUC_{all}/Dose (day/L)	MRT_{last} (day)
50 mg	N	4	4	2	2	2	4	4	4	4	2
	Mean	1.16	0.0232	2.04	1.61	3.01	2.36	3.97	0.0472	0.0795	2.01
	SE	0.913	0.0183	0.0535	1.28	0.0552	1.97	3.37	0.0393	0.0674	0.208
	CV%	157.	157.	3.70	113.	2.59	167.	170.	167.	170.	14.7
	Min	0	0	1.99	0.323	2.96	0	0	0	0	1.80
	Median	0.400	0.00800	2.04	1.61	3.01	0.626	0.949	0.0125	0.0190	2.01
	Max	3.84	0.0768	2.10	2.89	3.07	8.19	14.0	0.164	0.280	2.22
100 mg	N	4	4	4	4	4	4	4	4	4	4
	Mean	4.89	0.0489	2.80	1.83	5.79	25.5	29.1	0.255	0.291	3.00
	SE	2.26	0.0226	0.266	0.609	1.71	18.1	18.9	0.181	0.189	0.535
	CV%	92.7	92.7	19.0	66.4	59.2	142.	130.	142.	130.	35.7
	Min	1.77	0.0177	2.01	0.296	2.99	3.16	6.52	0.0316	0.0652	2.26
	Median	3.14	0.0314	3.05	1.91	5.05	9.82	12.3	0.0982	0.123	2.59
	Max	11.5	0.115	3.11	3.23	10.1	79.1	85.5	0.791	0.855	4.57
200 mg	N	4	4	4	4	4	4	4	4	4	4
	Mean	10.9	0.0545	3.00	0.985	14.0	90.0	93.3	0.450	0.466	5.59
	SE	1.19	0.00595	0.0206	0.404	0.00943	7.66	8.35	0.0383	0.0418	0.177
	CV%	21.8	21.8	1.37	82.0	0.135	17.0	17.9	17.0	17.9	6.33
	Min	8.75	0.0438	2.96	0.309	14.0	70.7	71.8	0.353	0.359	5.25
	Median	10.6	0.0532	3.01	0.830	14.0	93.2	96.3	0.466	0.481	5.51
	Max	13.6	0.0680	3.05	1.97	14.0	103.	109.	0.514	0.543	6.08

(Source – Table 11, TDU10809 CSR)

Pharmacodynamic results

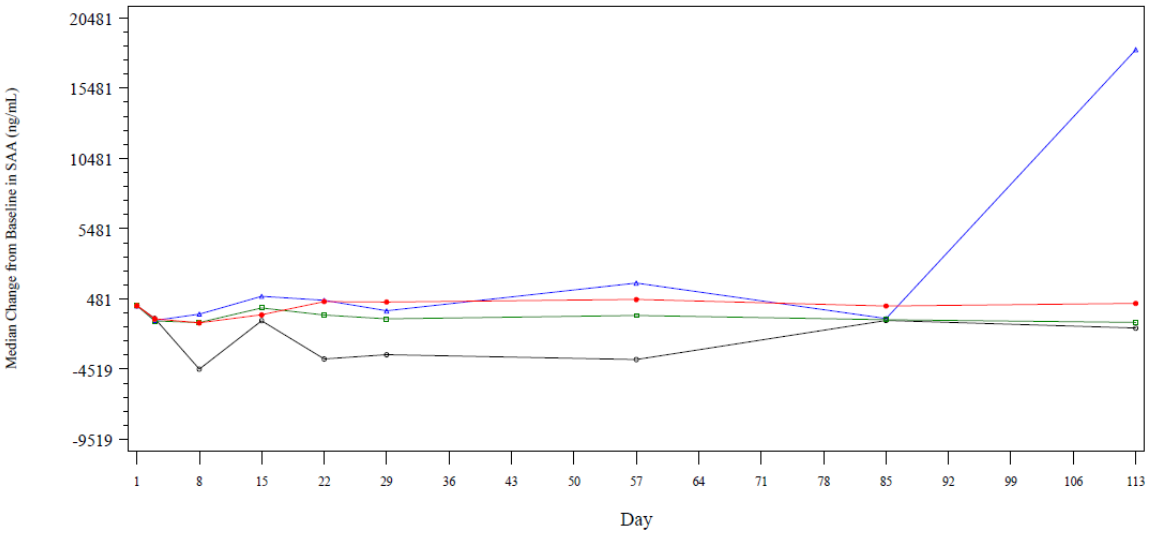
Since patients were not required to have active disease at the time of enrollment, baseline levels of hs-CRP, SAA, and ESR were low.

There was a trend for a dose-dependent decrease from baseline in hs-CRP to study day 3 for the 100 mg group and to study day 8 for the 50 mg and 200 mg groups, following administration of a single SC dose of REGN88. In all treatment groups, median hs-CRP returned to near baseline levels by study day 29 and remained relatively stable thereafter.

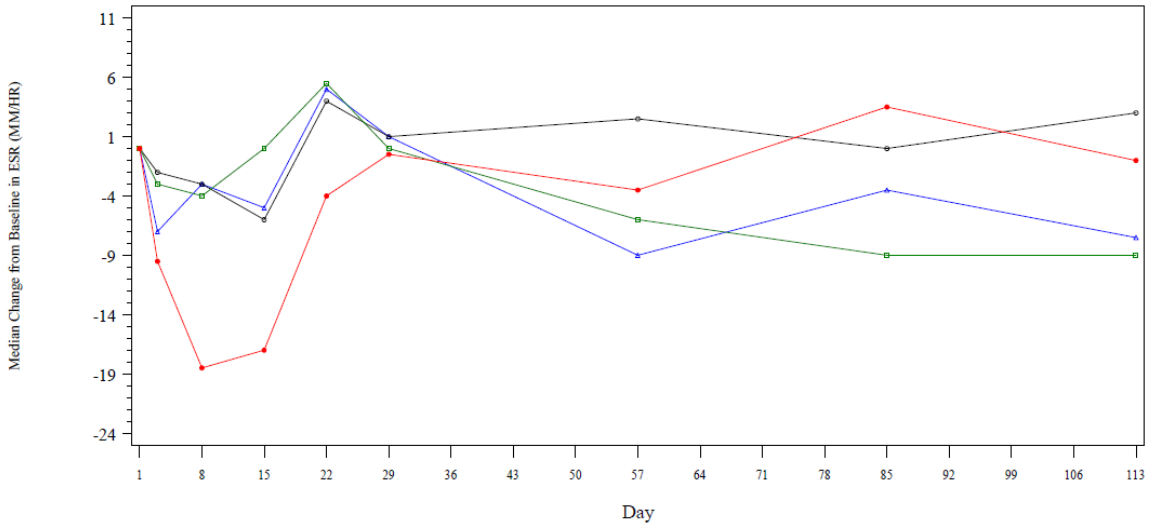
Similar to hs-CRP, there was a trend for a dose-dependent decrease from baseline in ESR to study day 8 for the 100 mg and 200 mg groups and to study day 15 for the 50 mg treatment group.

A decrease from baseline in SAA to study day 4 for the 100 mg and 200 mg groups and to study day 8 for the 50 mg group was observed following administration of a single SC dose of REGN88. The largest decrease in SAA was observed in the 50 mg group compared to the 100 mg and 200 mg groups.

A. SAA



B. ESR



C. hs-CRP

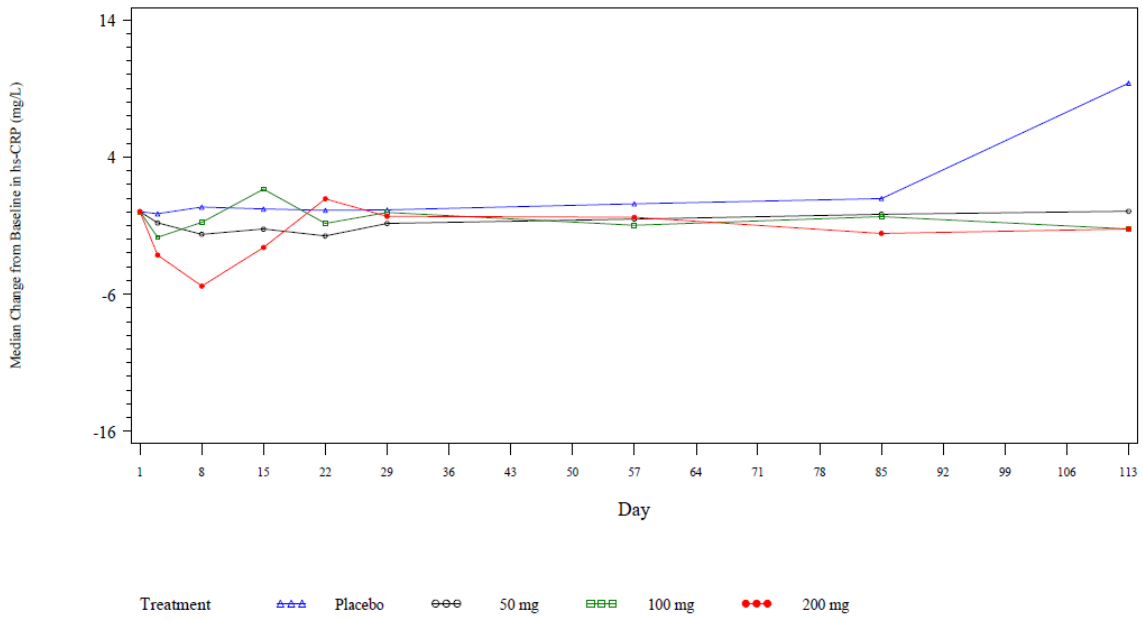


Figure 45. Median Change from Baseline in Serum Amyloid A-RUO-(-70) (SAA), Erythrocyte Sedimentation Rate(ESR) and C-Reactive Protein (hs-CRP) by Treatment and Visit

(Source: Figure 14, Figure 13, Figure 16TDU10809 CSR)

Immunogenicity results

One patient treated with 50 mg of REGN88 reported a shift in antinuclear antibodies (ANA) from normal at baseline to abnormal (1:80) on study day 54

Conclusions:

Sarilumab exposure increased more than dose-proportional within the dose of 50-200 mg SC. As the formulation is different from the to-be-marketed product, the PK information collected in this study was not presented in the label for (b) (4)

3. Multiple Ascending Dose SC

Trial # TDR10805/ 6R88-RA-0802

Study Type: Phase 1b multiple ascending dose, SC

Study Dates: 15/Dec/2008– 26/Aug/2009

Drug Product: REGN88 was administered via SC injection into the abdomen according to the following regimens: 50 mg qw, 100 mg q2w, 100 mg qw, 200 mg q2w, 150 mg qw, 150 mg q2w. Doses were administered on Days 1, 8, 15, 22, and 29 (qw regimens) or on Days 1, 15, and 29 (q2w regimens). The batch numbers of the REGN88 drug product were K07005M800A12B and K07005M800A11B.

Title: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Ascending Parallel Group Study of the Safety and Tolerability of REGN88 in Subjects with Rheumatoid Arthritis Receiving Concomitant Methotrexate

- **Objective:**
  - The primary objective was to assess the safety and tolerability of multiple doses of subcutaneously administered (SC) REGN88 in patients with rheumatoid arthritis (RA) who were receiving concomitant treatment with methotrexate (MTX).
  - The secondary objectives were to assess the pharmacokinetic (PK) profile of multiple SC doses of REGN88, to assess the immunogenicity of REGN88, and to evaluate exploratory efficacy endpoints.

- **Study design:** This was a multi-centered, randomized, double-blind, placebo-controlled multiple-ascending-dose, parallel-group study. The study was conducted in 3 parts and consisted of a total of 6 dose cohorts, each including a REGN88 group and a placebo group randomized 4:1. Patients received 5 weekly doses of study medication and were followed for an additional 6 weeks.

Table 39. Treatments and Subject Numbers

Part	Cohort	Study Treatments	Number of Patients REGN88 : Placebo
A	1	50 mg REGN88 or placebo qw	8:2
	2	100 mg REGN88 q2w alternating with placebo q2w, or placebo qw	8:2
B	3	100 mg REGN88 or placebo qw	8:2
	4	200 mg REGN88 q2w alternating with placebo q2w, or placebo qw	8:2
	5	150 mg REGN88 or placebo qw	8:2
C	6	150 mg REGN88 q2w alternating with placebo q2w, or placebo qw	8:2

(Source: Table 1, CSR6R88-RA-0802)

- **Sampling Schedule**

PK Sampling Schedule

Blood samples were collected for measuring functional REGN88 predose on Day 1 and at each subsequent weekly visit on Days 7, 14, 21, 28, 35, 42, 49, 56, 63, and 70.

Immunogenicity Sampling Schedule

Samples for assessment of anti-REGN88 antibodies (anti-drug antibodies, ADA) were collected predose, on Days 36, and at End of Study.

PD Sampling Schedule

Blood samples were collected for measurement of high-sensitivity C-reactive protein (hs-CRP) and complement at each visit. Interleukin-6 (IL-6), fibrinogen, erythrocyte sedimentation rate (ESR), and serum amyloid A (SAA) were measured at each visit through Day 36, at Day 57, and at End of Study. Immunoglobulins, rheumatoid factor, antinuclear antibodies (ANA), and anti-double-stranded DNA antibodies (dsDNA) were measured pre-dose and at End of Study.

Results:

Pharmacokinetic results

The mean steady-state trough concentrations of functional REGN88 after the last dose are summarized in Table 40. In the 150 mg qw group, the mean trough concentrations increased between Day 29 and Day 36 (designated Days 28 and 35 in Figure 46); based in those data, it is not clear whether the steady state was reached at Day 36.

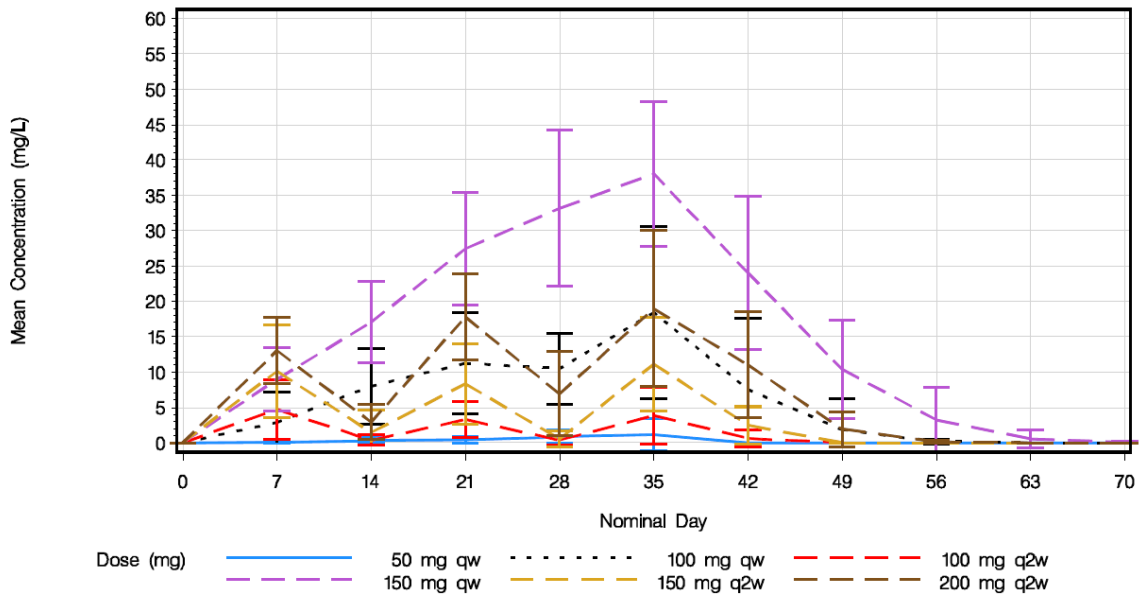


Figure 46: Mean Concentrations of Functional REGN88 versus Nominal Day by Dose, Linear Scale

(Source – Figure 8, CSR6R88-RA-0802)

Table 40. Mean Steady-State Trough Concentrations of Functional REGN88 by Dose Group

Treatment	Visit	Trough Concentration (mg/L)
50 mg qw	Day 36	1.14
100 mg qw	Day 36	18.4
100 mg q2w	Day 43	0.601
150 mg qw	Day 36	38.0
150 mg q2w	Day 43	2.47
200 mg q2w	Day 43	11.0

(Source: Table 16, CSR6R88-RA-0802)

Pharmacodynamic results

Hs-CRP: Higher and more frequent doses of REGN88 were associated with larger median percentage decreases in hs-CRP from baseline. In the 100 mg q2w and 150 mg q2w groups, the decreases in hs-CRP had a tendency to rebound towards the end of the dosing interval at the 150 mg dose, suggesting a lower IL-6Rα blockade at lower doses (Figure 47).

