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ORIGINAL RESEARCH

First-in-human (phase I) trial of SOL-116, a humanised IgG4 monoclonal antibody targeting bile salt-stimulated lipase, in healthy participants and rheumatoid arthritis patients

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ABSTRACT

Objective Bile salt-stimulated lipase (BSSL) is a digestive lipolytic enzyme and a potential novel drug target for treatment of rheumatoid arthritis (RA). Here, we report the results of the first-in-human study of SOL-116, a first-in-class humanised IgG4 monoclonal antibody targeting BSSL, conducted in healthy participants and patients with RA.

Methods This was a randomised, double-blind, placebo-controlled study of ascending single doses (0.075–6.075 mg/kg) and multiple doses (4 doses of 3.0 mg/kg every 4 weeks) of subcutaneously administered SOL-116 in healthy participants, as well as a single dose (2.025 mg/kg) in patients with RA. Safety and tolerability were assessed as the primary objective and pharmacokinetics (PK) and immunogenicity as secondary objectives. Exploratory objectives included evaluating BSSL concentrations and inflammatory markers.

Results SOL-116 was safe and well tolerated at the tested dose levels in 48 healthy participants and 8 patients with RA. There was a dose-proportional increase in area under the curve and maximum concentration across the single dose cohorts in healthy participants, with comparable PK characteristics between healthy participants and patients with RA and a low frequency of anti-drug antibodies. Notably, SOL-116 effectively reduced free BSSL levels in circulation, confirming target engagement although no clear changes in other exploratory inflammation markers were observed.

Conclusions This study demonstrated that SOL-116 has a favourable safety and PK profile. Combined with effective reduction of free BSSL in the circulation, findings in this study support ongoing clinical development of SOL-116, with a focus on elucidating the efficacy and mechanism of action of BSSL in the treatment of chronic inflammation, primarily RA.

Trial registration number NCT05576012.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite available pharmacological treatments for rheumatoid arthritis (RA), there remains an unmet medical need for new treatment options due to limitations in efficacy and tolerability of current therapies.

⇒ SOL-116 is a first-in-class humanised IgG4 monoclonal antibody targeting bile salt-stimulated lipase (BSSL), a digestive lipolytic enzyme which has also been identified as a potential novel drug target for treatment of RA based on studies in rodent models of RA, correlation between plasma BSSL concentration and disease activity in man, and effect on monocyte migration.

WHAT THIS STUDY ADDS

⇒ Our first-in-human study shows that SOL-116 has a favourable safety and pharmacokinetics (PK) profile and effectively reduces plasma BSSL levels in healthy participants and patients with RA.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study shows that SOL-116 is a potential novel drug with a promising safety and PK profile for treatment of autoimmune diseases, primarily RA, pending demonstration of efficacy.

⇒ The results of this study support the continued clinical evaluation of SOL-116.

INTRODUCTION

Various pharmacological treatment options are available for rheumatoid arthritis (RA). However, a substantial part of patients does not respond sufficiently or experiences dose-limiting side effects. Patients who are not responding satisfactorily to current treatment options are at risk for progressive articular damage with loss of cartilage and bone erosions and extra-articular symptoms as the disease progresses. Since there is no curative treatment for RA, today's treatment strategies aim at rapidly achieving a reduced disease activity. The introduction of biological

disease-modifying anti-rheumatic drugs (bDMARDs) and targeted synthetic (ts)DMARDs, which affect cytokines or intracellular pathways, has substantially improved disease remission rates.[1] Despite these new treatment advances, conventional DMARDs, such as methotrexate (MTX), currently remain the cornerstone of RA treatment.[2] However, up to one-third of patients discontinue MTX treatment, not only due to lack of efficacy, but also as a result of side effects including gastrointestinal intolerance, cytopenias and liver enzyme abnormalities.[3] Notably, more than 25% of all patients with RA experience inadequately controlled symptoms[1] and the current treatment options often come at the expense of broad immunosuppression.[4] Considering the increasing global prevalence of RA,[5] the unmet need for new treatment options is apparent.

Bile salt-stimulated lipase (BSSL) has been identified as a potential novel drug target for the treatment of RA.[6 7] BSSL was initially recognised as a lipolytic enzyme secreted from the exocrine pancreas and from the lactating mammary gland, contributing to efficient milk fat utilisation in breastfed infants.[8–10] Recently, BSSL was recognised for its role in monocyte migration and inflammatory arthritis.[6 7] In rodent models of RA, it was shown that BSSL knock-out (KO) mice were protected from developing collagen-induced arthritis (CIA). Moreover, early-stage developed anti-human BSSL antibodies were shown to reduce the incidence and severity of CIA and pristane-induced arthritis (PIA) in rodents. Additionally, BSSL levels in the human circulation were shown to be associated with disease activity and established inflammatory markers in RA and psoriatic arthritis (PsA) patients, and more recently also in juvenile idiopathic arthritis (JIA).[7 11] Overall, its measurable presence in blood, correlation with disease activity, and role in monocyte migration offer both mechanistic and translational appeal in humans, which collectively support the concept of an anti-BSSL antibody as a novel therapeutic approach in inflammatory diseases, such as RA.

With this knowledge, a humanised monoclonal anti-BSSL antibody of the IgG4 subclass (SOL-116) was developed. In vitro, SOL-116 has been shown to specifically bind to human BSSL with high affinity and to block the stimulatory effect of BSSL on human CD14+ monocyte migration, consistent with previously published findings demonstrating that the murine anti-BSSL antibody AS20 inhibits BSSL-induced cell migration.[7] In vivo, disease severity was reduced after administration of SOL-116 in PIA rats,[12] which was to a lesser extent also observed in mouse models with collagen antibody-induced arthritis.

The aim of the present study was to determine the safety and tolerability, pharmacokinetics (PK), immunogenicity and exploratory pharmacodynamic (PD) effects of subcutaneously (s.c.) administered SOL-116 following single ascending doses (SADs) and multiple doses (MD) in healthy participants and a single dose in patients with RA.

