Protocol title	A Randomized, Double-Blind, Placebo-Controlled, First-in-Human Phase I Study Evaluating Safety, Tolerability and Pharmacokinetics of Single Ascending Doses of SOL-116 (a Humanized Monoclonal Anti-BSSL Antibody) in Healthy Subjects and Patients with Rheumatoid Arthritis
Protocol ID	LPM-116-001
Authors	[redacted]
Document type	Clinical Study Protocol
Study Phase	I
Document status/version	Amendment 6
Date	05 August 2024
EudraCT number	2022-001489-37

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SPONSOR:	Lipum AB Tvistevägen 48C SE-907 36 Umeå Sweden

1 SIGNATURE PAGE FOR LIPUM AB

Hereinafter called Lipum AB

Investigational drug name: SOL-116

Protocol number: LPM-116-001

[redacted] 06 augusti 2024 | 20:25 CEST

[redacted] Signature Date

Chief Medical Officer

[redacted] 06 augusti 2024 | 16:38 CEST

[redacted] Signature Date

Chief Executive Officer

2 SIGNATURE PAGE FOR INVESTIGATORS

Investigational drug name: SOL-116

Protocol number: LPM-116-001

I agree to the terms and conditions relating to this study as defined in this protocol, electronic Case Report Form (eCRF), and any other protocol-related documents. I fully understand that any changes instituted by the Investigator(s) without previous agreement with the Sponsor would constitute a violation of the protocol, including any ancillary studies or procedures performed on study subjects/patients (other than those procedures necessary for the well-being of the subjects/patients).

I agree to conduct this study in accordance with the Declaration of Helsinki and its amendments, International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines and applicable regulations and laws. In particular, I will obtain approval by an Independent Ethics Committee or Institutional Review Board (IEC/IRB) prior to study start and signed informed consent from all subjects/patients included in this study. In addition, I will allow direct access to source documents and agree to inspection by auditors from the Sponsor and Health Authorities. I will ensure that the study drug(s) supplied by the Sponsor are being used only as described in this protocol. Furthermore, I confirm herewith that the Sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to worldwide Health Authorities.

*

[redacted]

Signature Date

[redacted]
Principal Investigator, CHDR

[redacted]

PROTOCOL CHANGES LOG

Amendment 6, dated 05 August 2024, original protocol issued 15 September 2022, Amendment 1 dated 30 November 2020, Amendment 2 dated 24 February 2023, Amendment 3 dated 28 July 2023, Amendment 4 dated 29 August 2023, and Amendment 5 dated 06 December 2023.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20EC of the European Parliament and the Council of the European Union.

In this amendment, the inclusion criterion regarding MTX treatment in RA patients and the exclusion criterion regarding evidence of tuberculosis in RA patients are updated. Furthermore, the Principal Investigator of QPS Netherlands B.V. is removed from the protocol and contact details for serious adverse event reporting are updated.

Section	Update
Header	~~06 December 2023,~~ **05 August 2024,** Amendment ~~5~~ **6**
Title Page	Document status/version Amendment ~~5~~ **6** Date ~~06 December 2023~~ **05 August 2024**
Contact Details	Principal investigator**s** [redacted] ~~Hanzeplein 1, entrance 53~~ ~~9713 GZ Groningen~~ ~~The Netherlands~~ Serious Adverse Event Reporting ~~QPS SU~~ **QPS Clinical Services GmbH** ~~Parkring 12~~ **Brückenkopfgasse 1, Top 4 und Top 5** ~~8074 Grambach~~ **8020 Graz** Austria
Section 2 – Signature Page for Investigators	[redacted] ~~QPS Netherlands B.V.~~
Synopsis – Inclusion Criteria	8. Fulfilling the 2010 American College of Rheumatology (ACR)/European Union League Against Rheumatism (EULAR) classification criteria for RA. • Treatment with ~~a stable dose of~~ MTX for at least 12 weeks prior to treatment start and planned to continue with MTX during the study**; if the MTX dose was changed during the 12-week period, such a patient may be included in the study based on Investigator judgement**.
Synopsis – Exclusion Criteria	12. Having evidence of active tuberculosis (TB) or latent TB at Screening as assessed by chest X-ray (RA patients only) and/or by QuantiFERON®-test. **Applicable for RA patients only: in case of rescreening within three months after Screening, negative results from the initial chest X-ray and/or QuantiFERON®-test performed during Screening do not need to be repeated.**