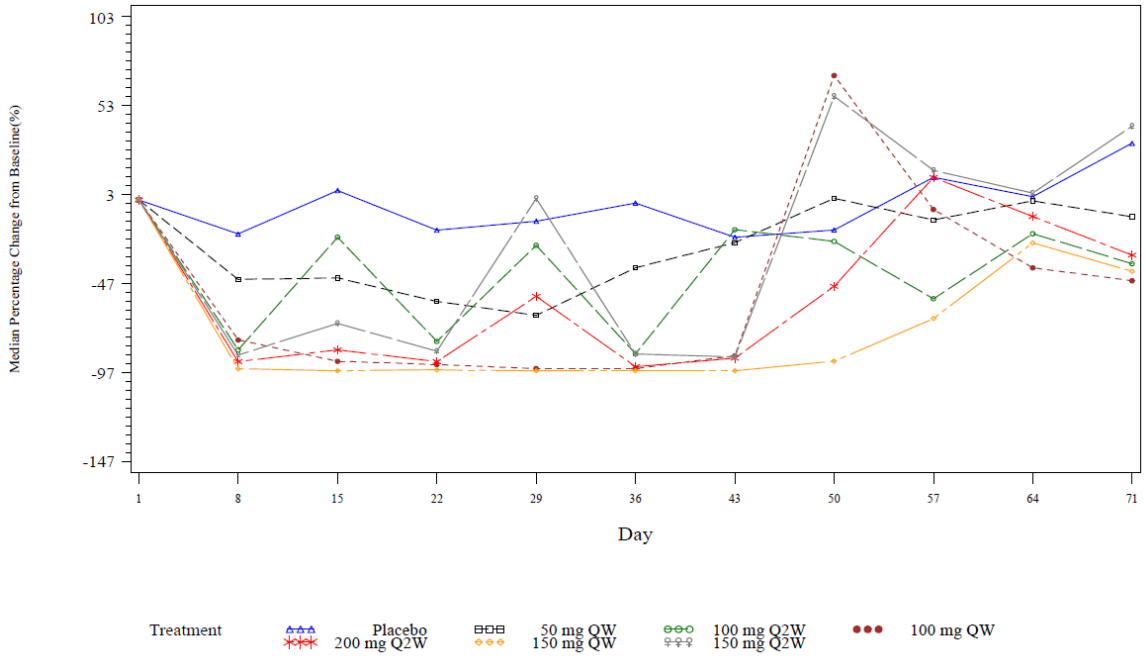


Figure 47. Median Percentage Change from Baseline in hs-CRP by Treatment Group and Visit (FAS)
(Source – Figure 22, CSR6R88-RA-0802)

IL-6: Treatment with REGN88 was associated with dose-dependent increases in IL-6, as shown in Figure 48. The median concentration of IL-6 increased with REGN88 dose and dosing frequency.

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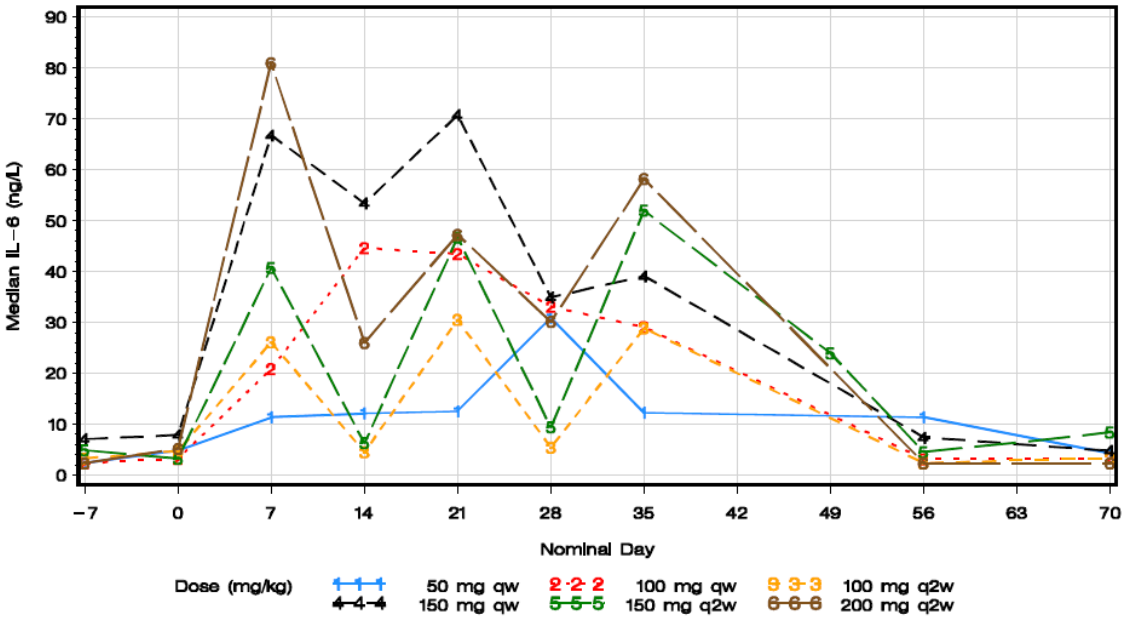

Figure 48. Median Concentration of IL-6 (ng/L) over Time by Treatment (Source – Figure 23, CSR6R88-RA-0802)

Fibrinogen: Treatment with REGN88 was associated with dose-dependent decreases in fibrinogen, with the 150 mg qw regimen having the greatest effect.

Erythrocyte Sedimentation Rate: Results for ESR were similar to those for fibrinogen. Treatment with REGN88 was associated with dose-dependent decreases, with the 150 mg qw regimen having the greatest effect.

Serum Amyloid A: Although results for SAA were highly variable, approximately 4 patients (in various REGN88 groups) displayed distinct decreases from baseline values. No clear dose response was observed.

Immunogenicity results

Sixteen of the 60 patients had at least one sample that was positive in this anti- REGN88 antibody assay. Overall, the highest titers were observed in patients who received the lowest dose: 50 mg qw. The lowest titers were observed in the 150 mg qw group and in the placebo group. The placebo, 100 mg qw, and 150 qw groups each had one patient with positive titers. The titers were low. One patient who tested positive for ADA (150 mg q2w group) had decreased concentrations of REGN88.

- **Conclusions**

The mean concentration of functional REGN88 increased with dose and dosing frequency, there was evidence of nonlinear kinetics with target-mediated clearance at low drug levels.

Decreases in hs-CRP, increases in IL-6, and decreases in fibrinogen, ESR, SAA, and patient's assessment of pain relative to placebo occurred with REGN88 treatment and were related to the dose and frequency of administration.
As the formulation is different from the to-be-marketed product, the PK information collected in this study was not presented in the label for (b) (4)

SPECIFIC POPULATION

4. Japanese subjects

Trial # TDU13402

Study Type: Phase 1 single dose

Study Dates: 14/May/2013– 21/Dec/2013

Drug Product:

• Sarilumab ((b) (4) F3 product) 100 mg/mL (2.55 mL/vial) or matching placebo. Sarilumab and placebo were provided in identically matched amber glass vials. Route(s) of administration: Subcutaneous injection in the left upper quadrant of the abdomen

Title: A randomized, double-blind, placebo-controlled, single ascending dose study of the safety and tolerability of subcutaneously administered sarilumab in Japanese patients with rheumatoid arthritis receiving concomitant methotrexate (TDU13402)

Objective:

- The primary objective is to assess the safety and tolerability of a single dose of subcutaneously administered sarilumab in Japanese patients with rheumatoid arthritis (RA) receiving concomitant treatment with methotrexate

- The secondary objective is to assess the pharmacokinetic profile of a single subcutaneous (SC) dose of sarilumab in Japanese RA patients

Study design: The study was a randomized, double blind, placebo-controlled, single subcutaneous, sequential-cohort, and dose-ascending Phase 1 study in Japanese RA patients, receiving concomitant methotrexate (MTX). Japanese patients (male and female) aged 20 through 65, with a diagnosis of RA were selected to participate in the study.

The study was conducted at 2 centers in Japan. A total of 24 patients were randomized into 3 cohorts of 8 patients per cohort, with 6 patients receiving active treatment (50 mg, 100 mg, or 200 mg), and 2 patients receiving placebo (**Table 41**).

Table 41. Dose escalation of sarilumab

Cohort	Dose (mg)	Number of Patients - Active: Placebo
1	50	6:2
2	100	6:2
3	200	6:2

- **Sampling Schedule**

PK Sampling Schedule

- Blood samples for PK evaluations were collected at predose (Day 1), and Days 1, 2, 3, 4, 8, 11, 15, 22, 29, 43, and 57 (± 1 for Days 15, 22, 29 and 43; ± 3 for Day 57) following sarilumab administration

Immunogenicity Sampling Schedule

Blood samples for ADA were collected at predose, and days 15 and 29.

Results:

Pharmacokinetic results

Plot of the mean (+SD) serum concentration-time profiles of functional and bound sarilumab are shown in Figure 49.

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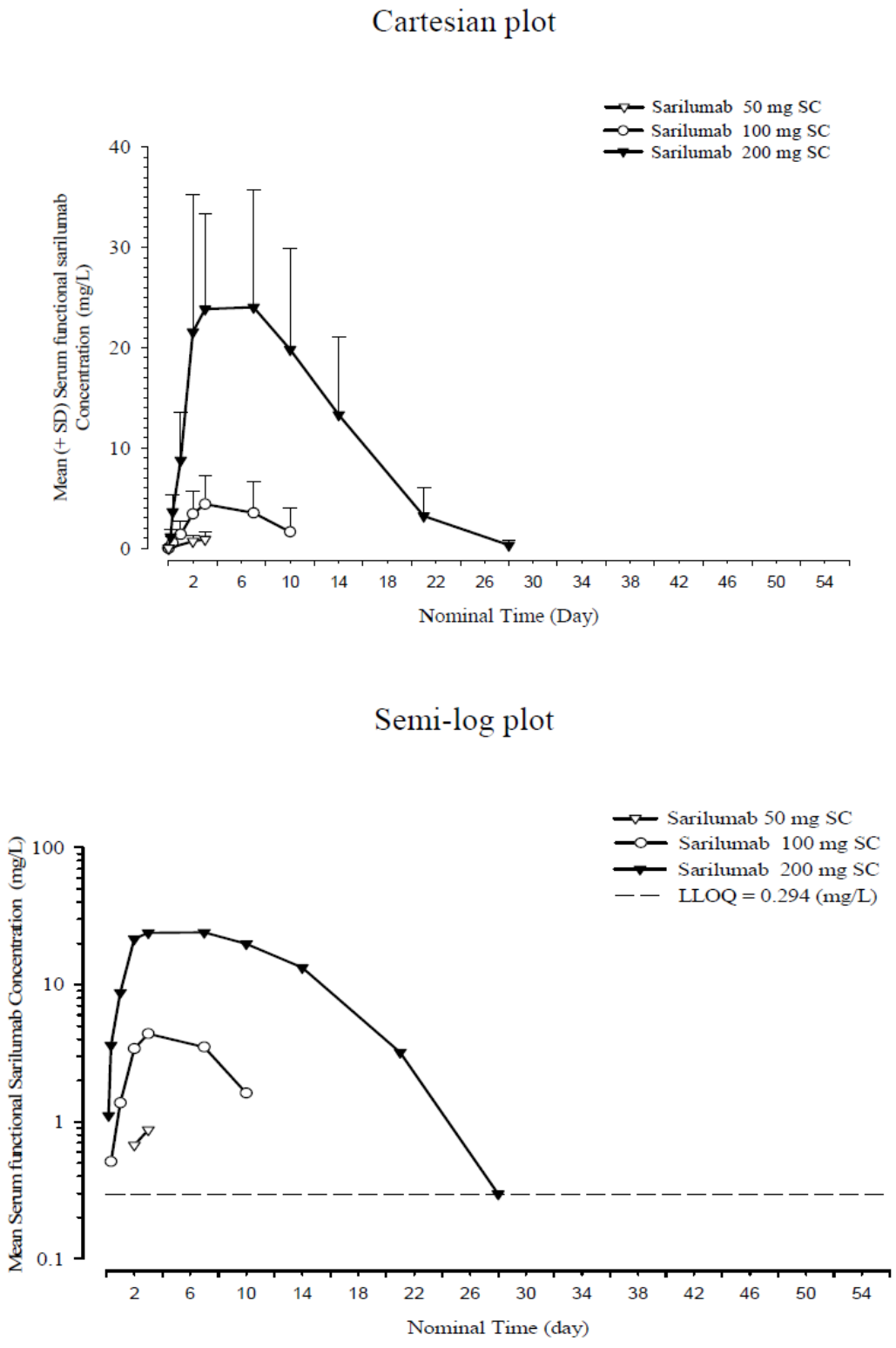

Figure 49. Mean (+ SD) serum concentration-time profiles of functional sarilumab (N≤6)
(Source: Figure 3, CSR TDU13402)

Descriptive statistics for serum functional and bound sarilumab PK parameter values are provided in Table 42. At the lowest SC dose of 50 mg, sarilumab concentrations were below LLOQ in either majority of the sampling times in most subjects (functional sarilumab) or at all the sampling times in all subjects (bound sarilumab). Median tmax of functional sarilumab was 3 days at all doses. At 200 mg, functional concentrations appeared to decline in a multiphasic manner. Functional sarilumab in serum had a mean terminal half-life (t1/2z) ranging from 1.62 days at 100 mg to 3.49 days at 200 mg, while the t1/2z of bound sarilumab could not be estimated.

Mean serum sarilumab exposure increased in a greater than dose proportional manner, with a 4-fold increase in dose over the entire range of 50 to 200 mg resulting in a 19.2- and 70.4 -fold increase in geometric mean Cmax, and AUClast of functional sarilumab, respectively. A 2-fold increase in dose from 100 to 200 mg resulted in a 6.9- and 13.3 -fold increase in geometric mean Cmax, and AUClast of functional sarilumab, respectively.

Table 42. Mean ± SD (geometric mean) [CV%] of functional sarilumab PK parameters in serum

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PK parameters	Sarilumab 50 mg SC	Sarilumab 100 mg SC	Sarilumab 200 mg SC
N	4[a]	6	6
C_{max} (mg/L)	1.36 ± 0.411 (1.31) [30.2]	4.54 ± 2.97 (3.66) [65.5]	27.7 ± 12.6 (25.1) [45.4]
C_{max}/Dose (1/L)	0.0272 ± 0.00822 (0.0262) [30.2]	0.0454 ± 0.0297 (0.0366) [65.5]	0.139 ± 0.0629 (0.126) [45.4]
t_{last}[b] (day)	7.00 (3.00 - 7.00)	8.50 (7.00 - 14.00)	21.07 (10.00 - 27.96)
t_{max}[b] (day)	3.00 (2.00 - 3.00)	3.00 (3.00 - 7.00)	3.00 (2.00 - 7.00)
$t_{1/2z}$ (day)	NC ± NC[c] (NC) [NC]	1.62 ± NC[d] (1.62) [NC]	3.49 ± 1.35[e] (3.31) [38.5]
AUC_{last} (mg•day/L)	4.69 ± 2.43 (3.99) [51.8]	33.0 ± 30.4 (21.1) [92.2]	339 ± 173 (281) [50.9]
AUC_{last}/Dose (day/L)	0.0938 ± 0.0486 (0.08) [51.8]	0.330 ± 0.304 (0.211) [0.922]	1.69 ± 0.863 (1.40) [50.9]
AUC (mg•day/L)	NC ± NC[c] (NC) [NC]	70.1 ± NC[d] (70.1) [NC]	409 ± 126[e] (391) [30.9]
V_z/F (L)	NC ± NC[c] (NC) [NC]	3.33 ± NC[d] (3.33) [NC]	2.53 ± 0.733[e] (2.44) [29.0]
V_{ss}/F (L)	NC ± NC[c] (NC) [NC]	8.51 ± NC[d] (8.51) [NC]	5.02 ± 1.47[e] (4.85) [29.2]
CL/F (L/day)	NC ± NC[c] (NC) [NC]	1.43 ± NC[d] (1.43) [NC]	0.536 ± 0.194[e] (0.511) [36.1]
MRT_{last} (day)	3.27 ± 0.722 (3.20) [22.1]	4.58 ± 1.18 (4.45) [25.8]	8.10 ± 1.96 (7.84) [24.2]

NC = not calculated.

[a] PK parameters at 50 mg could either not be calculated due to all concentrations below LLOQ (2 patients) or were based on only a few detectable concentrations (4 patients), [b] Median (Min - Max), [c] log-linear terminal phase could not be determined in all patients [d] N = 1 (log-linear terminal phase could not be determined in 5 patients), [e] N =5 (log-linear terminal phase could not be determined in 1 patient),

(Source –Table 15, CSR TDU13402)

Immunogenicity results

No patient had detectable anti-sarilumab antibodies.

Conclusions:

The PK of sarilumab is similar in Japanese population.

DRUG-DRUG INTERACTIONS

5. DDI with Simvastatin

Trial # INT12684, Part A

Study Type: Phase 1 single dose, DDI
Study Dates: 18/Feb/2014– 27/Feb/2015
Drug Product: Single-use prefilled glass syringe filled to 1.14 mL with 175 mg/mL (200-mg dose) of sarilumab solution for injection (P1F3)

Title: A multi-center, open-label, 2-treatment, single-sequence clinical study to evaluate the effects of a single 200 mg subcutaneous injection of sarilumab on the pharmacokinetics of a single 40 mg oral dose of simvastatin, with optional 1-year extension of open-label treatment of sarilumab, in patients with rheumatoid arthritis

- **Objective:**

The primary objectives was to evaluate the effect of a single 200-mg subcutaneous (SC) injection of sarilumab on the PK of simvastatin in patients with RA.
The secondary objectives was to describe the safety and efficacy (exploratory) of sarilumab.