METHODS

Study design

This was a randomised, double-blind, placebo-controlled, first-in-human (FIH) study of ascending single and multiple s.c. doses of SOL-116 in healthy adult participants and single dose in patients with RA. Up to five SAD levels were planned in five cohorts of eight healthy participants, with one optional cohort. Up to two MD cohorts of eight healthy participants were planned to be enrolled. One single dose cohort of eight patients with RA was included, primarily to compare PK and target engagement in a disease population. In all cohorts, participants were randomised in a ratio of 6:2 (SOL-116 vs placebo). Placebo consisted of a solution with the same composition as SOL-116 except for the active pharmaceutical ingredient and was indistinguishable from SOL-116 solution. Patients or the public were not involved in the design, reporting or dissemination plans of this research.

The healthy participant cohorts were conducted at QPS Netherlands B.V. and at ICON PLC (Groningen, the Netherlands). The RA part was performed at the Centre for Human Drug Research (CHDR, Leiden, the Netherlands).

Dose justification and dose escalation

In the SAD part in healthy participants, the start dose was set to 0.075 mg/kg, which was primarily based on the minimum anticipated biological effect level in a PIA model in Dark Agouti (DA) rats, of which the predicted exposure was 1800 µg/mL*hour in man. For this calculation, the 57-fold affinity difference for SOL-116-binding to rat versus human BSSL was taken into account as well as a 40% lower exposure in PIA-treated DA rats compared with the satellite DA rats (not receiving pristane). A dose of 0.225 mg/kg was expected to generate a similar exposure in humans based on interspecies scaling of clearance (CL/F) from rats and non-human primates (NHP), assuming a human body weight of 60 kg. Since SOL-116 is a first-in-class compound, an additional safety factor of 3 was applied, which resulted in an intended starting dose of 0.075 mg/kg. The predicted exposure of the starting dose was >270-fold fold below the no observed adverse effect level (NOAEL) in NHP. Doses that were predicted to generate exposures exceeding the exposure at the NOAEL in NHP were not to be administered. Since no findings of toxicological relevance were observed across the dose levels tested in rats and NHP, the NOAEL was determined as the highest dose tested in each species.

The planned starting dose in the first MD cohort was 3.0 mg/kg, which was based on the PK profile after a single dose in healthy participants, and was predicted to result in an exposure in humans within the same order of magnitude as the expected therapeutic concentration estimated from the PIA model in rats. A dosing regimen with drug administration every 4 weeks (Q4W) for 12 weeks (4 doses) was selected for the first MD cohort, with steady state expected to be reached within 12 weeks.

For the RA cohort, a dose previously used in one of the SAD cohorts (2.025 mg/kg) was selected to allow for a direct comparison of plasma SOL-116 PK in healthy participants versus patients with RA. This dose was believed to result in an exposure >20-fold fold below the NOAEL in NHP and within the predicted therapeutic concentration range in humans based on the RA-model (PIA) in rats.

Dose escalation decisions in the SAD part in healthy participants, with a maximal dose increment of 3, were based on the evaluation of the safety, tolerability and available PK data of at least six evaluable participants up to and including 14 days postdose. Initiation of the RA part and continuation of dosing in the MD part were based on review of safety, tolerability and available PK data up to and including 21 days postdose and 28 days post last dose, respectively.

Study population

This study enrolled male and female participants aged between 18 and 65 years (healthy participants) or 70 years (patients with RA). Participants were eligible if they were in good general health, apart from RA specific findings for patients with RA, confirmed through a comprehensive clinical assessment, which included medical history, physical examination, vital signs, ECG and laboratory tests at screening. Healthy participants had to be negative for anti-cyclic citrullinated peptide and rheumatoid factor (RF) at screening. The body mass index (BMI) range for healthy participants was between 19.0 and 30.0 kg/m^2 with a body weight between 50 and 100 kg (for patients with RA: between 50 and 120 kg, without BMI restrictions). Participants were excluded if they had ongoing infections, a history of acute inflammatory joint disease (for patients with RA: other than RA), or had used concomitant medication within 14 days or 5 half-lives of the drug used (healthy participants) or within 4 weeks (patients with RA) prior to the first dose of study drug, unless deemed by the investigator to not interfere with the study procedures or compromise participant safety.

Patients with RA were included if they were fulfilling the 2010 American College of Rheumatology (ACR)/European Union League Against Rheumatism classification criteria for RA, treated with a stable dose of MTX for at least 12 weeks prior to IMP start, and naïve to or washed out from other DMARDs. The use of folic acid and a stable dose of oral glucocorticosteroids (≤5 mg/day) was allowed for patients with RA.

Primary endpoints: safety and tolerability assessments

Safety assessments included occurrence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory evaluations (haematology, clinical chemistry including lipid status and α-tocopherol, coagulation tests, urinalysis), telemetry, ECG evaluations (heart rate, RR interval, PR interval, QRS duration, QT interval, QTcF, QTcB), use of concomitant medications, physical examination, vital signs, height and weight, and evaluation of immune reactions (eg, hypersensitivity, cytokine release syndrome) and injection site reactions (ISRs). Pregnancy testing was required for all females. For the patients with RA, a 28-joint status (number of swollen joints and number of tender joints) was performed, and the patients were asked to fill in a Patient Global Health Visual Analogue Scale (0-100 mm) score at baseline.

Secondary endpoints: PK and immunogenicity assessments

Serum concentrations of SOL-116 were measured by a validated ELISA method at QPS Bioanalytical lab (the Netherlands). The validated concentration range was between 0.3 and 500 ng/mL (in diluted samples). The method was based on solid phase extraction with acid dissociation (SPEAD) followed by a sandwich electrochemiluminescence immunoassay (ECLIA) with the light emitted signal detected by a Sector Imager (MSD). The PK parameters were calculated with non-compartmental methods using Phoenix WinNonlin V.8.3 by Pharsight Corporation in St. Louis, Missouri, USA. PK parameters included maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$), AUC from time zero to time t of the last measured concentration above the limit of quantification ($AUC_{0\text{-}t}$), terminal elimination half-life ($T_{1/2}$), apparent volume of distribution (V_z/F) and CL/F. In the MD part, minimum concentration (C_{trough}), time to steady state and accumulation ratio were also assessed. Dose proportionality was assessed after SADs based on AUC and C_{max}.

Anti-drug antibodies (ADA) to SOL-116 were analysed in serum at QPS Bioanalytical lab (the Netherlands) using a validated assay, which was based on SPEAD followed by a sandwich ECLIA. Drug tolerance was accepted up to 100 µg/mL of SOL-116 at 2.8 and 100 ng/mL of the positive control. For the analysis of RA samples, a dynamic cut-point was used. Confirmed positive samples for ADA were analysed for titre by a standard method.