Table 5-2: Visit and Assessment Schedule – Part 2	Footnote 4: Not to be performed when this assessment was done within 3 weeks prior to dosing and result is available. **In case of rescreening within three months after Screening, negative results from the initial QuantiFERON® test performed during Screening do not need to be repeated**. Footnote 5: If a chest X-ray was performed within the past three weeks prior to dosing and documentation is available, it is not necessary to repeat the chest X-ray. **In case of rescreening within three months after Screening, negative results from the initial chest X-ray performed during Screening do not need to be repeated.**
Section 8.3.4.8 QuantiFERON® Test	The QuantiFERON® test will be performed at ~~s~~**S**creening to test for active tuberculosis (TB) or latent TB unless this assessment was done within 3 weeks prior to dosing and result**s** are available. **Applicable for RA patients only: in case of rescreening within three months after Screening, negative results from the initial QuantiFERON®-test performed during Screening do not need to be repeated.** For this test 4 tubes of 1 mL blood each will be taken.
Section 8.3.4.9 Chest X-ray (RA Patients Only)	Only for RA patients, a chest X-ray will be taken at ~~s~~**S**creening to test for active TB or latent TB. If a chest X-ray was performed within the past three weeks prior to dosing and documentation is available, it is not necessary to repeat the chest X-ray. **In case of rescreening within three months after Screening, negative results from the initial chest X-ray performed during Screening do not need to be repeated.**
Table 8-4: Blood Volume (Part 2)	Footnote **: Unless this assessment was done within 3 weeks prior to dosing and result is available**. In case of rescreening within three months after Screening, negative results from the initial QuantiFERON® test performed during Screening do not need to be repeated.**
Section 8.4.1 Inclusion Criteria	8. Fulfilling the 2010 American College of Rheumatology (ACR)/European Union League Against Rheumatism (EULAR) classification criteria for RA [8]. Treatment with ~~a stable dose of~~ MTX for at least 12 weeks prior to treatment start and planned to continue with MTX during the study**; if the MTX dose was changed during the 12-week period, such a patient may be included in the study based on Investigator judgement**.
Section 8.4.2 Exclusion Criteria	12. Having evidence of active tuberculosis (TB) or latent TB at Screening as assessed by chest X-ray (RA patients only) and/or by QuantiFERON®-test. **Applicable for RA patients only: in case of rescreening within three months after Screening, negative results from the initial chest X-ray and/or QuantiFERON®-test performed during Screening do not need to be repeated.**

Amendment 5, dated 06 December2023, original protocol issued 15 September 2022, Amendment 1 dated 30 November 2020, Amendment 2 dated 24 February 2023, Amendment 3 dated 28 July 2023 and Amendment 4 dated 29 August 2023.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20EC of the European Parliament and the Council of the European Union.

In this amendment, the Principal Investigator of QPS Netherlands B.V. is updated and 2 additional clinical sites and Principal Investigators are added. The addition of the new clinical sites has resulted in several updates to the protocol to accommodate procedures at these sites.