- **Study design and treatment schedule:**

This study was composed of 2 parts. Part A was an open-label, single-sequence, 2-period, 2-treatment, nonrandomized study to evaluate the effect of a single dose of sarilumab on the PK of a single dose of simvastatin in patients with RA. Part B was an uncontrolled open-label extension study. This review will focus on the Part A of the study.

In Part A, 19 patients were enrolled. The patients received a single oral dose of 40 mg (2 x 20-mg tablets) simvastatin on Day 1 of Period 1 (total duration of Period 1 was 1 day) and a single oral dose of 40 mg simvastatin on Day 8 of Period 2, under fed conditions, after a single SC injection in the abdomen of 200 mg sarilumab was administered on Day 1 of Period 2.), as shown in Figure 50.

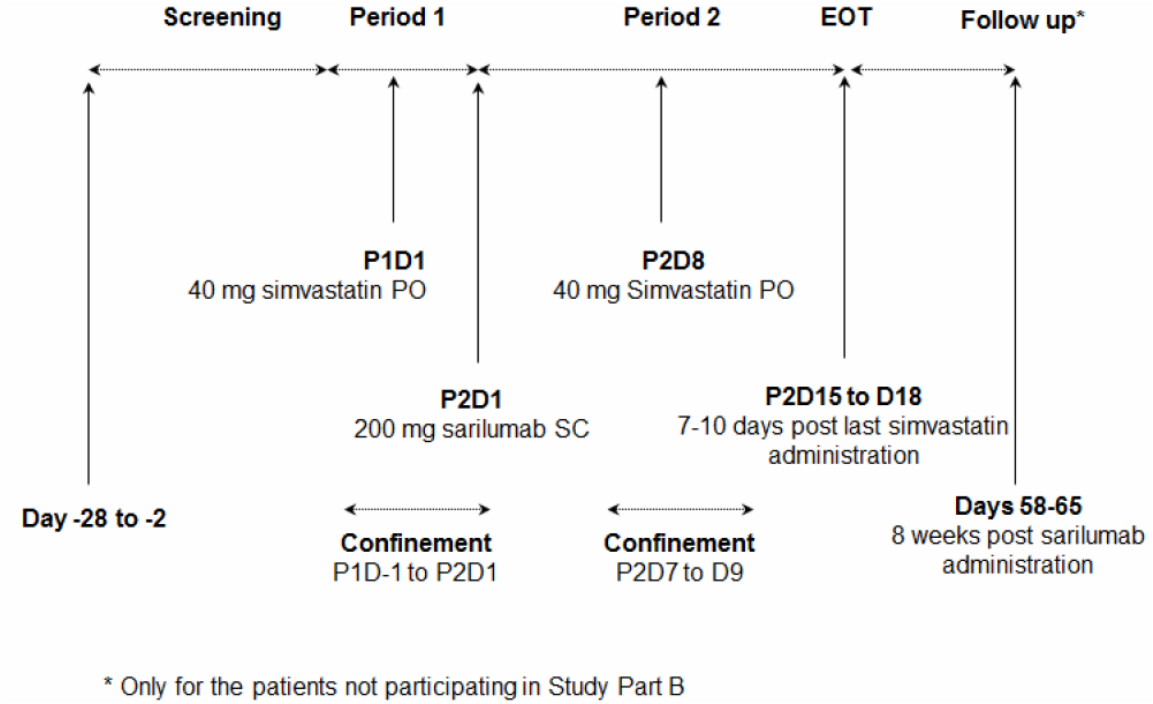


Figure 50. Study design of Part A
(Source: Figure 1, CSR INT12684)

- **Sampling Schedule**

PK Sampling Schedule

- Simvastatin: Blood samples were collected to determine plasma concentrations of simvastatin and simvastatin acid at predose, and 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, and 24 hours postdose on Day 1 of Period 1 and Day 8 of Period 2.
- Sarilumab: Blood samples were collected to determine serum concentrations of functional sarilumab: Period 1: Day 2; Period 2: Days 1 (prior to dosing), 7, and 9, at the end of treatment (prior to dosing for patients participating in Part B) between Days 15 to 18 and at the follow-up visit between Days 58 to 65 (for patients participating in Part A only).

PD (hs-CRP, sIL-6R, and IL-6) Sampling Schedule

Blood samples for sIL-6R, and IL-6 (Part A) were collected at Period 1: Day -1 Period 2: Prior to dosing on Day 8, at the end of treatment (prior to dosing for patients participating in Part B) between Days 15 to 18 (for patients completing in Part A only). A sample for hs-CRP only was collected at screening.

Immunogenicity Sampling Schedule

Blood samples for sIL-6R, and IL-6 (Part A) were collected at Period 1: Day -1 Period

- **Results and Conclusions:**

PK results

Administration of a single SC dose of 200 mg sarilumab with a single oral dose of 40 mg simvastatin to RA patients resulted in a reduction in exposure to simvastatin (45%) and simvastatin acid (36%). Descriptive statistics for PK parameters of plasma simvastatin and simvastatin acid are provided in Table 43. Results of the statistical analyses of PK data of simvastatin and simvastatin acid are presented in Table 44.

Individual and mean plasma simvastatin and simvastatin acid concentrations with descriptive statistics, as well as sampling times, are listed in 16-2-5-cdc-data [16.2.5.2.2]. Plots of the mean (+SD) plasma concentration-time profiles of simvastatin and simvastatin acid are presented in Figure 51 and Figure 52.

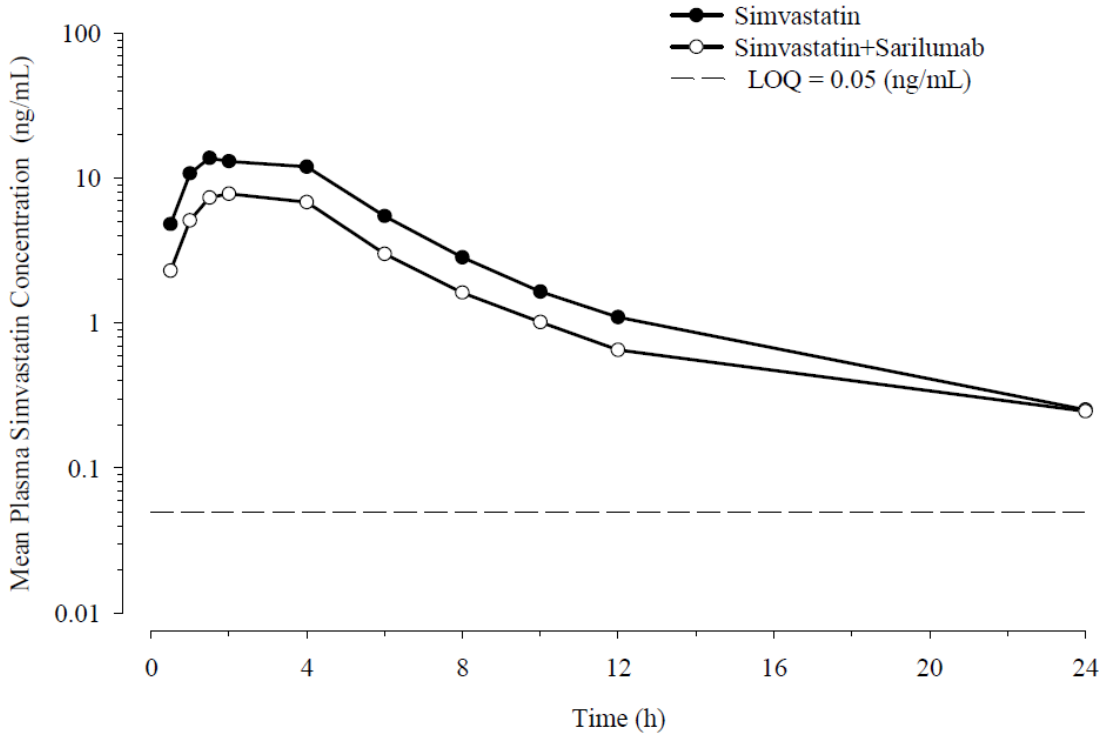


Figure 51. Mean plasma concentration-time profiles of simvastatin following a single oral dose of 40 mg simvastatin in RA patients

(Source: Figure 2, CSR12684)

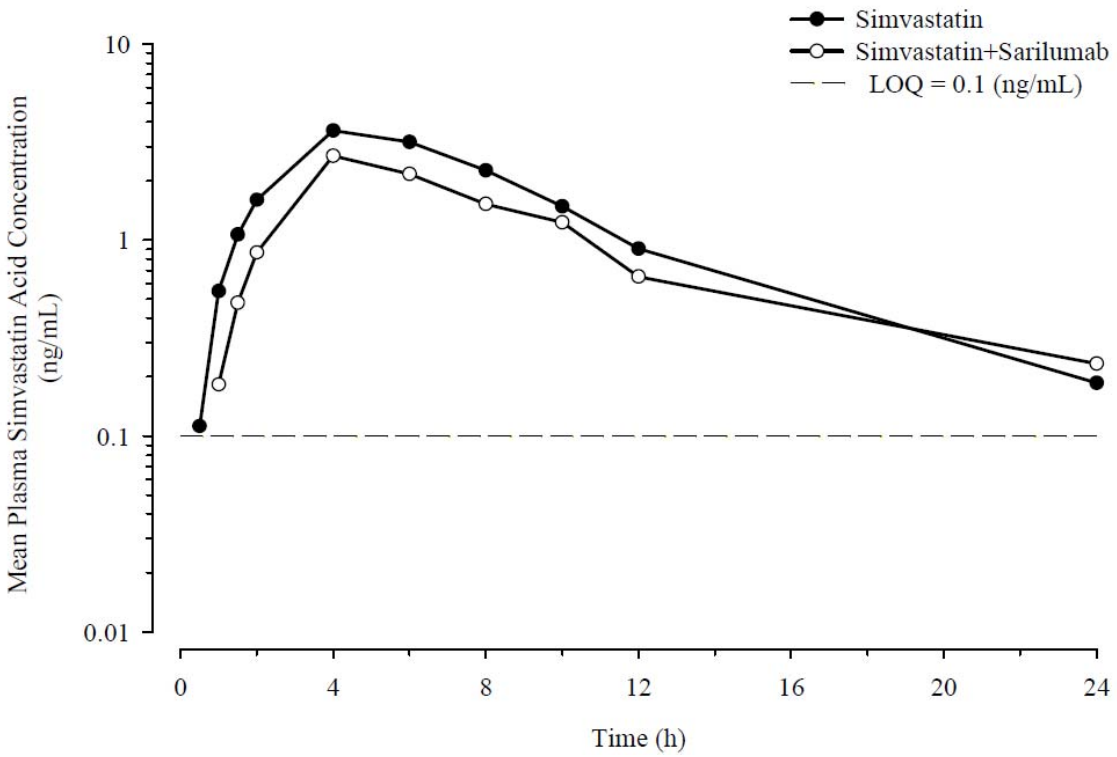


Figure 52. Mean (+SD) plasma concentration-time profiles of simvastatin acid following a single oral dose of 40 mg simvastatin in RA patients

(Source: Figure 3, CSR12684)

Table 43: Mean ± SD (Geometric Mean) [CV%] of simvastatin and simvastatin acid pharmacokinetic parameters following a single oral dose of 40 mg simvastatin in RA patients

Parameter	Plasma Simvastatin		Plasma Simvastatin Acid	
	Simvastatin alone	Simvastatin after Sarilumab	Simvastatin alone	Simvastatin after Sarilumab
N	17 [b]	17 [b]	17 [b]	17 [b]
C_{max}	21.3 ± 12.8	11.0 ± 5.83	4.18 ± 3.43	2.95 ± 2.83
(ng/mL)	(17.1) [60.3]	(9.28) [53.1]	(3.24) [82.1]	(2.07) [96.2]
t_{max}[a]	2.00	2.00	4.00	4.02
(h)	(1.00 - 4.00)	(0.50 - 4.00)	(2.00 - 6.02)	(4.00 - 6.00)
AUC_{last}	82.7 ± 52.8	46.6 ± 32.7	29.6 ± 22.9	20.5 ± 18.3
(ng•h/mL)	(67.2) [63.9]	(36.3) [70.1]	(22.4) [77.5]	(14.1) [89.4]
AUC	84.3 ± 53.6	47.9 ± 33.4	31.5 ± 23.3	22.2 ± 19.0
(ng•h/mL)	(68.7) [63.6]	(37.6) [69.7]	(24.3) [73.9]	(15.6) [85.5]
$t_{1/2z}$	3.74 ± 1.21	3.83 ± 1.43	3.82 ± 1.18	3.53 ± 1.30
(h)	(3.54) [32.4]	(3.57) [37.2]	(3.61) [30.9]	(3.34) [36.8]

[a] Median (Min - Max)

[b] PK parameters of 2 patients were not calculated due to missing concentration for the whole profile (sample stability issues during the bioanalysis).

(Source: Table 20, CSR INT12684)

Table 44: Treatment (Simvastatin after sarilumab vs simvastatin alone) ratio estimates for simvastatin and simvastatin acid with 90% CI

Analyte	Parameter	N	Estimate	90% CI
Simvastatin	C_{max}	17	0.541	(0.422 to 0.694)
	AUC_{last}	17	0.540	(0.465 to 0.628)
	AUC	17	0.547	(0.472 to 0.633)
Simvastatin Acid	C_{max}	17	0.641	(0.555 to 0.741)
	AUC_{last}	17	0.628	(0.536 to 0.737)
	AUC	17	0.641	(0.541 to 0.758)

(Source: Table 21, CSR INT12684)

PD results

The PD effect on IL-6 related biomarkers was significant one week after the administration of sarilumab (P2D8).

sIL-6R: At baseline the mean serum total sIL-6R level was 52.5 ng/mL. Mean total sIL-6R increased to 209.62 ng/ml 1 week after administration of sarilumab and 286.4 ng/mL approximately 2 weeks after administration of sarilumab and 1 week after administration of simvastatin (Figure 53).

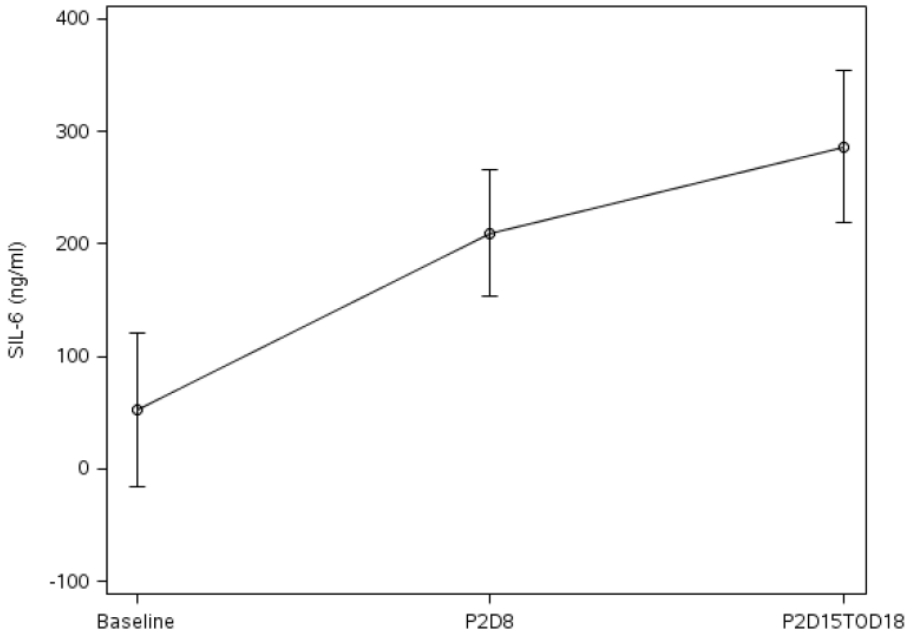


Figure 53. Raw data for SIL-6R from baseline to 1 week (P2D8) and 2 weeks (P2D15TOD18) post single dose of sarilumab 200 mg
(Source – Figure 16.2.6.1.2.1, IND12684-16-2-6 PD response)

IL-6: The mean serum IL-6 level was 47.5 pg/mL before sarilumab alone and increased to 219.9 pg/mL 1 week after sarilumab alone, then decreased to 138.5 pg/mL approximately 2 weeks after administration of sarilumab and 1 week after administration of simvastatin (Figure 54).