Exploratory endpoints: PD assessments

Bile salt-stimulated lipase

Free BSSL concentrations were quantified in plasma by means of a ligand binding assay based on electrochemiluminescence sandwich immunoassay (MSD) at BioAgilytix Europe (Hamburg, Germany). The assays' lower limit of quantification (LLOQ) and upper limit of quantification (ULOQ) were 35 pg/mL and 70.000 pg/mL, respectively.

Other inflammatory markers

C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were assessed for all participants, whereas calprotectin and high sensitivity (hs) CRP were exclusively analysed in patients with RA. Analysis of calprotectin in plasma was performed using a Human S100A8/S100A9 Heterodimer ELISA kit (Catalogue number D8900, R&D Systems), at Lipum AB (Umeå, Sweden). The LLOQ (lowest standard) was 0.625 ng/mL and the ULOQ (highest standard) was 40 ng/mL. Plasma samples

were diluted 100-fold prior to assay to ensure quantification within the dynamic range of the standard curve.

Cytokines and chemokines

Protein markers (48 cytokines and chemokines including IFNγ, IL-1β, IL-6, IL-10, IL-12, IL-18, MCP-1 and TNFα) were analysed in plasma by means of a validated Olink Target 48-plex Cytokine Panel[13] at the Olink accredited TATAA Biocenter AB (Gothenburg, Sweden).

Flow cytometry and whole blood stimulation assays in patients with RA

Flow cytometry panels were run at CHDR on whole blood samples from patients with RA and included a T-cell and B-cell and myeloid (monocyte and neutrophil) focused panel. The myeloid panel was also performed after 1 hour of fMLP (N-formyl-methionyl-leucyl-phenylalanine) stimulation of the cells. Red blood cell lysis was performed on sodium heparinised whole blood using RBC lysis buffer (Thermo Fisher Scientific). Leucocytes were stained with fluorochrome labelled antibodies (see online supplemental table 1 for complete list), for 30 min at 4°C. After a wash step, the samples were measured on a MACSQuant16 analyser (Miltenyi Biotec, Bergisch-Gladbach, Germany) and analysed using Flowlogic software (Inivai, Mentone, Australia). The gating strategy is provided in online supplemental figures 1; 2.

Sample size justification and statistical methods

The proposed sample size was based on empirical considerations. No formal sample size calculation was performed. The randomisation code was generated using SAS V.9.4 by the Biostatistics department of QPS Qualitix Taiwan.

Analyses have been performed separately per study part with healthy participants under placebo pooled from different SAD cohorts. Safety, PK and PD parameters have been listed and summarised descriptively, if applicable. Change from baseline (CFB) has been calculated for selected parameters. SAS for Windows V.9.4 or higher was used for analysis.

ECG variables (3-lead (telemetry) and 12-lead ECG), vital sign measurements and laboratory measurements were summarised at each time point using mean, median, SD, min, max, number of available observations and CFB. Individual participant listings of ECG data, vital signs data, physical examination data, immune reactions, ISRs, concomitant medication/therapy and laboratory measurements were provided.

Serum concentrations and PK parameters of SOL-116 were listed by dose level and summarised by time point. The following descriptive statistics were calculated: number of participants (N), arithmetic mean, SD, geometric mean, median, minimum, maximum and coefficient of variation (CV%). Nominal blood sampling times were used in the summary. Immunogenicity and exploratory parameters were listed individually, displayed in appropriate graphics. The Mann-Whitney U test was used for unpaired t-tests of non-normally distributed data (applying a false discovery rate of 5%). Statistical analysis and data visualisations were performed in GraphPad Prism V.10 or later (GraphPad, La Jolla, California, US) and principal component analysis (PCA) in SIMCA-P V.16 (Sartorius Stedim Data Analytic–Umetrics, Umeå, Sweden).

RESULTS

Participant disposition

The clinical study was conducted between 21 October 2022 (first subject dosed) and 28 November 2024 (last subject visit). A total of 135 healthy participants were screened, of whom 48 were eligible and randomised. In addition, a total of 15 patients with RA were screened, of which 8 were eligible and randomised. One placebo participant of the MD cohort was discontinued due to a study drug unrelated SAE after receiving all doses of study treatment. All the other randomised participants completed the study.

In total, 42 participants were exposed to SOL-116 and 14 participants were given placebo, divided over 5 SAD cohorts (dose range between 0.075 and 6.075 mg/kg) and one MD cohort (4 doses of 3.0 mg/kg Q4W) in healthy participants and one single dose cohort in patients with RA (2.025 mg/kg) (figure 1). The sixth optional SAD cohort was omitted, as the exposure obtained in the preceding fifth SAD cohort was already above the corresponding efficacious exposure observed in the RA model (PIA) in rats. A second MD cohort was not run as it was concluded that sufficient safety data was obtained from the first MD cohort and the peak concentration (C_{max} at steady state of 33.5 µg/mL) came close to the previously highest observed safe and tolerable C_{max} after a single dose in healthy participants (34.1 µg/mL), with some margin for AUC_{tau}.

Table 1 shows the baseline characteristics and demographics of the study participants. Overall, the median age was 51.5 years (range: 20–65) in the SAD part, 57.5 years (range: 53–62) in the MD part and 63.5 years (range: 39–69) in the RA part. In total, 38%, 50% and 50% of the participants were female in the SAD, MD and RA part, respectively. All patients with RA had mild disease activity at baseline as assessed with the Disease Activity Score in 28 joints (DAS28)-CRP (mean (SD) of 2.09 (0.71) in the SOL-116 group and 2.40 (0.25) in the placebo group) and DAS28-ESR (mean (SD) of 2.03 (1.08) in the SOL-116 group and 2.54 (0.50) in the placebo group).