Section	Update
Header	~~29 August 2023~~ **06 December 2023,** ~~Amendment 4~~ **Amendment 5**
Title Page	Authors [redacted] Document status/version ~~Amendment 4~~ **Amendment 5** Date ~~29 August 2023~~ **06 December 2023**
Contact Details	Principal investigator**s** [redacted] [redacted] **CHDR** **Zernikedreef 8** **2333 CL Leiden** **The Netherlands** [redacted] **ICON** **Van Swietenlaan 6** **9728 NZ Groningen** Clinical ~~facility~~**facilities** **CHDR** **Zernikedreef 8** **2333 CL Leiden** **The Netherlands** **ICON** **Van Swietenlaan 6** **9728 NZ Groningen** **The Netherlands** Clinical laboratory: **Laboratory – chemistry and haematology** **AKCL LUMC, E2-P** **Albinusdreef 2** **2333 ZA Leiden** **The Netherlands** **LUMC Laboratory – Microbiology**

	Laboratory – Microbiology, E4-P **Albinusdreef 2** **2333 ZA Leiden** **The Netherlands** **Chest X-Ray:** **DC klinieken** **Krimkade 20** **2251 KA Voorschoten** **The Netherlands** ~~Pharmacy~~**Pharmacies:** **Apotheek LUMC, LO-P30** **Einthovenweg 6** **2333 ZC Leiden** **The Netherlands**
Section 1 – Signature Page for Lipum AB	[redacted]
Section 2 – Signature Page for Investigators	2. SIGNATURE PAGE FOR INVESTIGATORS [redacted] **QPS Netherlands B.V.** [redacted] **Principal Investigator, CHDR** [redacted] **Principal Investigator, ICON**
Section 4 – List of Abbreviations	**DAS28 Disease activity score 28** **DAS28-CRP DAS28 with CRP** **DAS28-ESR DAS28 with ESR** **hsCRP High sensitive C-reactive protein** **RDW-CV Red blood cell distribution width** **VAS Visual analogue scale**
Synopsis - Center	CENTERS **CHDR, Leiden, The Netherlands** **ICON, Groningen, The Netherlands**
Synopsis - Treatments	Part 2 There should be at least ~~48~~**24** hours between administration of SOL- 116 and the preceding methotrexate (MTX) dose and at least ~~48~~**24** hours between administration of SOL-116 and the subsequent MTX dose.

Synopsis – Summary of Study Design	Eligibility will be assessed during a screening period of up to ~~28~~**42** days.
Synopsis – Inclusion Criteria	3. Normal clinically physical findings, apart from RA specific findings (including deviating laboratory values e.g., mild anaemia **or swollen joints**) for RA patients, including pulse rate, blood pressure, electrocardiogram (ECG), physical examination, and laboratory values (haematological/clinical chemistry) as judged by the Investigator. Healthy subjects must be negative for anti-cyclic citrullinated peptide (CCP) and have Rheumatoid Factor <1.5 ULN at Screening. 8. • **Use of oral glucocorticosteroids is allowed if equivalent to ≤5 mg/day of prednisolone on a stable dose for a least 4 weeks prior to dosing (Day 1) and expected to remain on that dose level for at least 4 weeks after dosing (Day 1).**
Synopsis – Exclusion Criteria	6. Use of any prescription or non-prescription drugs (excluding paracetamol, hormonal contraceptives), antacids, herbal, and dietary supplements (including St John's Wort) within 14 days (or 28 days if the drug is a potential hepatic enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study drug **for healthy subjects and within 4 weeks prior to the first dose of study drug for RA patients**, unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise subject/patient safety. In RA patients, MTX and folic acid use are exempted. 7. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≥ 2.0 times upper limit of normal (ULN); alkaline phosphatase and bilirubin ≥ 1.5 times the ULN at Screening or on Day -1. **At Screening, these assessments may be repeated once, at the discretion of the Investigator.** 8. Serum creatinine > 1.5 times the ULN or estimated glomerular filtration rat (eGFR) <60 at Screening or on Day -1 **(for Part 1 and Part 3). Estimated glomerular filtration rat (eGFR) <60 at Screening or on Day -1 (for Part 2). At Screening, these assessments may be repeated once, at the discretion of the Investigator.** 9. Subjects/patients who have experienced surgery within 6 months of the screening visit that could negatively impact on the subject's/patient's participation in the opinion of ~~the~~**a** Principal Investigator or responsible physician. 10. ~~Systolic~~**High** blood pressure ~~of >140 mmHg or a diastolic blood pressure of >90 mmHg, confirmed by a repeat test,~~ at Screening or on Day -1**, judged as clinically relevant by a Principal Investigator or responsible physician. A repeat test may be performed.**