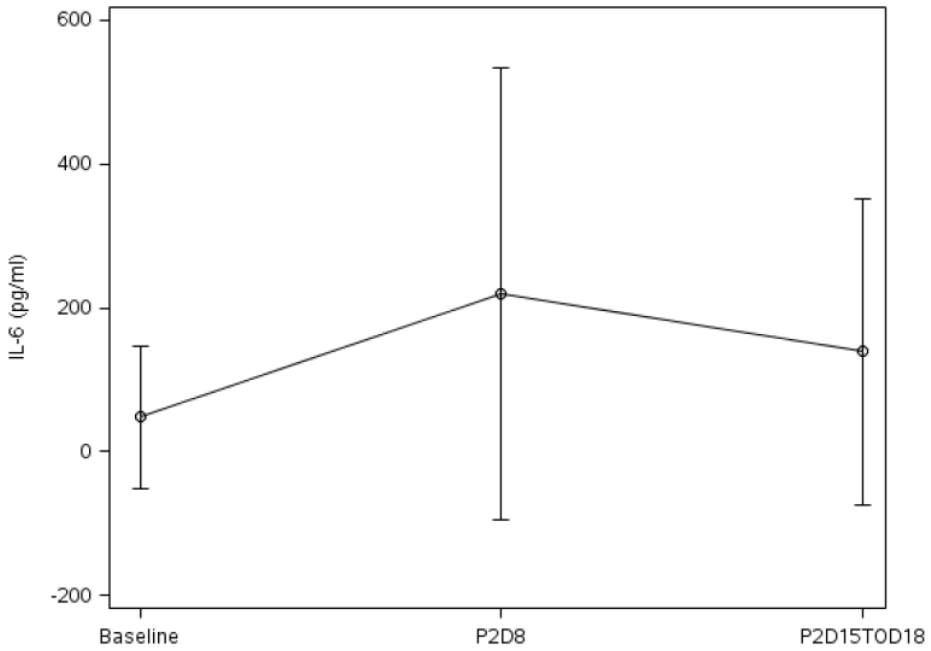


Figure 54. Raw data for IL-6 from baseline to 1 week (P2D8) and 2 weeks (P2D15TOD18) post single dose of sarilumab 200 mg
(Source – Figure 16.2.6.1.1.1, IND12684-16-2-6 PD response)

Hs-CRP: Baseline levels of CRP were elevated (22.1 mg/L), as is anticipated in patients with active RA and as required per the protocol. The baseline levels of CRP, however, were highly variable, with values for individual patients ranging from 1.40 to 92.90 mg/L. Mean CRP decreased reaching a nadir (1.88 mg/L) 1 week after sarilumab alone, and remained lower than baseline approximately 2 weeks after administration of sarilumab and 1 week after administration of simvastatin on Period 2, Day 8, with mean levels of 5.94 mg/L (Figure 55).

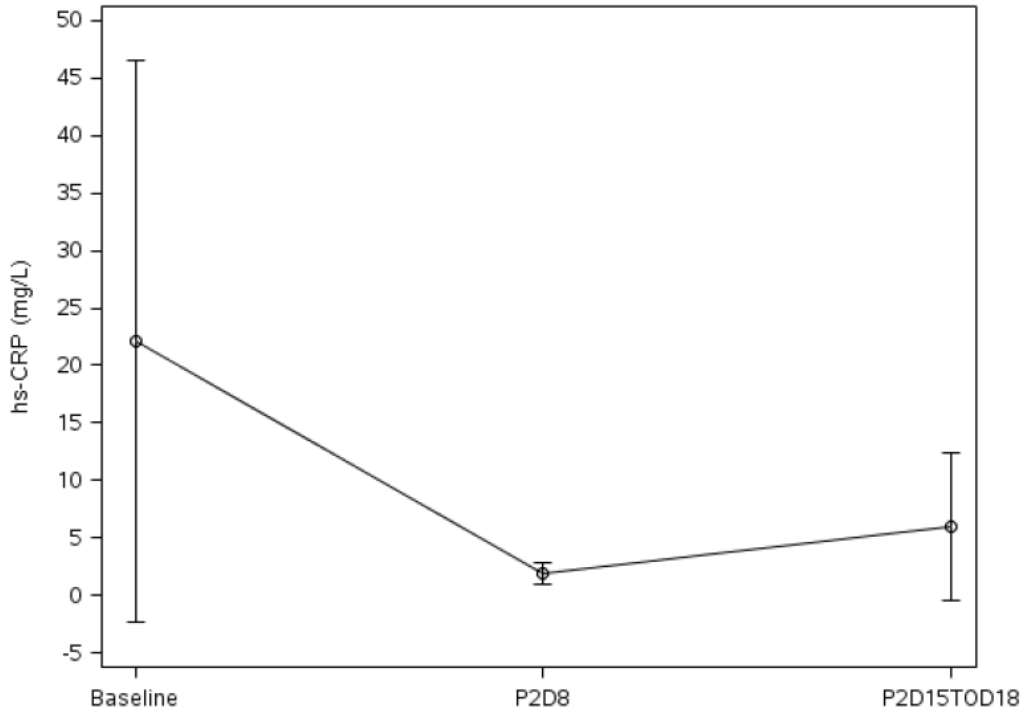


Figure 55. Raw data for hs-CRP from baseline to 1 week (P2D8) and 2 weeks (P2D15TOD18) post single dose of sarilumab
(Source – Figure 16.2.6.1.3.1, IND12684-16-2-6 PD response)

Rheumatoid factor: Mean rheumatoid factor levels approximately 2 weeks after administration of sarilumab and 1 week after administration of simvastatin on Period 2, Day 8 were similar to those observed at baseline.

Immunogenicity results

One patient had a positive result for ADA during the TEAE period of Part A of the study.

- **Conclusions:**

The exposure of CYP3A substrates simvastatin and simvastatin acid was reduced when coadministered with sarilumab. This is consistent with similar studies with tocilizumab and sarilumab, suggesting that sarilumab may reverse IL-6-mediated suppression of CYP3A activity in patients with active RA.

The PD profiles of sarilumab in this study were consistent with the anticipated effects of IL-6 inhibition and previous observations with this molecule. The PD effect on IL-6 related biomarkers was significant one week after the administration of sarilumab (P2D8).

BIOPHARMACEUTICS

6. Relative Bioavailability Healthy

Trial # TDU11373

Study Type: Phase 1 single dose, formulation bridging study in healthy male subjects

Study Dates: 09/Jul/2010– 21/Dec/2010

Drug Product: sarilumab administered as different drug products generated from different cell lines, manufacturing processes, and formulations, and considered for future clinical development

- 175 mg/mL solution of sarilumab – (b) (4) F3 drug product
- 150 mg/mL solution of sarilumab – (b) (4) F3 drug product
- 100 mg/mL solution of sarilumab – (b) (4) F3 drug product
- 100 mg/mL solution of sarilumab – (b) (4) F3 drug product

(b) (4)

Table 45. Summary of sarilumab drug products

Drug product	Process	Antibody-producing cell line	Excipients
(b) (4) F1	(b) (4)	(b) (4)	Formulation 1 [a]
F2			Formulation 2 [b]
F3			Formulation 3 [c]
F3			Formulation 3 [c]

[a] (b) (4) mM histidine, 0.2% polysorbate 20, and (b) (4) % sucrose;
[b] mM histidine, 0.2% (w/v) polysorbate 20, and (b) (4) % (w/v) sucrose;
[c] mM histidine, 0.2% polysorbate 20, (b) (4) mM arginine, and 5% sucrose.

(Source: Table 4.29, CSR TDU11373)

Title:

Randomized, double-blind, single subcutaneous dose, parallel-design study of the tolerability of different SAR153191 drug products that differ with respect to manufacturing processes and formulation, at different concentrations and doses, in healthy male subjects

Objective:

- The primary objective:

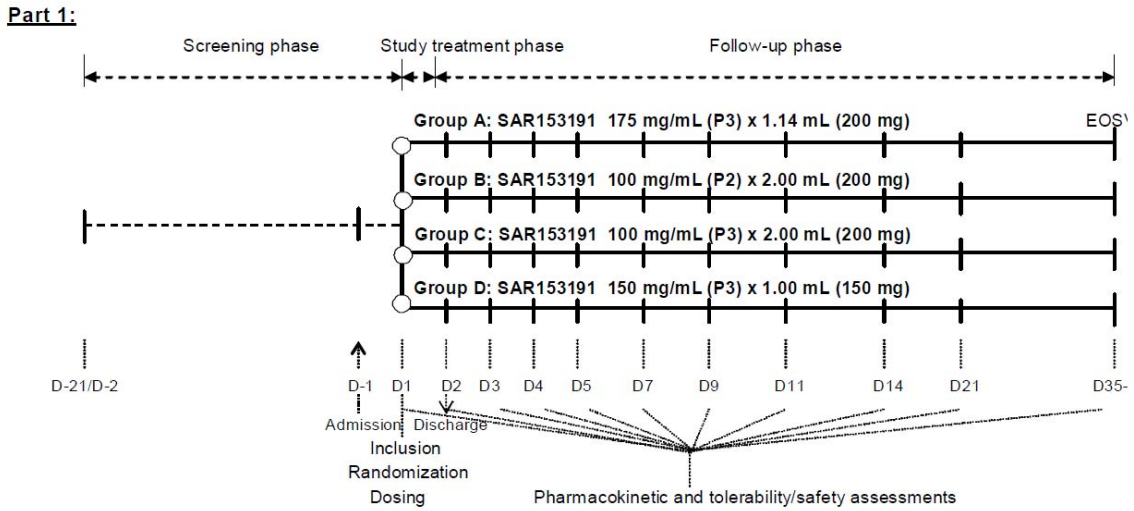
  To determine the tolerability of different SAR153191 (sarilumab) drug products that differ with respect to manufacturing processes and formulation, at different

concentrations and doses, after administration of single subcutaneous doses to healthy male subjects.

- The secondary objective were:
  - To determine the pharmacokinetic (PK) profile of the different SAR153191 drug products administered subcutaneously
  - To assess the safety of the different sarilumab drug products administered subcutaneously

Study Design:

This was a multicenter, double-blind, randomized, no-placebo, parallel-group, single-dose study of sarilumab administered subcutaneously (SC) in healthy male subjects. The (b) (4) F2 drug product was used as a comparator to the new drug products ((b) (4) F3 and (b) (4) F3). Part 1 was terminated for safety reasons after the inclusion of 12 subjects, and Part 2 was completed. The study design was illustrated in Figure 56.



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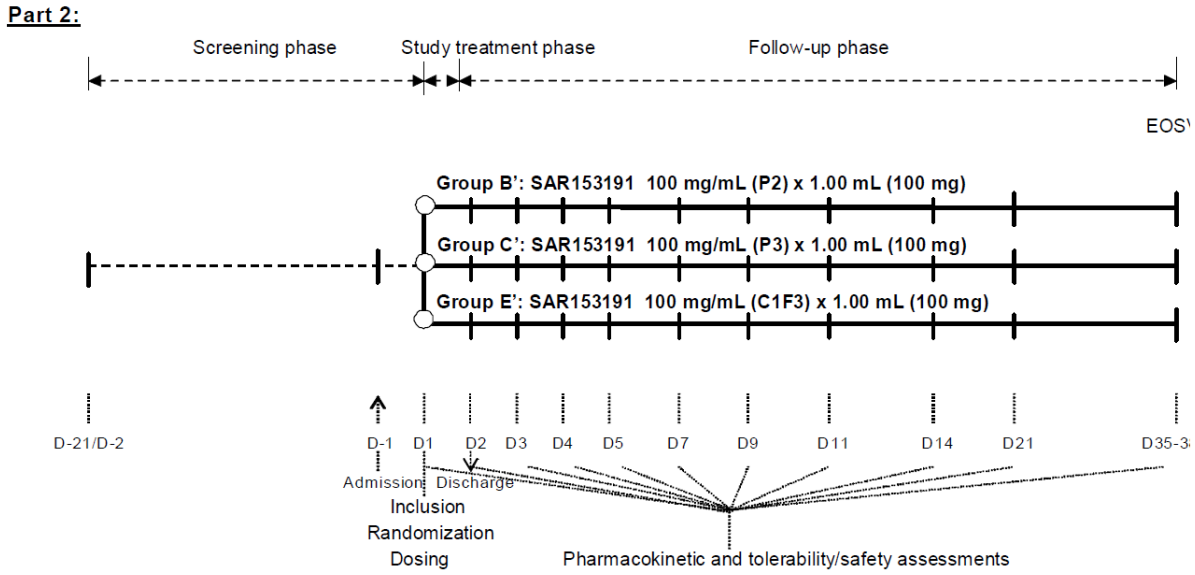

Note: P3 refers to the C2F3 formulation and P2 refers to the C1F2 formulation

Figure 56. Study design.
(Source: Figure 1, CSR TDU11373)

- **Sampling Schedule**

PK Sampling Schedule

Blood samples for the determination of sarilumab concentrations in serum were collected at predose, and on Days 1, 2, 3, 4, 5, 7, 9, 11, 14, 21, and at the EOS visit (Days 35 to 38) following sarilumab administration.

Immunogenicity Sampling Schedule

Serum samples were collected for analysis of antibodies to sarilumab. These samples were collected predose, and on Day 7, 21, and at the EOS visit (Days 35 to 38) following sarilumab administration.

PK Results:

Plots of the mean (+SD) serum concentration-time profiles are shown in Figure 57 and Figure 58 for Part 1 and Part 2, respectively. Descriptive statistics for functional sarilumab PK parameter values are provided in Table 46 for Study Part 2 (i.e., 100 mg dose groups).

Estimates and 95% CIs for the formulation ratios for functional sarilumab Cmax and AUClast geometric means ((b) (4) F3 and (b) (4) F3 versus (b) (4) F2) from study Part 2 are provided in Table 47 below. When administered at a dose of 100 mg (100 mg/mL x 1.00 mL), the geometric mean ratios of (b) (4) F3 versus (b) (4) F2 and (b) (4) F3 versus (b) (4) F2 were 0.91 (95% CI = 0.55 to 1.51) and 0.90 (95% CI = 0.54 to 1.50) for Cmax, respectively; and 0.86 (95% CI = 0.43 to 1.71) and 0.94 (95% CI = 0.47 to 1.89) for AUClast, respectively.

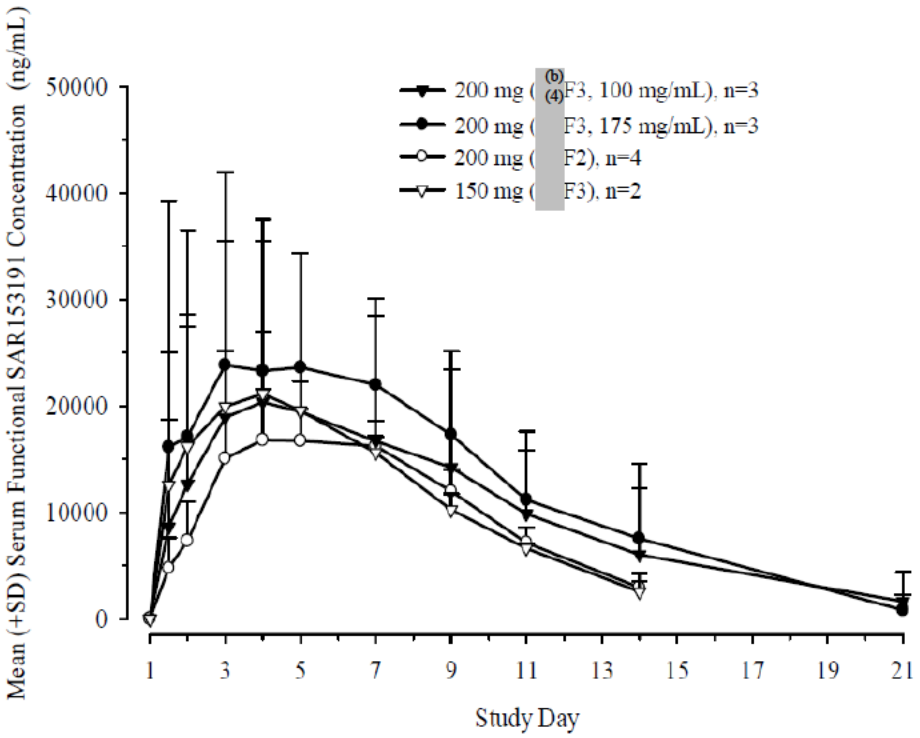

Figure 57. Mean serum functional sarilumab concentrations (study Part 1: 150 and 200 mg sarilumab)

(Source: Figure 6, CSR TDU11373)

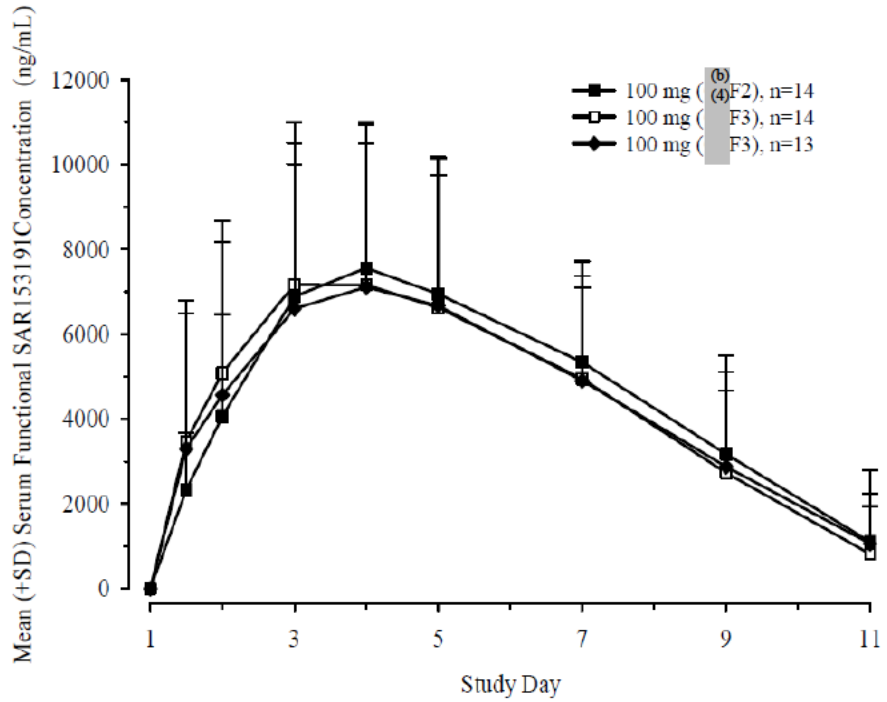

Figure 58. Mean serum functional sarilumab concentrations (study Part 2: 100 mg sarilumab)