Single and MDs of SOL-116 were safe and well tolerated up to and including the highest dose level tested

Across all study parts, a total of 103 TEAEs were reported, of which the majority was classified as mild (table 2 and online supplemental table 2). The most frequent TEAEs were ISRs, which were reported 14 times in 6 participants treated with SOL-116 (3 healthy participants in the SAD part, 1 healthy participant in the MD part and 2 patients

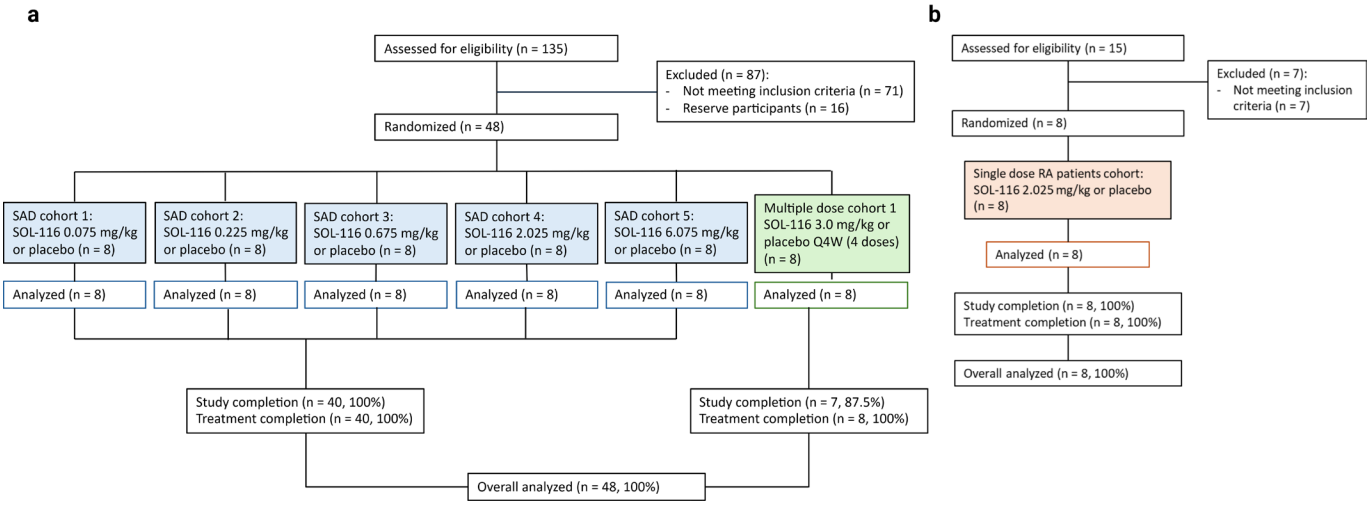

Figure 1 Study flow diagram. There were five single ascending dose (SAD) cohorts in healthy participants with subcutaneous (s.c.) dose levels tested ranging from 0.075 to 6.075 mg/kg, one multiple dose cohort in healthy participants with 4 doses of 3.0 mg/kg Q4W (a), and one cohort in patients with rheumatoid arthritis (RA) with a single dose of 2.025 mg/kg (b). Participants were randomised in a ratio of 6:2 to receive either SOL-116 or placebo. Study completion is defined as completing the study visits up to and including the end of study (EOS) visit; treatment completion is defined as completing the planned dose administration(s). Q4W, every 4 weeks.

in the RA part) and 1 ISR was reported in a placebo-treated participant. ISR symptoms included erythema, swelling, pain and pruritus. All ISRs were of mild intensity and resolved spontaneously.

One moderate TEAE of sinusitis was reported in a healthy participant 32 days after the administration of a single dose of SOL-116 (cohort 4; 2.025 mg/kg), which was assessed as unlikely related to the treatment and resolved spontaneously within 10 days. Furthermore, one severe TEAE of non-ST-segment elevation myocardial infarction was reported in a placebo participant of the MD cohort 29 days after the fourth dose, which was assessed as unlikely related. In addition, one TEAE of supraventricular tachycardia (SVT) was reported in a healthy participant treated with SOL-116 in the MD part 26 days after the fourth dose. The severity of the TEAE was assessed as mild, the TEAE was judged as unrelated to the treatment and resolved within 1 day. One moderate TEAE of SVT was also reported in a 70-year-old patient with RA, which was observed on the telemetry 1.5 hours

Table 1 Baseline characteristics and demographics

	SAD Placebo (n=10)	All SAD SOL-116 (n=30)*	MD Placebo (n=2)	MD SOL-116 (n=6)	RA Placebo (n=2)	RA SOL-116 (n=6)
Sex (n)						
Female	3 (30%)	12 (40%)	0 (0%)	4 (67%)	1 (50%)	3 (50%)
Male	7 (70%)	18 (60%)	2 (100%)	2 (33%)	1 (50%)	3 (50%)
Age (years)						
Mean (SD)	52.0 (14.3)	46.5 (17.7)	57.5 (0.7)	58.2 (3.7)	63.5 (0.5)	58.2 (10.5)
Median (min, max)	58.0 (25, 65)	58.0 (20, 63)	57.5 (57, 58)	58.0 (53, 62)	63.5 (63, 64)	61.5 (39, 69)
Ethnicity (n)						
Not Hispanic or Latino	9 (90%)	27 (90%)	2 (100%)	6 (100%)	2 (100%)	6 (100%)
Hispanic or Latino	1 (10%)	3 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
BMI (kg/m²)						
Mean (SD)	24.9 (2.4)	24.0 (2.8)	27.6 (0.2)	25.3 (0.8)	29.8 (1.7)	27.7 (4.6)
Median (min, max)	24.3 (21.0, 29.1)	23.6 (19.7, 29.6)	27.6 (27.4, 27.7)	25.0 (24.5, 26.8)	29.8 (28.6, 31.0)	26.9 (23.1, 36.6)
Concomitant medication (n)						
Yes	2 (20%)	2 (7%)	1 (50%)	3 (50%)	1 (50%)	4 (67%)
No	8 (80%)	28 (93%)	1 (50%)	3 (50%)	1 (50%)	2 (33%)

Demographics and participant characteristics at baseline for the SAD, MD and RA part.
*Parameters per SAD cohort are available in online supplemental table 4.
BMI, body mass index; MD, multiple doses; RA, rheumatoid arthritis; SAD, single ascending dose.