(Source: Figure 4, CSR TDU11373)

Table 46. Mean ± SD (geometric mean) [CV%] serum PK parameters of functional sarilumab (100 mg sarilumab) (Part 2)

Parameters	100 mg/mL ([b](4)F2) x 1.00 mL 100 mg (Group B') (n=14)	100 mg/mL ([b](4)F3) x 1.00 mL 100 mg (Group C') (n=14)	100 mg/mL ([b](4)F3) x 1.00 mL 100 mg (Group E') (n=13)
C_{max}	7880 ± 3270	7770 ± 3650	7350 ± 3790
(ng/mL)	(7060) [41.5]	(6450) [47.0]	(6360) [51.6]
t_{max} [a]	72.00	60.00	72.00
(h)	(48.00 - 192.45)	(24.00 - 144.00)	(48.00 - 96.00)
$t_{1/2z}$	45.7 ± 21.2	53.5 ± 25.6	49.5 ± 17.7
(h)	(41.2) [46.4]	(48.3) [47.9][b]	(46.6) [35.7][b]
AUC_{last}	1140000 ± 565000	1080000 ± 544000	1080000 ± 643000
(ng•h/mL)	(943000) [49.7]	(812000) [50.1]	(886000) [59.4]
AUC	1240000 ± 609000	1320000 ± 601000	1280000 ± 712000
(ng•h/mL)	(1050000) [49.0]	(1200000) [45.6][b]	(1110000) [55.6][b]

[a] Median (Min - Max); [b] n=12 due to a poorly defined terminal phase in 2 subjects

(Source: Table 31, Study TDU11373)

Table 47. Estimates of formulation geometric mean ratio with 95% confidence interval (100 mg sarilumab) (Part 2)

Parameter	Comparison	Geometric Mean Ratio Estimate	95% CI
Cmax	100mg ([b](4)F3) / 100mg ([b](4)F2)	0.91	(0.55 to 1.51)
	100mg (F3) / 100mg (F2)	0.90	(0.54 to 1.50)
AUClast	100mg ([b](4)F3) / 100mg ([b](4) F2)	0.86	(0.43 to 1.71)
	100mg (F3) / 100mg (F2)	0.94	(0.47 to 1.89)

(Source: Study TDU11373 synopsis, page 6)

Immunogenicity Results:

Twenty-three out of 53 subjects had positive anti-sarilumab antibodies at some point during the study (4 of 12 subjects in Part 1 and 19 of 41 subjects in Part 2) and 18 of 53 subjects at the EOS visit, on Day 35 (4 of 12 subjects in Part 1 and 14 of 41 subjects in Part 2). The incidence of subjects with positive or negative anti-sarilumab antibodies by visit for part 2 is shown in **Table 48**. While it is not possible to draw conclusions for the first part of the study due to the limited number of subjects, in Part 2 the incidence of anti-sarilumab antibodies was similar among subjects receiving the 3 drug products, and titer levels were in the same range as well (highest titers = 960, 960, and 1920 in Groups B', C', and E', respectively). No association was observed between antidrug antibody development and adverse events or IMP exposure.

Table 48. Number (%) of subjects negative/positive for anti-sarilumab antibody by theoretical time and treatment – Part 2

		SAR153191					
		Group B' (N=14)		Group C' (N=14)		Group E' (N=13)	
Visit	Theo. time	Neg	Pos	Neg	Pos	Neg	Pos
D1	T0H	14 (100%)	0	14 (100%)	0	13 (100%)	0
D7	T144H	12 (85.7%)	2 (14.3%)	11 (78.6%)	3 (21.4%)	10 (76.9%)	3 (23.1%)
D21	T480H	8 (57.1%)	6 (42.9%)	11 (78.6%)	3 (21.4%)	8 (61.5%)	5 (38.5%)
EOS	T816H	9 (64.3%)	5 (35.7%)	10 (71.4%)	4 (28.6%)	8 (61.5%)	5 (38.5%)

Note: Neg. = Negative, Pos = Positive

Note: Result on D1/T0H is predose test.

Group A: 175 mg/mL ((b)(4)F3) x 1.14 mL (200 mg of SAR153191); Group B: 100 mg/mL ((b)(4)F2) x 2.00 mL (200 mg of SAR153191); Group C: 100 mg/mL ((b)(4)F3) x 2.00 mL (200 mg of SAR153191); Group D: 150 mg/mL ((b)(4)F3) x 1.00 mL (150 mg of SAR153191); Group B': 100 mg/mL ((b)(4)F2) x 1.00 mL (100 mg of SAR153191); Group C': 100 mg/mL ((b)(4)F3) x 1.00 mL (100 mg of SAR153191); Group E': 100 mg/mL ((b)(4)F3) x 1.00 mL (100 mg of SAR153191)

(Source: Table 27, CSR 11373)

Conclusions:

PK profiles and sarilumab exposure after administration of (b)(4)F3 or (b)(4)F3 drug product were similar to that of (b)(4)F2 drug product. Note the sample size is small for a formal BE assessment. However, the phase 3 product is the same as the to-be-marketed product, and no information from earlier formulations were in the final label.

7. Relative Bioavailability RA

Trial # PKM12058

Study Type: Phase 1 single dose

Study Dates: 16/May/2011– 30/Sep/2011

Drug Product:

- Group A (Test): (b)(4)F3, 175 mg/mL × 1.14 mL, solution of sarilumab in prefilled syringes
- Group B (Reference): (b)(4)F2, 100 mg/mL × 2.00 mL, solution of sarilumab in vials

Title: A randomized, single-blind, parallel group study of the safety, tolerability and pharmacokinetics of a new SAR153191 drug product, that differs with respect to manufacturing process, cell line, formulation and concentration, in comparison to a previously tested drug product, after administration of a 200 mg single subcutaneous dose to rheumatoid arthritis patients

- **Objectives**

- To determine the safety and tolerability of a new sarilumab drug product, that differs with respect to manufacturing process, cell line, formulation, and concentration, in comparison to a previously tested drug product, after administration of a 200 mg single subcutaneous (SC) dose to rheumatoid arthritis (RA) patients.
- To determine the pharmacokinetic (PK) profile in RA patients of the new sarilumab drug product, administered subcutaneously, in comparison to the previously tested drug product.

- **Study design and treatment schedule:**

This was a randomized, single-blind, single SC dose, no placebo, multicenter study in 32 patients with RA undergoing MTX co-therapy. It was conducted in 2 parallel groups of patients, each receiving 200 mg sarilumab as either 175 mg/mL of (b) (4) F3 (test group) or 100 mg/mL of (b) (4) F2 (reference group).

This study was designed to provide information on the safety and pharmacokinetics of the highest possible dose of sarilumab (200 mg, single dose) using the highest concentration (175 mg/mL) of (b) (4) F3, selected for Phase 3, and to compare the obtained data to the data observed at the same dose of (b) (4) F2 (100 mg/mL) used in Phase 2.

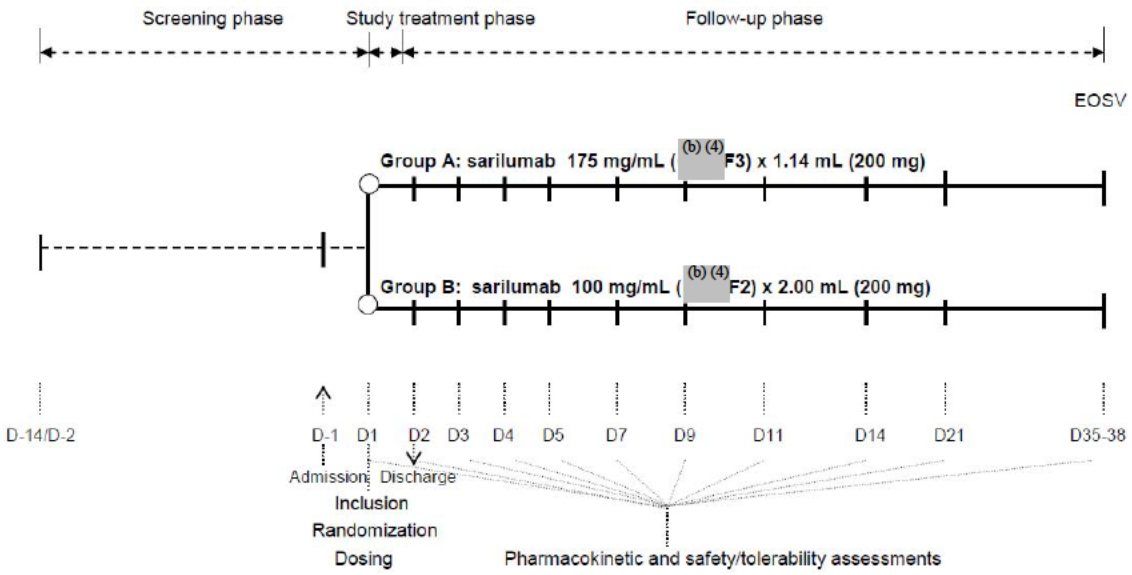

Figure 59. Study design.
(Source: Figure 1, CSR PKM12058)

- **Sampling Schedule**

PK Sampling Schedule

PK blood samples were collected predose on Day 1 and 12h postdose, and on Days 2 (i.e., 24h postdose), 3, 4, 5, 7, 9, 11, 14, 21, and 35 following sarilumab administration.

Immunogenicity Sampling Schedule

Anti-drug antibodies (ADA) to sarilumab were assessed predose and on Days 7, 21, and at EOS visit (Day 35). In case of positive result at the EOS visit, an additional sample was collected 3 months after IMP administration.

- **Results and Conclusions**

Mean (+SD) serum concentration-time profiles of functional sarilumab are shown in Figure 60. Descriptive statistics of PK parameter values are shown in Table 49. The geometric mean ratios for Cmax and AUC of Lot B relative to the Site 1 lot were both approximately 1.2. The 95% CIs for the geometric mean ratios for Cmax and AUC were listed in Table 50.

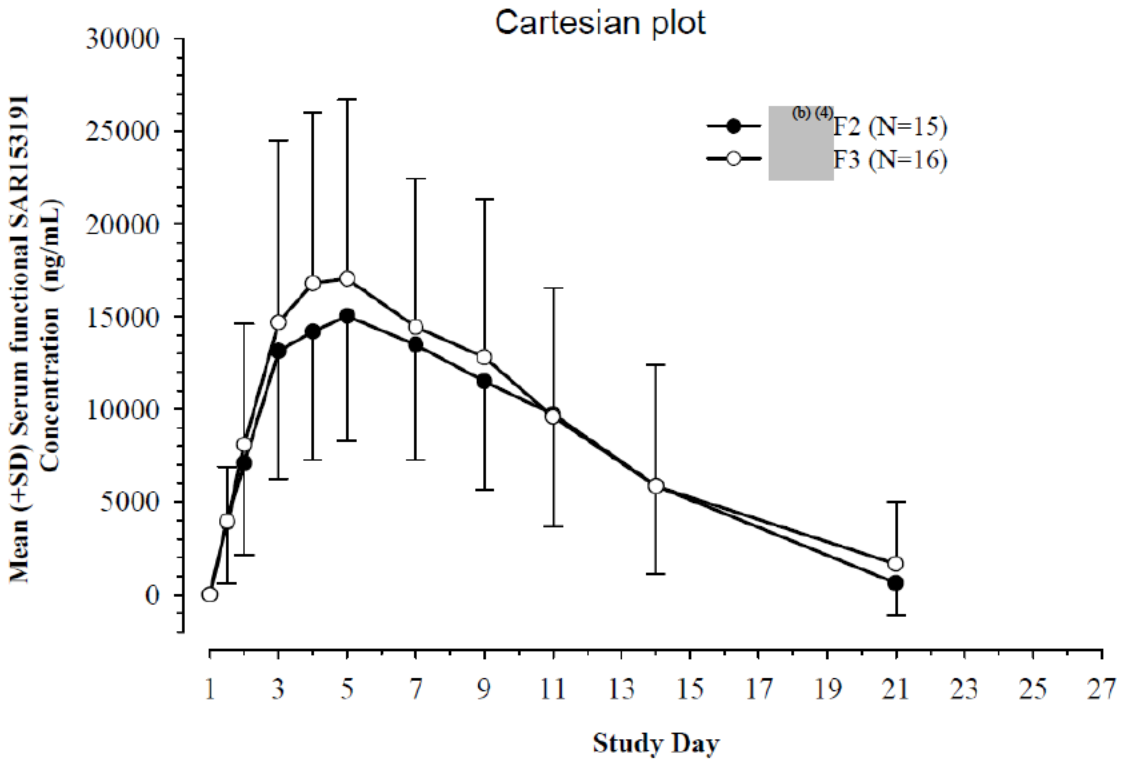

Figure 60. Mean serum concentrations of functional sarilumab

(Source: Figure 4, pkm12058)

Table 49. Mean ± SD (Geometric Mean) [CV %] of serum functional sarilumab PK parameters

Parameters	[redacted] F3 (N=16)	[redacted] F2 (N=15)
C_{max} (ng/mL)	17900 ± 9980 (15400) [55.8]	15800 ± 7020 (14400) [44.4]
t_{max}[a] (h)	95.9 (48.0 – 192)	96.0 (48.0 – 145)
AUC_{last} (ng•h/mL)	4280000 ± 3510000 (3280000) [82.1]	3680000 ± 2220000 (3180000) [60.3]
AUC (ng•h/mL)	4850000 ± 3640000 (3790000) [75.1][b]	4290000 ± 2580000 (3670000) [60.2][b]
CL/F (mL/h)	67.3 ± 49.7 (52.7) [73.9][b]	62.9 ± 34.1 (54.5) [54.1][b]
V_{ss}/F (mL)	11500 ± 7110 (9760) [61.7][b]	12000 ± 6040 (10600) [50.3][b]
$t_{1/2z}$ (h)	86.2 ± 39.8 (76.6) [46.1]	110 ± 60.2 (96.6) [54.9]

[a] Median (min-max); [b] N=15 ([redacted] F3) and N=13 ([redacted] F2) due to AUC extrapolation >30%

(Source: Table 21, csr pkm12058)

Table 50. Point estimates of treatment ratios with 95% confidence interval

Comparison	Parameter	Estimate	95% CI
[redacted] F3 vs. [redacted] F2	C_{max}	1.18	(0.83 to 1.66)
	AUC_{last}	1.21	(0.82 to 1.79)

The estimates are based on the linear fixed effect model with fixed terms for gender, weight, and treatment.

(Source: Table 22, csr pkm12058)

Immunogenicity Results:

Anti-sarilumab antibodies were positive in 3 patients in each treatment group at the EOS visit on Day 35. No previous time points were positive for anti-sarilumab antibodies. Among the 6 patients with positive ADAs at the EOS visit, 4 patients remained positive (2 patients in each treatment group) and 2 became negative at a 3-month follow-up visit (1 patient in each treatment group).

- **Conclusions**

These data demonstrated that, in patients with RA, there was comparable PK and immunogenicity between the (b) (4) F3 drug product (175 mg/mL, PFS, the phase 3 and to-be-marketed drug product) and the (b) (4) F2 drug product (100 mg/mL, vial) used in the Phase 2 study (EFC11072, Part A).

Note the sample size is small for a formal BE assessment. However, the phase 3 product is the same as the to-be-marketed product, and no information from earlier formulations were in the final label. Therefore, the PK bridging study is acceptable.

PHARMACODYNAMICS

8. On background of MTX

Study # ACT10804/6R88-RA-0803

Study Type: Phase 1b PD study

Study Dates: 14/Jan/2009– 12/May/2009

Drug Product:

• REGN88: One dose of 50, 100 or 200 mg

Title: A Single-dose, Double-Blind, Placebo-Controlled, Parallel Group, Safety, Tolerability, and Pharmacodynamic Study of Subcutaneous REGN88 in Patients with Rheumatoid Arthritis Receiving Concomitant Methotrexate

- **Objective:**
  - The primary objective was to assess the bioeffect of a single dose of REGN88 compared with placebo in patients with active rheumatoid arthritis (RA) who were receiving concomitant treatment with methotrexate (MTX).
  - The secondary objectives were to determine the safety and tolerability of REGN88 in patients with active RA who were receiving concomitant MTX.

- **Study design –** This study was a multi-center, single-dose, double-blind, placebo-controlled, parallel group, safety, tolerability, and pharmacodynamic (PD) study in patients with RA receiving concomitant MTX. Thirty-two patients who met all of the eligibility criteria and none of the exclusion criteria were randomized into 4 dose cohorts (1:1:1:1) to receive a

single subcutaneous (SC) dose of placebo or 50 mg, 100 mg, or 200 mg REGN88 into the abdomen. Patients were followed for a total of 10 study visits over 6 weeks (screening, day 1, day 4, day 8, day 12, day 15, day 22, day 29, day 36 and day 43).

- **Sampling Schedule**

PK Sampling Schedule

PK blood samples were collected predose on Day 1, and on Days 4 (i.e., 24h postdose), 8, 12, 15, 22, 29, 36, and 43 following sarilumab administration.

Immunogenicity Sampling Schedule

Anti-drug antibodies (ADA) to sarilumab were assessed predose and on Days 1, 4, 29 and at EOS visit (Day 43).