Table 2 Treatment emergent adverse events (TEAEs)

	SAD Placebo (n=10)	All SAD SOL-116 (n=30)*	MD Placebo (n=2)	MD SOL-116 (n=6)	RA Placebo (n=2)	RA SOL-116 (n=6)
Participant with any TEAE						
Yes, n (%)	6 (60)	20 (67)	2 (100)	5 (83)	2 (100)	6 (100)
Participant with any Treatment emergent serious adverse event						
Yes, n (%)	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)
Participant with any related TEAE†						
Yes, n (%)	2 (20)	7 (23)	1 (50)	3 (50)	1 (50)	4 (67)
Intensity						
Mild, n (%)	6 (60)	20 (67)	2 (100)	5 (83)	2 (100)	6 (100)
Moderate, n (%)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	1 (17)
Severe, n (%)	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)

Number (%) of participants with treatment emergent adverse events of the SAD, MD and RA part.
*Details per SAD cohort can be found in online supplemental table 5.
†Related includes possible, probable and definite relationship to study drug.
MD, multiple dose; RA, rheumatoid arthritis; SAD, single ascending dose.

after the administration of SOL-116. It was a SVT with LBBB morphology for 20 s, assessed as unlikely related to the treatment. Notably, in a placebo-treated patient with RA, paroxysmal atrial fibrillation was observed on day 1, requiring extended telemetry monitoring. All other AEs were assessed as mild. There was no apparent dose-dependent increase in TEAE frequency or severity.

During the 28-joint status performed at baseline, four patients with RA had swollen or tender joints. No other clinically significant abnormalities or apparent changes over time were observed across all cohorts in physical examinations, vital signs, ECGs and laboratory assessments including lipid status and α-tocopherol (online supplemental figures 3 and 4).

PK of SOL-116

Single s.c. administration of SOL-116 in healthy participants resulted in relatively slow absorption, as indicated by median T_{max} values ranging from 122 to 173 hours (5.1 to 7.2 days) across the different dose levels. The mean $T_{1/2z}$ ranged from approximately 389 to 495 hours (16.2 to 20.6 days). The mean CL/F and Vz/F of SOL-116 ranged from 0.013 to 0.014 L/h and 7.6 to 10.2 L, respectively (figure 2a and table 3). Analysis of the dose proportionality showed that systemic exposures ($AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$) as well as peak exposures (C_{max}) of SOL-116 increased linearly within the dose range of SAD cohorts 1 to 5 (0.075 to 6.075 mg/kg).

After four doses of 3.0 mg/kg Q4W SOL-116 in healthy participants in the MD cohort, the accumulation of SOL-116 was low, with mean accumulation ratios of 2.20 in AR_{cmax} and 2.15 in AR_{auc}. Based on visual inspection, it appeared that SOL-116 had reached close to steady state by day 85 (predose of the fourth dose administration) (figure 2b and table 3).

The PK characteristics of SOL-116 following a single s.c. injection of 2.025 mg/kg in patients with RA were found to be comparable to the SOL-116 PK in healthy participants receiving a similar dose, with CL/F of 0.0183 vs 0.0130 L/hour, respectively (figure 2c, table 3). Variability was slightly higher in patients with RA than in healthy participants, without a clear identifiable cause (figure 2d).

SOL-116 showed no clinically relevant induction of ADAs

ADAs were detected in only one of 336 post-dose samples from 56 participants, which was a sample collected on day 49 from a patient with RA treated with SOL-116 (titre of 2.46). The patient tested negative at the next timepoint (day 90).

PD results

BSSL levels were reduced following SOL-116 administration

After administration of a single dose of SOL-116 in healthy participants, free circulating BSSL levels decreased to below LLOQ, already from the lowest dose level (0.075 mg/kg), from day 4 and remained so up to day 90, with the exception of 4 out of 240 (2%) reported measures from different individuals on single occasions during the last three visits. Among placebo participants BSSL was detected in 63% (50/80) of samples (figure 3a and online supplemental figure 5).

In participants treated with MDs of SOL-116 a comparable trend of reduction in plasma BSSL was observed, but from day 29 to 169 (except one reported value on day 95). The proportion of BSSL positive samples from day 4 was substantially lower in the SOL-116 treated participants (8%, 7/84) compared with placebo participants (89%, 25/28) (figure 3b).

In patients with RA, the reduction in plasma BSSL was slightly less pronounced. BSSL was detected in 23% (11/48) of post dose samples of SOL-116 treated participants, compared with 63% (10/16) among placebo