PD Sampling Schedule

Bioeffect was assessed by evaluation of hs-CRP, interleukin-6 (IL-6), serum amyloid A (SAA) and erythrocyte sedimentation rate (ESR) levels at predose on Day 1, and on Days 4 and at EOS visit (day 43.

Other exploratory assessments included collection of samples for rheumatoid factor (RF)/anti-nuclear antibody (ANA)/double-stranded deoxyribonucleic acid (dsDNA) at visit 2 (day 1), visit 8 (day 29) and visit 10 (day 43); and for proteomic and RNA analyses at visits 2 (day 1), visits 3 to 5 (days 4, 8, and 12) and visits 7 to 10 (days 22, 29, 36 and 43).

- **Results and Conclusions:**

PK results

In the 50, 100 and 200 mg treatment groups, greater than dose-proportional increases were observed in Cmax (0.516, 3.96, and 12.9 mg/mL, respectively) and AUCall (1.79, 21.2, and 102 mg*day/L, respectively).

The Cmax/dose ratio increased with dose, but to a lesser extent than the AUCall/dose ratio. This is consistent with the rapid target-mediated clearance of REGN88 bound to IL-6α at lower doses.

PD results

Three doses of sarilumab (50 mg SD, 100 mg SD, and 200 mg SD) were compared with placebo after a single dose. REGN88 demonstrated better bioeffect and longer duration at the higher doses, based on the assessment of the levels of inflammatory markers associated with RA.

• hs-CRP: Overall, higher doses of REGN88 showed better bioeffect and of longer duration as assessed by suppression of hs-CRP values. There is significant decrease in hs-CRP from day 4 to visit 5 day 12 for the 200 mg group, with the largest change at day 8 (-27.92 mg/mL).

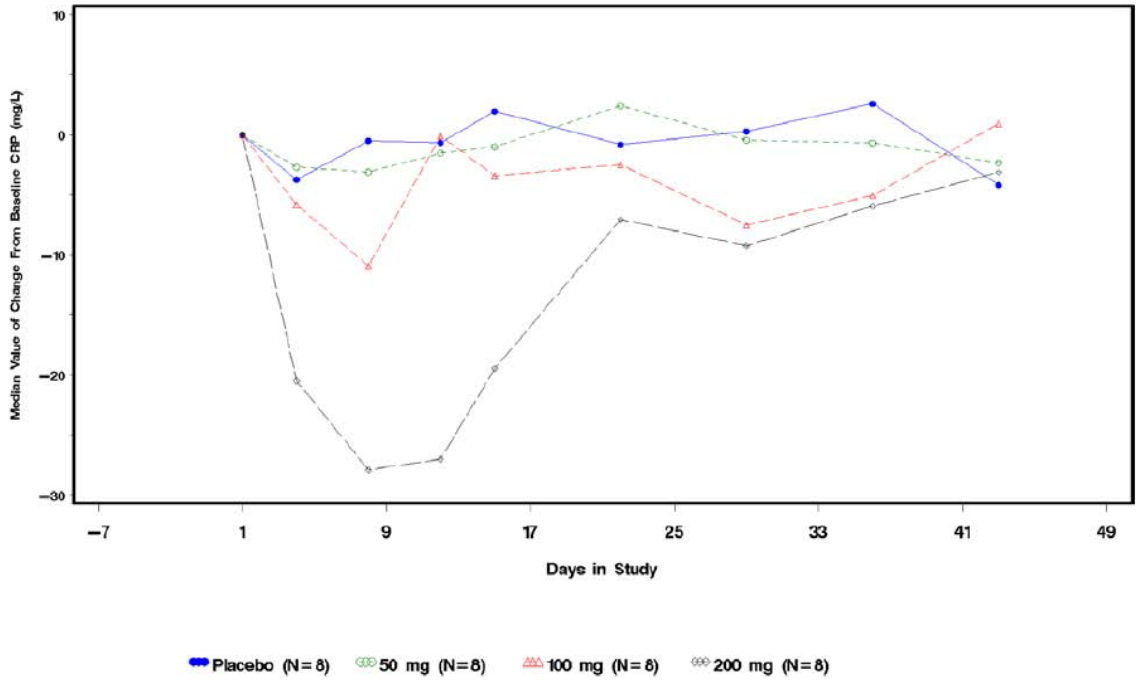

Figure 61. Median Change in hs-CRP (mg/mL) from Baseline by Treatment Groups
(Source: Figure 2, study report 6R88-RA-0803)

• SAA and ESR: Trends similar as those observed with hs-CRP were also observed for SAA and ESR. Overall, higher doses of REGN88 showed greater reductions from baseline and for longer duration.

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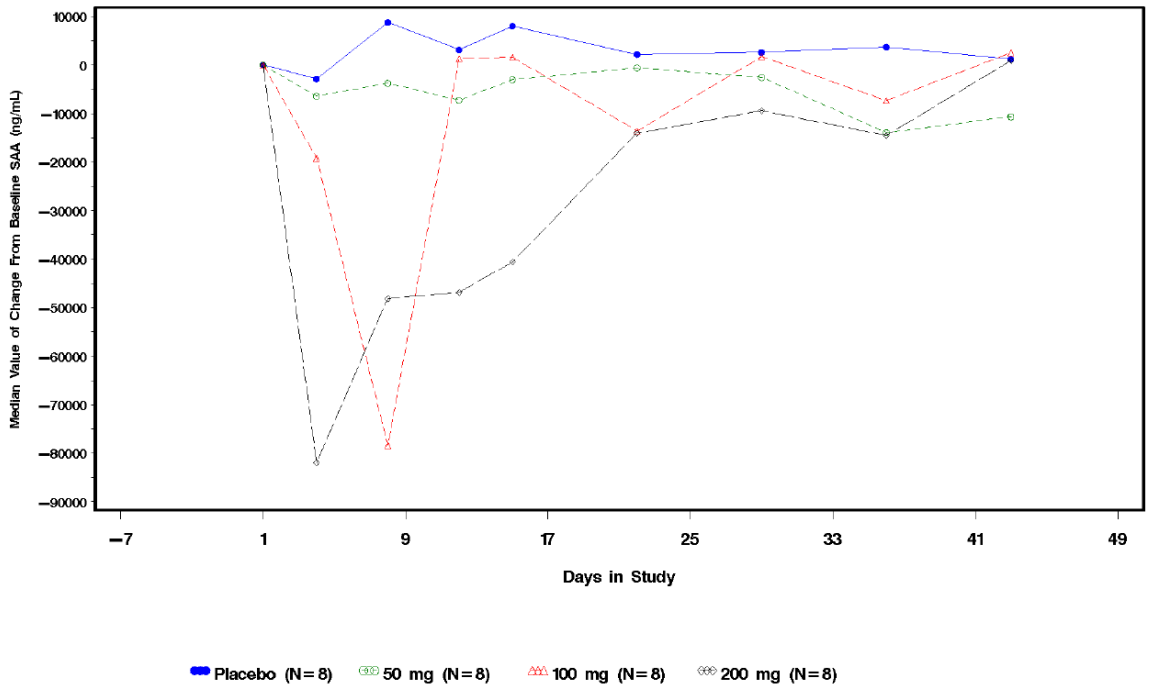


Figure 62. Median Change in SAA (ng/mL) from Baseline by Treatment Groups
(Source: Figure 12.2, study report 6R88-RA-0803)

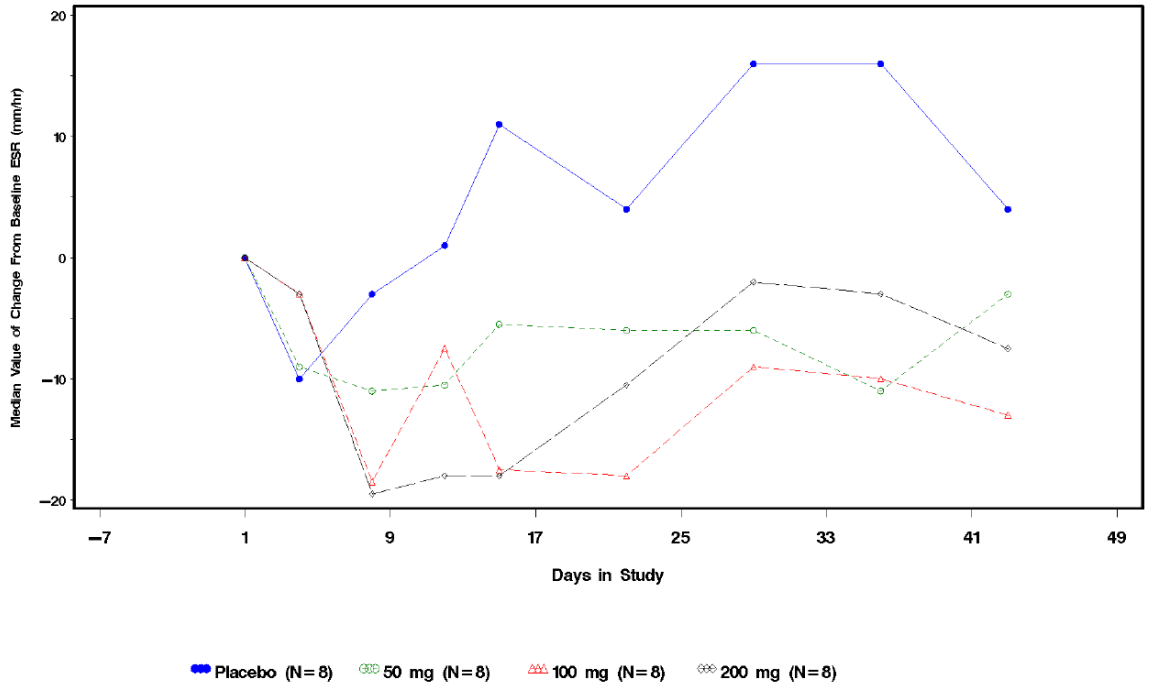


Figure 63. Median Change in ESR (mm/hr) from Baseline by Treatment Groups
(Source: Figure 10.2, study report 6R88-RA-0803)

• IL-6: As was observed for hs-CRP, SAA and ESR, median change and percent change in IL-6 values appeared to be dose-dependent. However, unlike the other inflammatory markers, IL-6 values increased in response to REGN88 treatment. For both the 100 and 200 mg treatment groups, IL-6 values increased quickly and dropped off quickly towards baseline values; by visit 6, IL-6 values in all REGN88 treatment groups were comparable to baseline values.

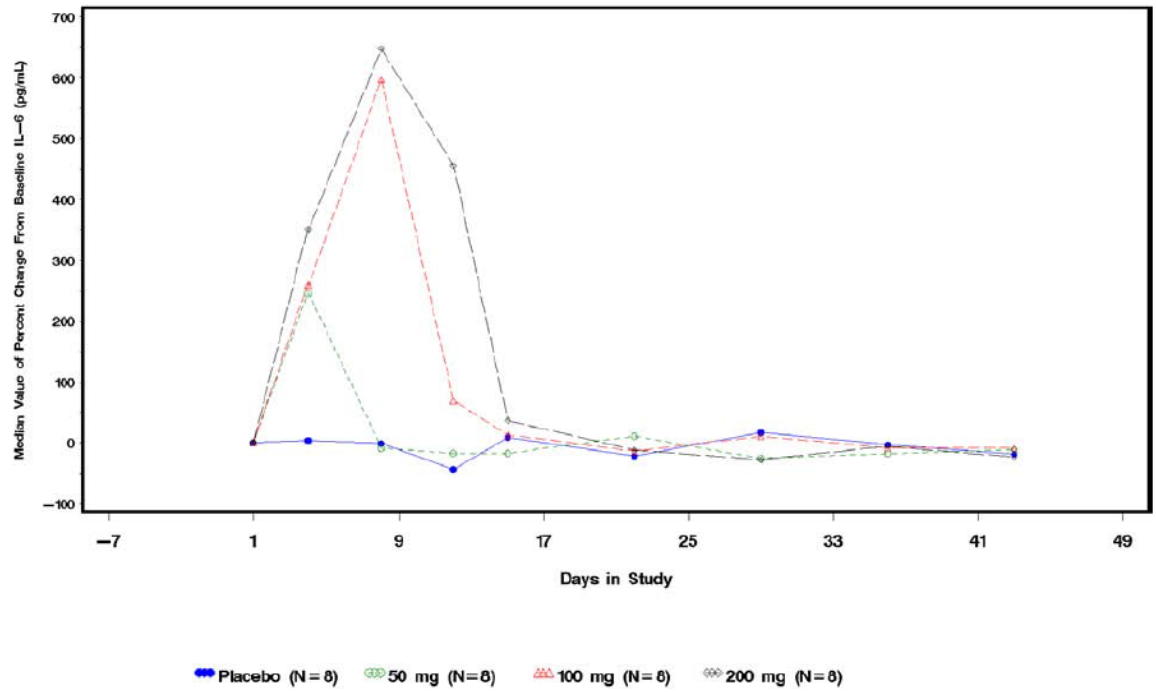


Figure 64. Median Percent Change from Baseline for IL-6 (pg/mL) by Treatment Group
(Source: Figure 5, study report 6R88-RA-0803)

- **Conclusions:**

Single doses of REGN88 show pharmacodynamic evidence of bioeffect in active RA patients based on dose-dependent changes in hs-CRP and other biomarkers of inflammation, including SAA, ESR and IL-6. Reductions in hs-CRP, SAA and ESR were paralleled by increases in IL-6 levels in the 200 mg group.

9. Compare with tocilizumab, on background of MTX

Study # 6R88-RA-1309

Study Type: Phase 1b PD study
Study Dates: 13/Mar/2014– 20/Apr/2015
Drug Product:
• Sarilumab (C2P1F3, to be marketed product) was supplied in single-use prefilled syringes: Glass syringes were filled to deliver a minimum volume of 1.14 mL drug product at 131.6 mg/mL (150 mg dose), or 175 mg/mL (200 mg dose).

•Commercially available tocilizumab was provided by the study site and was diluted to 100 mL in 0.9% sodium chloride. Tocilizumab was administered as 4 mg or 8 mg per kg of body weight in a 60-minute single IV drip infusion followed by a flush of approximately 15 minutes.

Title: A Multicenter, Open-Label, Randomized, Single-Dose Study Assessing The Pharmacodynamic Parameters Of IL-6 Receptor Blockade With Sarilumab Or Tocilizumab In Patients With Rheumatoid Arthritis On Stable Methotrexate Treatment

- **Objective:**
  - The primary objective of the study was to describe the pharmacodynamics (PD) of absolute neutrophil count (ANC), C-reactive protein (CRP), interleukin 6 (IL-6), and soluble IL-6 receptor (sIL-6R) following a single dose of sarilumab subcutaneously (SC) or tocilizumab intravenously (IV) in patients with rheumatoid arthritis (RA), who were on a stable dose of methotrexate (MTX).
  - The secondary objectives of the study were to describe PK of sarilumab and tocilizumab, safety and tolerability, and immunogenicity.

Only results related to PK/PD are reviewed here. For efficacy and safety results, please refer to clinical review by Dr. Suzette Peng.

- **Study design –** This was a 6-week, randomized, multicenter, open-label, parallel group, single-dose study to assess the PD and safety of sarilumab and tocilizumab in adults with RA who are on a stable dose of MTX.

  Approximately 100 patients were planned for enrollment. Patients who met eligibility criteria were randomized in a 1:1:1:1 ratio to 1 of 4 treatment groups:
    - sarilumab 150 mg SC
    - sarilumab 200 mg SC
    - tocilizumab 4 mg/kg IV
    - tocilizumab 8 mg/kg IV

- **Sampling Schedule**

  PK Sampling Schedule

  PK blood samples were collected pre-dose and at 1, 4, and 8 hours on Day 1, and Days 2, 3, 4, 5, 6, 7, 9, 11, 13, 15, 19, 22, 29 and day 43 following sarilumab administration.

  Immunogenicity Sampling Schedule

  Anti-drug antibodies (ADA) to sarilumab were assessed predose on Day 1 and on Days 7, 15, 29 and at EOS visit (Day 43).