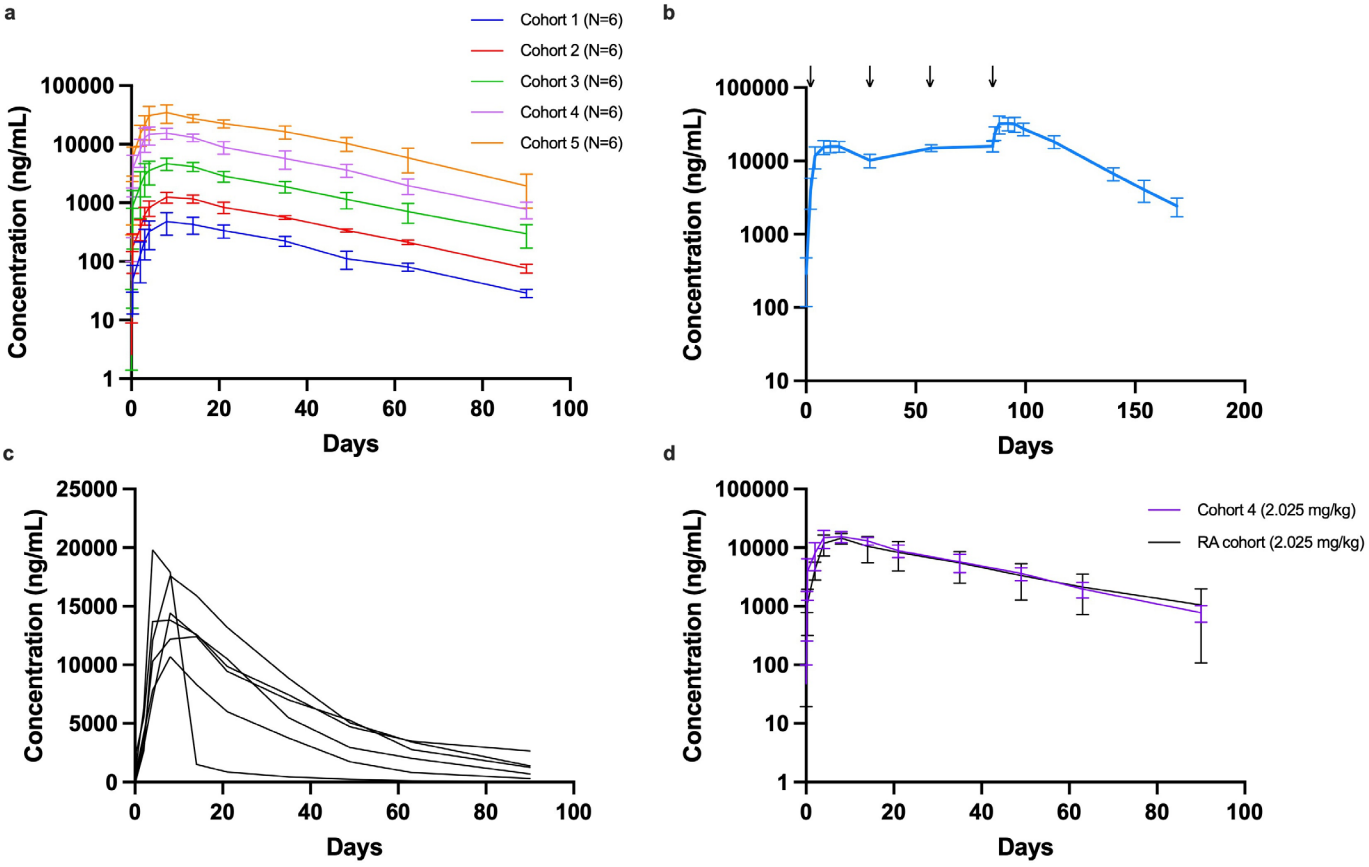

Figure 2 Pharmacokinetics of SOL-116. (a) Mean (SD) serum SOL-116 concentration—time profiles following a single s.c. injection of 0.075, 0.225, 0.675, 2.025 and 6.075 mg/kg SOL-116 in healthy participants under fasting conditions in SAD cohorts 1–5. (b) Mean (SD) serum SOL-116 concentration—time profiles following four s.c. injections of 3.0 mg/kg SOL-116 Q4W in healthy participants with arrows indicating dosing days. (c) Individual serum concentration-time graph of SOL-116 following a single s.c. injection of 2.025 mg/kg SOL-116 in patients with RA. (d) Mean (SD) SOL-116 concentration time profiles after a single s.c. SOL-116 dose of 2.025 mg/kg in healthy participants (purple) and patients with RA (black). See online supplemental table 6 for the actual data points of all graphs. Q4W, every 4 weeks; RA, rheumatoid arthritis; SAD, single ascending dose; s.c., subcutaneous.

participants. Overall, BSSL was found absent in all patients with RA from day 22 to 90, except for one patient (figure 3c).

Due to limitations in BSSL assay sensitivity, predose concentrations were only detectable in 48% of SAD samples, in 63% of MD samples and in 50% of the RA cohort samples. BSSL levels per cohort and time point are summarised in online supplemental table 3.

Other inflammatory markers

No clear change in ESR, CRP, hsCRP and calprotectin was observed over time in the SOL-116 and placebo groups (online supplemental figure 6).

Cytokines and chemokines

Cytokines and chemokines analysed in plasma from cohorts 1, 4 and 5 of the SAD part in healthy participants, and from the RA cohort, showed no change following SOL-116 administration in both groups. At baseline, there were numerical differences in some protein levels between healthy participants and patients with RA, but none was statistically significant. A PCA of predose samples demonstrated no difference between healthy participants and patients with RA (online supplemental figure 7).

Exploratory flow cytometry and whole blood stimulation assays in patients with RA

No clinically relevant differences were observed in B-cells and T-cells, neutrophils and monocytes as measured with flow cytometry and whole blood stimulation assay between patients with RA treated with SOL-116 and placebo-treated patients, with comparable findings in the unstimulated and fMLP-stimulated samples. Although some minor changes over time were observed in a limited number of parameters, no clear trends could be identified.

DISCUSSION

This study assessed the safety, tolerability, PK, immunogenicity and exploratory PD of SOL-116 following single ascending and repeated doses in healthy participants and single doses in patients with RA. The primary

Table 3 Serum pharmacokinetic (PK) parameters of SOL-116

	SAD Cohort 1	SAD Cohort 2	SAD Cohort 3	SAD Cohort 4	SAD Cohort 5	MD Cohort	RA Cohort
	0.075 mg/kg (N=6)	0.225 mg/kg (N=6)	0.675 mg/kg (N=6)	2.025 mg/kg (N=6)	6.075 mg/kg (N=6)	3.0 mg/kg Q4W (4 doses) (N=6*)	2.025 mg/kg (N=6)
T_{max} (hours) Median (min, max)	173 (172, 485)	172 (172, 316)	172 (172, 316)	122 (72, 172)	172 (172, 292)	169.73 (71.88, 239.78)	170.82 (72.70, 337.10)
C_{max} (ng/mL) AM (CV%)	489 (36.4)	1280 (18.9)	4680 (23.0)	16300 (21.8)	35300 (31.5)	34600 (26.1)	14800 (22.8)
C_{trough} (ng/mL) AM (CV%)	NA	NA	NA	NA	NA	15200 (16.2)	NA
$AUC_{0\text{-}inf}$ (hour*ng/mL) AM (CV%)	0.418 *10^6 (25.2)	1.11 *10^6 (10.2)	3.93 *10^6 (18.1)	12.3 *10^6 (19.4)	30.2 *10^6 (20.9)	NA	11.4 *10^6 (43.6)
$AUC_{0\text{-}tau}$ (hour*ng/mL) AM (CV%)	NA	NA	NA	NA	NA	17.5 *10^6 (21.8)	NA
$T_{1/2Z}$ (hour) AM (CV%)	446 (9.4)	459 (9.5)	495 (12.7)	465 (6.6)	389 (28.3)	NA	475 (22.4)
CL/F (L/hour) AM (CV%)†	0.0146 (28.0)	0.0145 (20.4)	0.0144 (26.2)	0.0130 (24.0)	0.0145 (33.8)	0.0125 (17.1)	0.0183 (63.9)
V_z/F (L) AM (CV%)	9.58 (38.3)	9.67 (29.3)	10.2 (25.1)	8.75 (25.2)	7.59 (20.9)	NA	11.5 (42.7)
ARcmax AM (CV%)	NA	NA	NA	NA	NA	2.20 (19.2)	NA
ARauc AM (CV%)	NA	NA	NA	NA	NA	2.15 (7.4)	NA

PK parameters of SOL-116 following single doses in healthy participants (Non-Compartmental Analysis), multiple doses in healthy participants (descriptive statistics of day 85) and single doses in patients with RA (descriptive statistics).
*There is one participant whose PK parameters except Ctrough cannot be reliably determined due to missing sample around Tmax, thus the PK parameters are not included in the summary statistics except Ctrough.
†CLss/F for the MD cohort.
AM, arithmetic mean; AR_{cmax}, accumulation ratios for maximum concentration; AUC, area under the curve; CL/F, interspecies scaling of clearance; C_{max}, maximum concentration; C_{trough}, minimum concentration; CV, coefficient of variation; MD, multiple dose; NA, not available; RA, rheumatoid arthritis; SAD, single ascending dose; T_{max}, time to maximum concentration; V_z/F, apparent volume of distribution.