PD Sampling Schedule

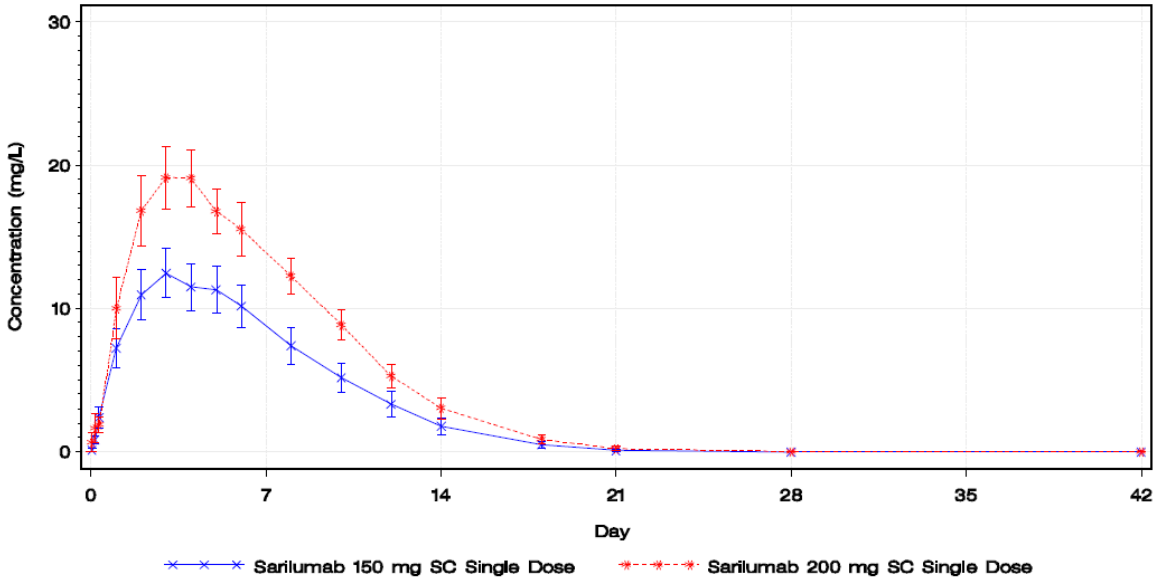
ANC, sIL-6R and IL-6 were assessed at predose on Day 1, and on Days 2, 3, 4, 5, 6, 7, 9, 11, 13, 15, 19, 22, 29 and at EOS visit (day 43). CRP and CRPM were assessed at predose on Day 1, and on Days 2, 3, 4, 5, 6, 7, 15, 29 and at EOS visit (day 43). C1M and C3M were assessed at predose on Day 1, and on Days 7, 15, 29 and at EOS visit (day 43).

- **Results and Conclusions:**

PK results

The functional sarilumab concentration-time profiles for after SC administration consisted of an initial absorption phase followed by a short beta-elimination phase and then a terminal target-mediated elimination phase which predominates at low concentrations. These concentration-time profiles are indicative of target-mediated drug-disposition and concentration-dependent limination (Figure 65). Following SC administration of 150 mg or 200 mg of sarilumab, functional sarilumab concentrations were maximal after approximately 3 days to 4 days (Table 51). The median Cmax/Dose values observed after a single SC dose of 150 mg or 200 mg sarilumab were close to dose-proportional, while The AUClast increased 1.6-fold (106 day•mg/L to 169 day•mg/L) for a 1.33-fold increase in sarilumab SC dose (from 150 mg to 200 mg). Concentrations declined to below the limit of detection after 2.5 weeks for 150 mg dose and after 3 weeks for the 200 mg dose (LLOQ = 0.313 mg/L).

A.



B.

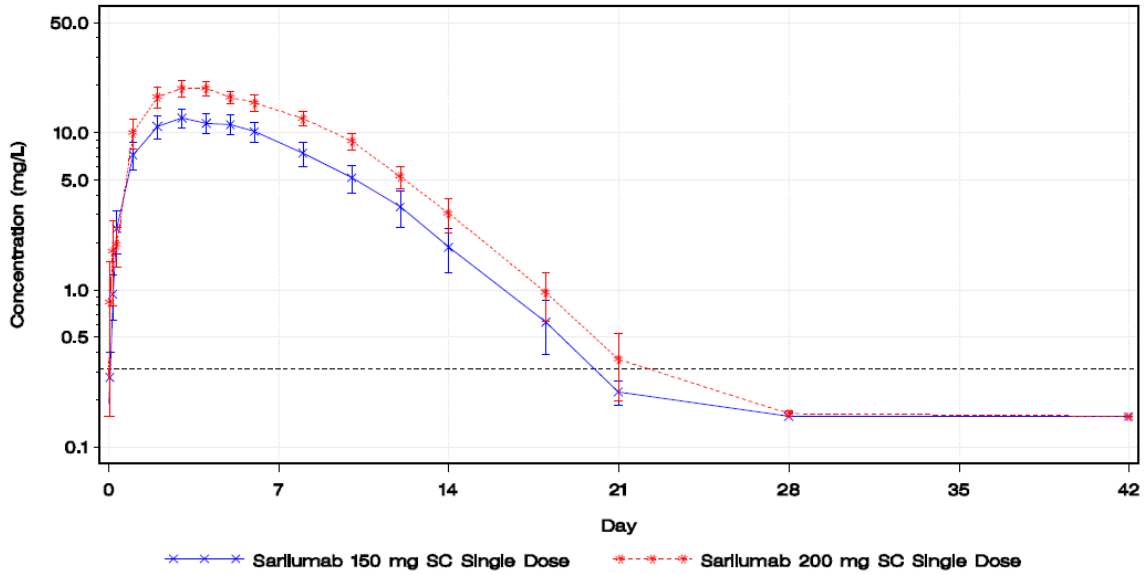


Figure 65. Mean (±SE) Functional Sarilumab Concentrations in Serum by Nominal Time and Treatment Group Following a Single SC Dose of 150 mg or 200 mg Sarilumab to Patients with Rheumatoid Arthritis. (A). Linear scale (B). Log-scaled

(Source: Figure 10 and Figure 11, CSR 6R88-RA-1309)

Table 51. Summary of Pharmacokinetic Parameters of Functional Sarilumab in Serum by Treatment Group Following a Single SC Dose of 150 mg or 200 mg Sarilumab to Patients with Rheumatoid Arthritis (Study 6R88-RA-1309)

Parameter	Units	Functional Sarilumab									
		Sarilumab 150 mg SC					Sarilumab 200 mg SC				
		n	Mean	Median	SD	SE	n	Mean	Median	SD	SE
C_{max}	mg/L	26	13.9	12.8	9.28	1.82	26	21.6	20.3	11.7	2.29
C_{max}/Dose	L^{-1}	26	0.0927	0.0850	0.0618	0.0121	26	0.108	0.101	0.0585	0.0115
t_{max}	day	26	3.56	3.02	1.12	0.219	26	3.67	3.99	1.11	0.217
C_{last}	mg/L	26	0.688	0.606	0.313	0.0614	26	0.964	0.569	0.923	0.181
t_{last}	day	26	13.6	13.1	4.29	0.840	26	16.2	14.2	3.67	0.719
AUC_{day28}	day•mg/L	26	107	84.4	92.2	18.1	26	171	144	105	20.6
AUC_{day28}/Dose	day/L	26	0.713	0.563	0.615	0.121	26	0.855	0.720	0.525	0.103
AUC_{last}	day•mg/L	26	106	83.3	91.9	18.0	26	169	143	105	20.5
AUC_{last}/Dose	day/L	26	0.707	0.555	0.613	0.120	26	0.847	0.716	0.523	0.103
AUC_{inf}	day•mg/L	26	108	85.3	92.2	18.1	26	173	144	105	20.6
AUC_{inf}/Dose	day/L	26	0.718	0.568	0.614	0.120	26	0.863	0.722	0.526	0.103
CL/F	L/day	26	4.34	1.76	5.94	1.17	26	2.33	1.38	4.62	0.906
V_{ss}/F	L	26	13.8	8.02	16.7	3.28	26	29.1	8.71	55.2	10.8

SC = Subcutaneous; n = Number of patients; SD = Standard deviation; SE = Standard error; C_{max} = Maximum concentration; t_{max} = Time to maximum concentration; C_{last} = Last positive (quantifiable) concentration; t_{last} = Time of the last positive (quantifiable) concentration; AUC_{day28} = Area under the curve (AUC) from time zero to day 28; $AUCl_{ast}$ = AUC computed from time zero to the time of the last positive (quantifiable) concentration; AUC_{inf} = AUC estimated from time zero to infinity; CL/F = Apparent clearance; V_{ss}/F = Volume of distribution at steady-state

(Source: Table 17, CSR 6R88-RA-1309)

PD results

Administration of a single dose of sarilumab (150 mg and 200 mg SC) or tocilizumab (4 mg/kg and 8 mg/kg IV) to patients with RA resulted in a similar onset of effect on ANC, CRP, IL-6, and sIL-6R concentrations during the first week post-dose and showed a more prolonged effect with tocilizumab. For both sarilumab and tocilizumab, the maximal effect observed after a low or high dose was similar, while the maximal effect was more prolonged at the high dose compared to the low dose, particularly for tocilizumab.

By study Day 15, the approximate time that a second dose of sarilumab would be given in a q2w dosing regimen, ANC values in the sarilumab groups had increased, but had not yet returned to baseline. By study Day 29, the approximate time a second dose of tocilizumab would be given in a q4w dosing regimen, ANC values had essentially returned to baseline in the tocilizumab 4 mg/kg group, but not in the tocilizumab
8 mg/kg group.

For ANC, the median time to nadir ranged from 3 to 5 days post-dose and the mean ANC nadir values ranged from 1.55 Giga/L to 1.78 Giga/L across treatment groups.

Despite differences in PK profiles due to route of administration and 10-fold lower functional drug concentrations with sarilumab SC as compared to tocilizumab IV at the low and high dose, the onset of the decrease in ANC and CRP and of the increase in IL-6 and total sIL-6R during the first week post-dose were similar. The effect of sarilumab and tocilizumab on the decrease in ANC or CRP and on the increase in IL-6 and total sIL-6R appeared to be saturable.

Concentration-time profiles in serum for the PD endpoints, ANC, CRP, Il-6, or total sIL-6 showed a similar onset of effect during the first week post-dose across all treatment groups, except for IL-6 concentrations, that closely resembled the drug concentration profiles and thus differed by route of administration. In agreement with drug concentration-time profiles and anticipated therapeutic dosing regimen, these PD endpoints returned toward baseline earlier with sarilumab than with tocilizumab and the effect lasted generally longer with tocilizumab.

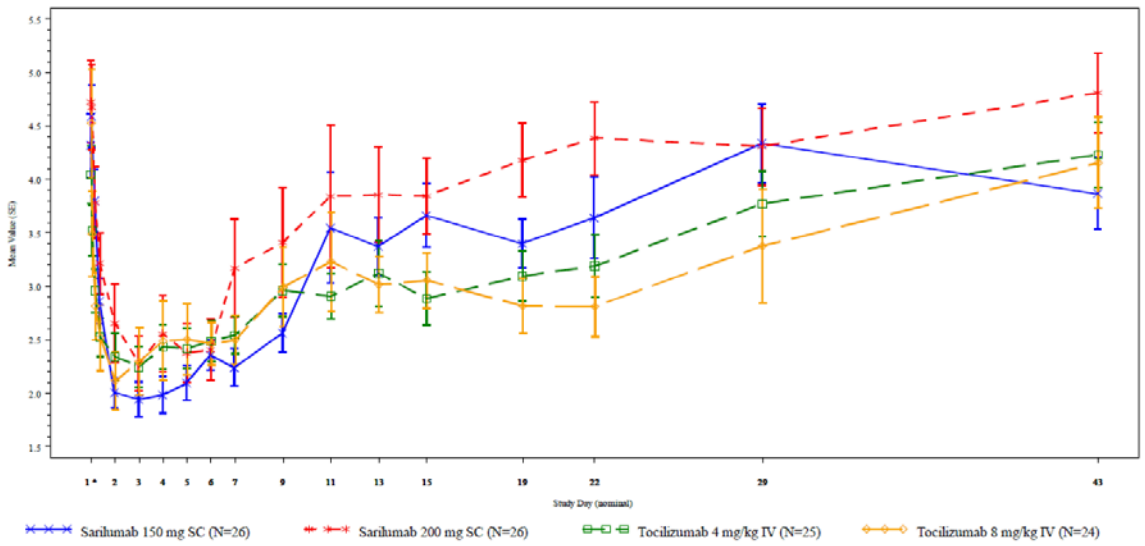


Figure 66. Mean Value (± SE) in ANC (Giga/L) - by Treatment and Day – Day 1 - 43
(Source: Figure 3, CSR 6R88-RA-1309)

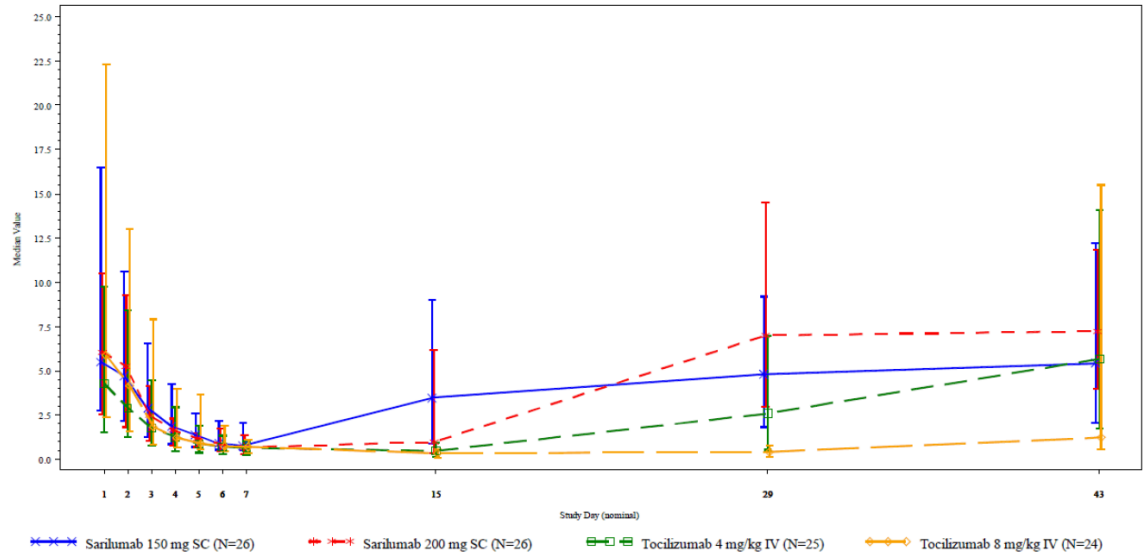


Figure 67. Median Value in CRP (mg/L) - by Treatment and Day – Day 1 – 43
(Source: Figure 5, CSR 6R88-RA-1309)

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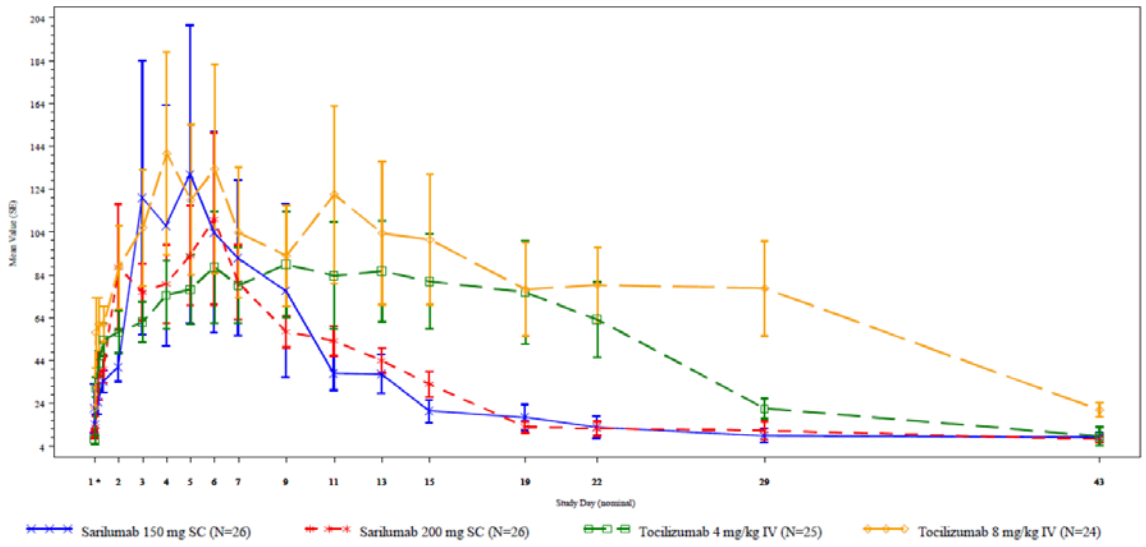

Figure 68. Median Value in CRP (mg/L) - by Treatment and Day – Day 1 – 43
(Source: Figure 7, CSR 6R88-RA-1309)

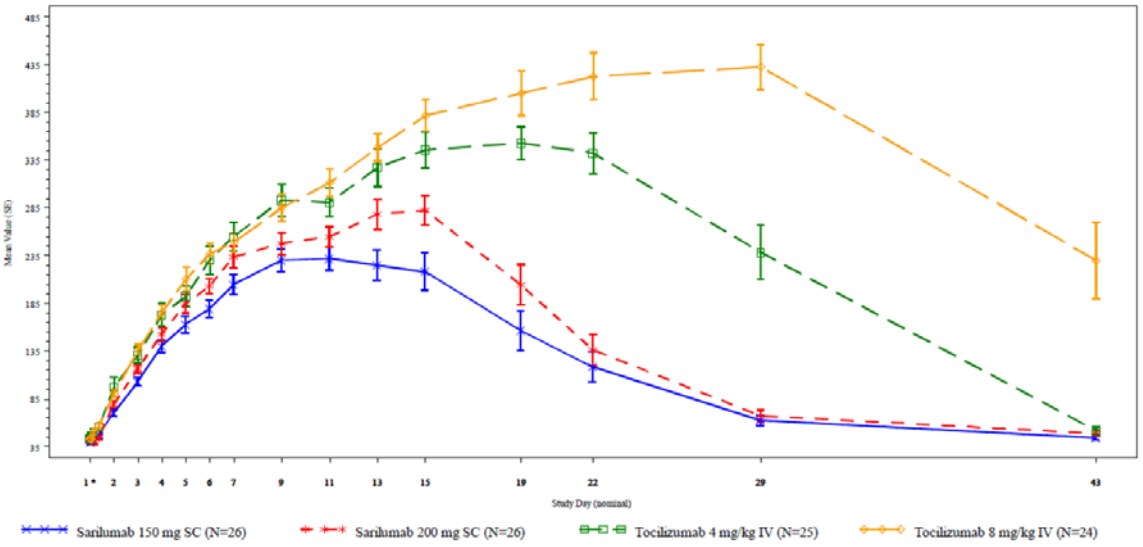

Figure 69. Mean Value (±SE) for sIL-6R (ng/mL) by Treatment and Day - Day 1 to 43 - PDAS
(Source: Figure 9, CSR 6R88-RA-1309)

Immunogenicity results

Of the 52 sarilumab-treated patients, 9 patients (17.3%) had a positive ADA response. The percent of patients with a positive anti-sarilumab antibody response was comparable in the sarilumab 150 mg and 200 mg dose groups. A higher median titer was reported in the sarilumab 150 mg group compared with the 200 mg group, but in both groups all titers were ≤ 240. There

was no apparent effect of ADA positivity on the PK of functional sarilumab. Antidrug antibody for tocilizumab was not measured.

- **Conclusions:**

Administration of a single dose of sarilumab (150 mg and 200 mg SC) or tocilizumab (4 mg/kg and 8 mg/kg IV) to patients with RA resulted in a similar onset of effect on ANC, CRP, IL-6, and sIL-6R concentrations during the first week post-dose and showed a more prolonged effect with tocilizumab. For both sarilumab and tocilizumab, the maximal effect observed after a low or high dose was similar, while the maximal effect was more prolonged at the high dose compared to the low dose, particularly for tocilizumab.

By study Day 15, the approximate time that a second dose of sarilumab would be given in a q2w dosing regimen, ANC values in the sarilumab groups had increased, but had not yet returned to baseline. By study Day 29, the approximate time a second dose of tocilizumab would be given in a q4w dosing regimen, ANC values had essentially returned to baseline in the tocilizumab 4 mg/kg group, but not in the tocilizumab 8 mg/kg group. For ANC, the median time to nadir ranged from 3 to 5 days post-dose and the mean ANC nadir values ranged from 1.55 Giga/L to 1.78 Giga/L across treatment groups.

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4.3 Appendix – CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	761037	**SDN**	
Applicant	Sanofi	**Submission Date**	10/30/2015
Generic Name	Sarilumab	**Brand Name (Proposed)**	(b) (4)
Drug Class	inhibitor of IL-6		
Indication	Moderate to severe active RA		
Dosage Regimen	200 mg SC once every 2 weeks		
Dosage Form	Prefilled syringe	**Route of Administration**	SC
OCP Division	II	**OND Division**	Pulmonary, Allergy, and Rheumatology Products (DPARP)

OCP Review Team	Primary Reviewer(s)	Secondary Reviewer/ Team Leader
Division	Sheetal Agarwal	Ping Ji
Pharmacometrics	Jianmeng Chen	Yaning Wang
Genomics		
Review Classification	☑ Standard ☐ Priority ☐ Expedited	
Filing Date	12/29/2015	**74-Day Letter Date** 1/12/2016
Review Due Date	8/29/2016	**PDUFA Goal Date** 10/30/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?
☑ Yes
☐ No

Is there a need for clinical trial(s) inspection?
☐ Yes
☑ No

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		

☐ Distribution		
☐ Drug-Drug Interaction		
In Vivo Studies		
Biopharmaceutics		
☐ Absolute Bioavailability		
☑ Relative Bioavailability	3	TDU11373 and PKM12058 (PK studies comparing PK of Phase 1 to Phase 2 and Phase 2 to Phase 3 formulations). (b) (4) [redacted]
☐ Bioequivalence		
☐ Food Effect		
☐ Other		
Human Pharmacokinetics		
Healthy Subjects — ☐ Single Dose		
Healthy Subjects — ☐ Multiple Dose		
Patients — ☑ Single Dose	2	TDU10808/6R88-RA-0703 (0.6 and 2.0 mg/kg; a single IV dose in RA patients), TDU10809/6R88-RA-0801 (50, 100, and 200 mg; a single SC dose in RA patients)
Patients — ☑ Multiple Dose	2	TDR10805/6R88-RA-0802 (50, 100, and 150 mg qw; 100, 150, and 200 mg q2w) in RA patients and EFC11072 Part A (100, 150, and 200 mg q2w; 100 and 150 mg qw SC) in RA patients
☐ Mass Balance Study		
☐ Other (e.g. dose proportionality)		
Intrinsic Factors		
☑ Race	1	TDU13402 (50, 100, and 200 mg; a single SC dose in Japanese RA patients)
☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☐ Hepatic Impairment		
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☑ Effects on Primary Drug		DDI with MTX studied as pop PK in Phase 3
☑ Effects of Primary Drug	1	INT12684 Part A (effect of 200 mg single SC dose sarilumab on exposure of simvastatin, a CYP3A4 substrate, in RA patients)
Pharmacodynamics		

☐ Healthy Subjects		
☑ Patients	2	PD for biomarkers, PK/PD for key safety parameters, and biomarkers evaluated in 2 studies: ACT10804/ 6R88-RA-0803 (50, 100, and 200 mg; a single SC dose) and 6R88-RA-1309 150 (200 mg; a single SC dose) in RA patients
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☑ Population Pharmacokinetics	4	POH0428 (pop PK), POH0455 (PK/PD for key efficacy and safety parameters), POH0429 (Population PK/PD for absolute neutrophil count) and POH0446 (Population PK/PD for DAS28-CRP)
☑ Exposure-Efficacy	6	EFC11072 Part B, EFC10832, SFY13370, MSC12665, EFC13752 and LTS11210
☐ Exposure-Safety		

Total Number of Studies and reports	**In Vitro**		**In Vivo**	21
Total Number of Studies/reports to be Reviewed				20

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/s/

JIANMENG CHEN
08/29/2016

JINGYU YU
08/29/2016

ANSHU MARATHE
08/29/2016

SURESH DODDAPANENI
08/29/2016

CLINICAL PHARMACOLOGY FILING FORM

Application Information

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Dosage Regimen	200 mg SC once every 2 weeks		
Dosage Form	Prefilled syringe	**Route of Administration**	SC
OCP Division	2	**OND Division**	Pulmonary, Allergy, and Rheumatology Products (DPARP)

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Sheetal Agarwal	Ping Ji
Pharmacometrics	Jianmeng Chen	Yaning Wang
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	12/29/2015	**74-Day Letter Date**	1/12/2016
Review Due Date	8/29/2016	**PDUFA Goal Date**	10/30/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
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Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		
☐ Distribution		
☐ Drug-Drug Interaction		
In Vivo Studies		
Biopharmaceutics		
☐ Absolute Bioavailability		
☑ Relative Bioavailability	3	TDU11373 and PKM12058 (PK studies comparing PK of Phase 1 to Phase 2 and Phase 2 to Phase 3 formulations). (b) (4)

			(b) (4) [redacted]
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☑ Single Dose	2	TDU10808/6R88-RA-0703 (0.6 and 2.0 mg/kg; a single IV dose in RA patients), TDU10809/6R88-RA-0801 (50, 100, and 200 mg; a single SC dose in RA patients)
	☑ Multiple Dose	2	TDR10805/6R88-RA-0802 (50, 100, and 150 mg qw; 100, 150, and 200 mg q2w) in RA patients and EFC11072 Part A (100, 150, and 200 mg q2w; 100 and 150 mg qw SC) in RA patients
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☑ Race		1	TDU13402 (50, 100, and 200 mg; a single SC dose in Japanese RA patients)
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
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☐ Patients			
☐ QT			
Pharmacometrics			
☑ Population Pharmacokinetics		4	POH0428 (pop PK), POH0455 (PK/PD for key efficacy and safety parameters), POH0429 (Population PK/PD for absolute neutrophil count) and POH0446 (Population PK/PD for DAS28-CRP)
☑ Exposure-Efficacy		6	EFC11072 Part B, EFC10832, SFY13370, MSC12665, EFC13752

		and LTS11210		
☐ Exposure-Safety				
Total Number of Studies and reports	**In Vitro**		**In Vivo**	21
Total Number of Studies/reports to be Reviewed				20

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Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	An IR for a missing dataset to be sent
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☑No ☐N/A	

Filing Memo

Background information is provided below. Clin Pharm filing slides attached. Filing meeting was held on 12/17/15. The BLA was determined to be fileable by all the disciplines. An AC meeting was not recommended by the clinical team as the molecule (IL-6 inhibitor) is not first in class.

Background:

- Product: SAR153191 (sarilumab or (b) (4)
- Mechanism of action: Fully human IgG1 mAb binds to IL-6R (same as tocilizumab)
- Proposed indication: treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to one or more DMARDs
- Proposed dosing: 200 mg SC every 2 weeks, Reduction of dose to 150 mg every 2 weeks for management of neutropenia, thrombocytopenia, and elevated liver enzymes
- Proposed available dosage forms: Prefilled syringe (PFS, 150 mg and 200 mg)
- Milestone regulatory interactions:
  - PIND meeting with Sponsor - August 2007
  - EOP2 meeting - September 2011
  - iPSP submitted and agreed upon (Aug 2013, Jan 2014)
  - Pre-BLA meeting – Oct 2014
- Pediatric plan: iPSP letter of agreement – January 2014 (Partial waiver for children <24 months with pJIA and deferral for children ages 2-17 years with pJIA)
  - Planned pediatric studies: PK (dose finding) and safety and efficacy studies

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Filing meeting
BLA 761037
[redacted] (b) (4) (Sarilumab)
Sanofi/Regeneron

Filing meeting: Dec 17, 2015

Clin Pharm review team:

Sheetal Agarwal, Jianmeng Chen

Ping Ji, Yaning Wang

Clinical Pharmacology filing summary

- Application is fileable

- Key review considerations:
  - Is the proposed dosing regimen appropriate?
  - Is the proposed dose reduction for management of neutropenia, thrombocytopenia and elevated liver enzymes appropriate?
  - Exposure response for efficacy and safety: PK/PD (neutrophil, DAS28, ACR)

- IR for PK dataset/code

Clinical Pharmacology package

- 2 formulation comparability studies
- 3 single and multiple dose studies
- Effect of race
- DDI with MTX
- Dose ranging in Phase 2
- Pop PK analysis
  - Effect of age, gender, body weight, race, lab measurements
  - Mild and moderate renal impairment
  - Exposure/efficacy, Exposure/safety-response in Phase 2 and 3

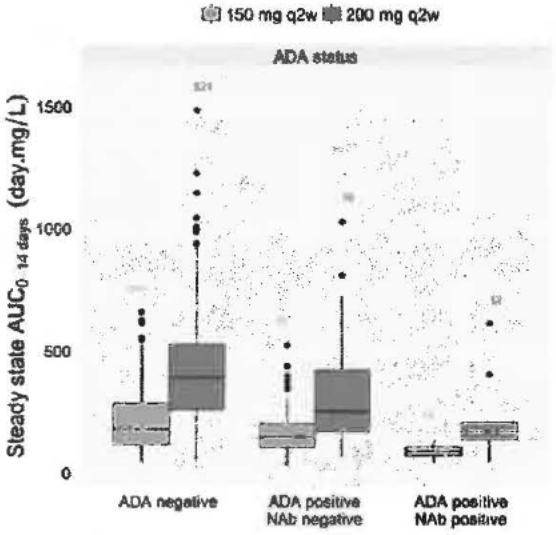
PK summary

- Nonlinear PK with target mediated drug disposition
  - AUC increased 2 fold from 150 mg to 200 mg (more than dose proportional)
- Tmax of 2 to 4 days and a bioavailability of 80% after single dose SC
- Effective half-life 2-3 weeks
- SS achieved 14-16 weeks (q2w dosing), 2-3 fold accumulation for AUC0-14 days

Impact of ADA on PK

- Incidence of ADA+ 10-20%, Nab+ <5%
- ADA+ ↓24-28% (AUC), Nab+ ↓ 49-59% (AUC)

ADA positive (NAb positive or NAb negative) versus ADA negative

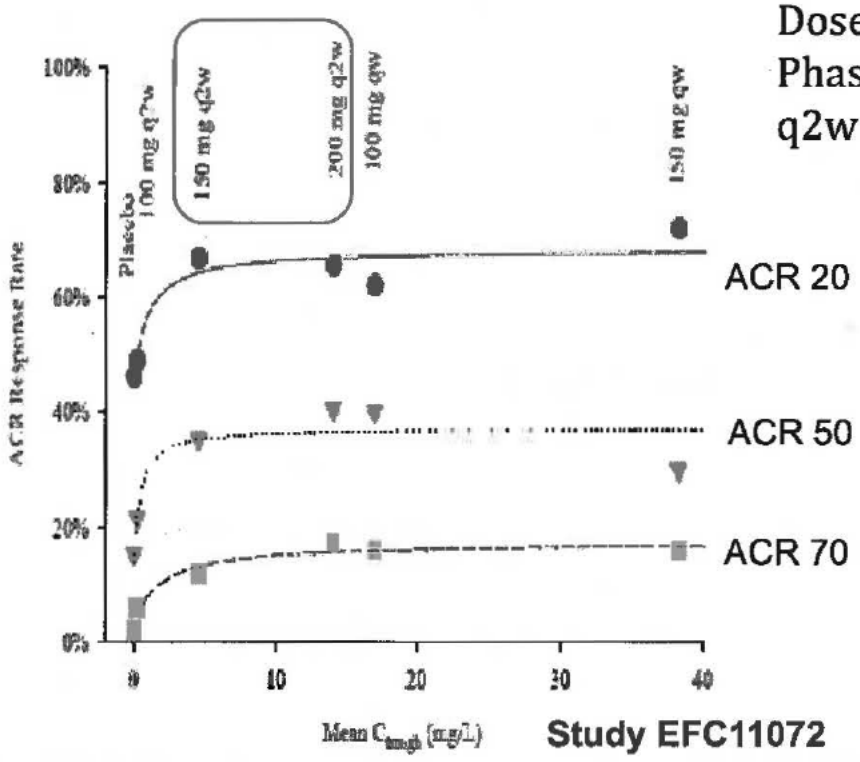


POH0428

Intrinsic and Extrinsic factors

- Effect of intrinsic factors
  - **Body weight, ADA status**, drug product, albumin, sex, creatinine clearance, and baseline CRP level found to be significant covariates
  - No effect of age, race, total bilirubin, AST, or ALT levels, or concomitant MTX use
- Effect of extrinsic factors
  - No DDI with MTX
  - DDI with CYP3A4 substrate: simvastatin exposure reduced by 45%

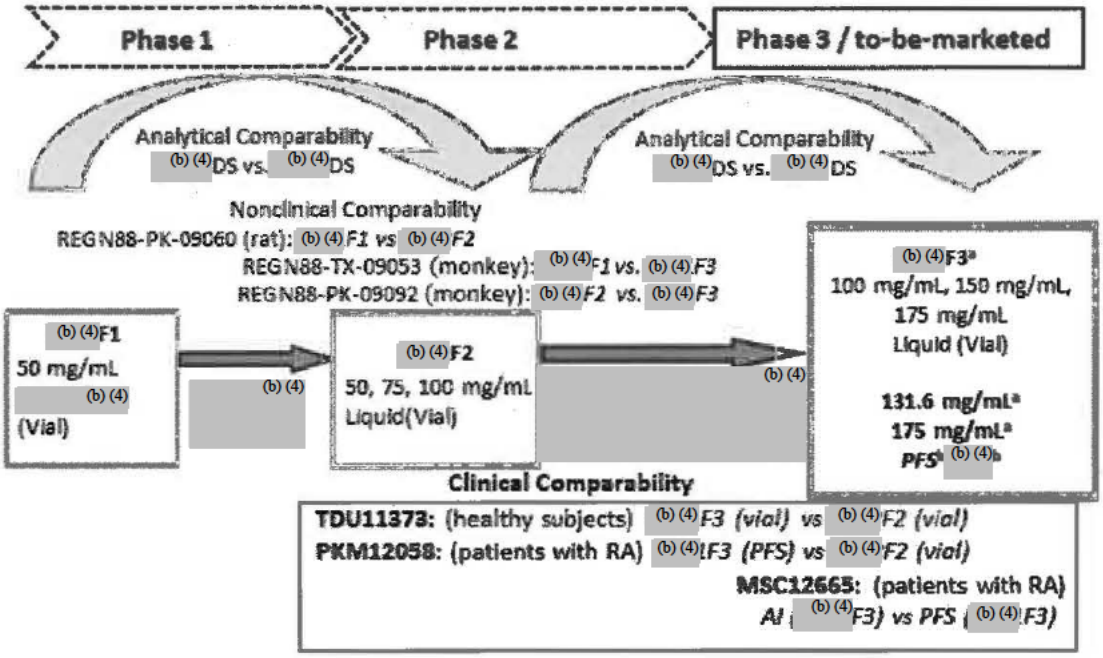
Dose selection for Phase 3



Study EFC11072

Doses carried forward to Phase 3: 150 mg and 200 mg q2w in Phase 3

PK comparability studies: PK comparable between formulations



Clinical Pharmacology filing summary

- Application is fileable
- No OSI inspection required for clin pharm
- Midcycle deliverables: Complete reviews of
  - Dose Selection
  - Exposure-Response Evaluation
  - Drug-rug Interaction and Extrinsic/Intrinsic Factors

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/s/

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