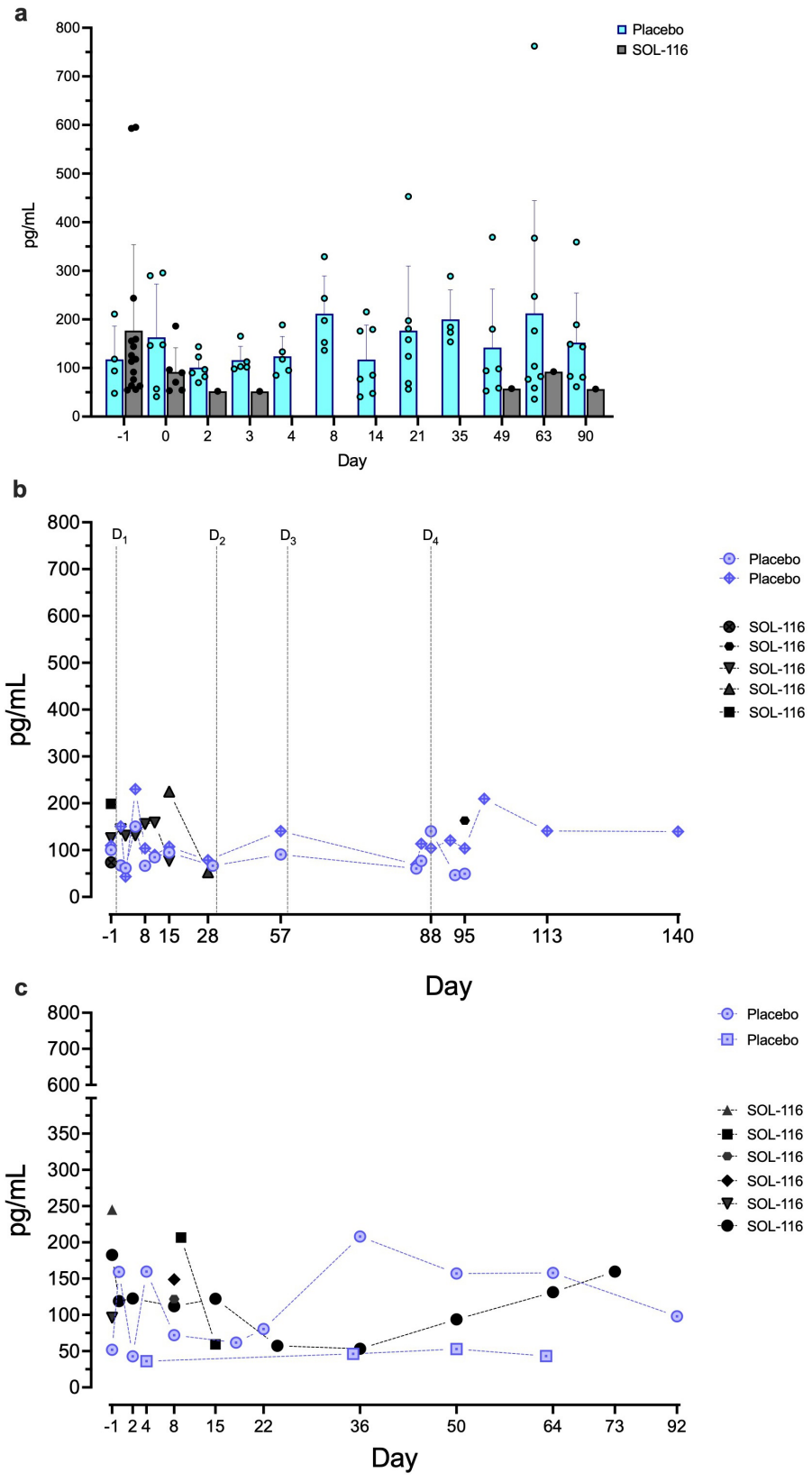

Figure 3 Plasma BSSL concentrations. Mean (SD) plasma BSSL concentrations in healthy participants receiving single doses of SOL-116 (n=30) or placebo (all SAD cohorts 1–5, n=10). From day 4 to day 35, the BSSL concentrations were below the LLOQ for all participants treated with SOL-116 (a). Individual curves in healthy participants receiving four doses (3.0 mg/kg) of SOL-116 (n=6) or placebo (n=2) Q4W (dosing timepoints indicated with D1–4) (b), and in patients with RA following a single dose (2.025 mg/kg) of SOL-116 (n=6) or placebo (n=2) (c). See online supplemental table 7 for the actual data points of all graphs. BSSL, bile salt-stimulated lipase; LLOQ, lower limit of quantification; Q4W, every 4 weeks; RA, rheumatoid arthritis; SAD, single ascending dose.

objective, demonstrating that s.c. administered SOL-116 was safe and well tolerated at the tested dose levels in both healthy participants and patients with RA, was successfully met. A dose-proportional increase in SOL-116 serum concentration was observed in AUC as well as C_{max} across the single dose cohorts in healthy participants, with low accumulation after MDs administered Q4W, and steady state reached prior to the fourth dose. Importantly, the PK characteristics of SOL-116 appear to be comparable between healthy participants and patients with RA. Furthermore, the findings of this study showed a low frequency of ADA. As anticipated, SOL-116 effectively reduced free plasma BSSL levels in the systemic circulation.

The favourable safety profile was consistent with preclinical findings of SOL-116 and studies with BSSL KO mice.[14–17] Mild ISRs were observed, which is in line with observations of preclinical studies and with findings of other monoclonal antibodies administered s.c.[18] Despite BSSL being a lipase digesting dietary lipids, including fat-soluble vitamin esters (eg, tocopherol-esters), no abnormalities were observed in plasma lipoprotein levels and α-tocopherol status, alleviating concerns of fat malabsorption similar to that obtained with orally administered Orlistat (tetrahydrolipstatin), a broad lipase inhibitor, also acting on BSSL.[19–22]

The cardiac abnormalities that were observed in two participants, non-sustained SVTs, were assessed as unlikely related to SOL-116. First, at the timing of these AEs, starting either within several hours after dosing or 26 days after the last dose and resolving within 1 day, only limited exposure of SOL-116 was observed. In addition, the absence of preclinical cardiac abnormalities and no known interaction between either BSSL or SOL-116 and the cardiovascular system supported the conclusion that these AEs were most likely pre-existing medical conditions, although both participants had no documented cardiac history. Notably, clinically significant arrhythmia was also observed in one of the placebo-treated patients with RA. This finding highlights that such arrhythmias can occur in the studied population independently of drug administration, especially since patients with RA, even with mild disease, may have elevated cardiovascular risk. Nevertheless, given that SOL-116 is a first-in-class therapeutic and this represents an FIH study, a causal relationship between the observed cardiac events and SOL-116 cannot be definitively excluded. Accordingly, cardiac monitoring should be included in the further clinical evaluation of SOL-116.

Furthermore, the PK results are comparable to findings of other IgG4 isotype monoclonal antibodies in therapeutic use.[23] The PK observed in the present study aligns with the dosing predictions based on preclinical data, which was within the potential therapeutic range and within a safe range, with the C_{max} and AUC well below the NOAEL in animals. Except for a larger variability in patients with RA, PK results after a single dose of SOL-116 were comparable between healthy participants and patients with RA, which also suggests that MTX is unlikely to have a major impact on PK. In contrast, slightly lower systemic exposure was observed in a preclinical arthritis model in rats as compared with healthy animals. Since it is hypothesised that penetration (distribution) of SOL-116 into inflamed BSSL containing tissue may affect the systemic SOL-116 exposure, the low disease activity of the patients enrolled in the present study may have contributed to the similarities in clinical PK profiles observed across groups. The effect of disease activity on PK should therefore be further elucidated in patients with RA with higher disease activity.

The effective reduction of BSSL in plasma observed across cohorts indicates target engagement of SOL-116. Previous studies in healthy participants have shown average BSSL serum levels ranging from 1.7 to 3.2 ng/mL,[7 24 25] which are substantially higher than the baseline levels observed in plasma from the healthy participants enrolled in the present study, in which approximately half of the predose BSSL samples were below the LLOQ. The BSSL concentrations are higher in serum than in plasma, which may be due to release of BSSL from thrombocytes during blood clotting.[26] Furthermore, the lack of difference in BSSL concentrations between healthy controls and patients with RA might be explained by the relatively low disease activity in the RA cohort in the present study, as BSSL has been shown to be associated with disease activity.[7] Recent insights suggesting thrombocytes as the primary source of BSSL, together with the observation that thrombocyte levels are elevated in patients with RA with active disease, further support this interpretation.[26 27] It is therefore plausible that the BSSL reduction following SOL-116 administration may be more pronounced in patients with moderate to severe disease activity. Improved assay sensitivity may also enhance the utility of BSSL as a PD marker in future trials. Nevertheless, plasma BSSL was effectively reduced from day 4 up to 12 weeks in SOL-116 treated participants, already at the lowest dose level (0.075 mg/kg), whereas BSSL remained detectable in a substantially larger proportion of placebo-treated participants. These findings demonstrate a high binding capacity of SOL-116 and a sustained systemic clearance of BSSL from plasma for up to 12 weeks.

The precise mechanism by which BSSL contributes to inflammation in RA remains to be determined. No specific receptor for BSSL signalling has been confirmed, despite proposed candidates,[26 28–30] and the main source of circulating BSSL is still under investigation. We hypothesised that BSSL might exert inflammatory effects via modulation of monocyte adhesion molecules (CD11a/CD11b) and CXCR4 expression. However, no clear changes or trends were observed after SOL-116 administration in any of these proteins, either in unstimulated or fMLP-stimulated samples. In line with the favourable clinical safety profile, plasma cytokine concentrations were also unaffected, further supporting the absence of systemic pro-inflammatory immune activation in response to SOL-116. The lack of clinically relevant findings in these PD parameters may be explained by the small patient population with mild disease activity while on stable MTX

doses, or by the possibility that the selected readouts and stimulation conditions did not adequately capture BSSL-related mechanisms, or because BSSL does not lead to monocyte activation.[31] Future studies should therefore investigate BSSL-related effects in patients with RA with higher disease activity and consider alternative cellular pathways and experimental approaches. Despite these uncertainties, previous studies showing that elimination of BSSL in rodents results in a significant reduction of disease severity and that systemic BSSL levels are associated with disease severity in RA, PsA and JIA patients,[6 7 11] support the continued development of anti-BSSL treatment to counterbalance chronic inflammation.

Other relatively new treatment options registered for the treatment of RA, such as bDMARDs or tsDMARDs, mostly target cytokines or the more downstream Janus kinases. Even though these bDMARDs and tsDMARDs are quite effective, their use is associated with significant adverse effects, including an increased risk of infection for both classes and cardiovascular side effects specifically linked to tsDMARDs.[2] Given that SOL-116 targets a new mechanism of action, it represents a potentially promising new therapeutic approach for RA, pending demonstration of efficacy. Future studies are needed to evaluate whether SOL-116 can have a potential role either as a standalone treatment or in combination with other DMARDs.

The present study has some important potential limitations. First, since the study was designed for safety and PK outcomes and not PD outcomes, the study was not statistically powered to detect differences in exploratory PD endpoints. Second, the RA cohort included patients with mild disease who were on stable MTX, limiting the ability to assess potential changes in exploratory PD endpoints including BSSL and inflammatory markers. Hence, additional research in larger and more diverse RA populations is warranted to evaluate SOL-116's potential therapeutic impact on disease activity and to refine dosing strategies, facilitating the translation to patients with active, moderate to severe RA.

In conclusion, SOL-116 was well tolerated, with robust and predictable PK and no clinically relevant induction of ADAs. Circulating plasma BSSL was reduced after SOL-116 administration, demonstrating expected target engagement. These findings support the continued clinical evaluation of SOL-116, with particular emphasis on elucidating its efficacy in chronic inflammation, for example, RA, and the mechanism of action of BSSL as a pro-inflammatory mediator.

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