	18. Positive urine drug screen or alcohol ~~breath~~ test at Screening or on Day -1. 20. The subject currently smokes or uses nicotine-containing products. Former smokers will be eligible, provided they have not smoked for at least 1 month prior to Screening. Positive cotinine test results at Screening or on Day -1 are reason for exclusion. **Such positive test results can be repeated once to exclude environmental influence on the subject.** 22. Intra-articular or systemic corticosteroid injection ~~and/or oral administration~~ within 4 weeks prior to dosing.
Synopsis – Exploratory Parameters	• Inflammatory biomarkers (except BSSL): C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) for all subjects/patients, and S-calprotectin **and high sensitive CRP (hsCRP)** (only RA patients); • Cytokine/chemokine panel (including but not limited to IFNγ, IL-1β, IL-6, IL-10, IL-12, IL-18, MCP-1 and TNFα).); **• Flow cytometry panel (only RA patients);** **• Whole blood stimulation assays (only RA patients).**
Table 5-2: Visit and Assessment Schedule – Part 2	Screening Day ~~-28~~ **-42** to Day -2 **Patient Global Health VAS Score on Day -1** **DAS28-CRP and DAS28-ESR on Day -1** **Blood sampling for flow cytometry and whole blood stimulation assay on Day 1, Day 2, Day 4 Day 8, Day 21 and Day 49** **Additional blood sampling for future exploratory analysis on Day 1, Day 8 and Day 21** Abbreviation: **DAS28-CRP, disease activity score 28 with C-reactive protein; DAS28-ESR, disease activity score 28 with erythrocyte sedimentation rate; hsCRP, high sensitive C-reactive protein; SAE, serious adverse event; VAS, visual analogue scale** Updated footnotes (number in table also updated): **7. The 28-joint assessment will only be performed on Day -1 (baseline).** 8. There should be at least ~~48~~**24** hours between administration of SOL-116 and the preceding MTX dose and at least ~~48~~**24** hours between administration of SOL-116 and the subsequent MTX dose. **14. On Day 1 prior to dosing. Based on emerging data, collection time points may be updated.** 16. Fasting glucose and lipid status determined at Screening, pre-dose on Day 1, Day 14 and Day 35. α-tocopherol status

	determined pre-dose on Day 1, Day 14 and Day 35 only. S-calprotectin **and hsCRP** determined prior to dosing and 4 hours post-dose on Day 1, on Day 2, on Day 4, **on Day 21,** on Day 49 and on Day 90. Subjects should be fasting for at least 4 hours prior to blood sampling at Screening, and 10 hours prior to blood sampling on Day 1, Day 14 and Day 35. Rheumatoid factor and anti-CCP antibodies only at Screening. **Urinalysis only at Screening, on Day 1, on Day 2, on Day 8, on Day 14, on Day 21, and on Day 90. At Screening, laboratory assessments may be repeated once, at the discretion of the Investigator.**
Table 5-3: Visit and Assessment Schedule for Repeated Dosing Part (every Q4W dosing) – Part 3	Day 86 and 88 ~~(+3)~~ Alcohol ~~breath~~ test Updated footnote: 11. Fasting glucose determined at Screening only. Lipid status determined only at Screening and Day 169 only (10 hours' fasting at both occasions). **No pancreatic lipase on Day 92.**
Section 6.1.3 – Clinical Experience with SOL-116 (current study)	To date, Part 1 has been concluded. Five cohorts with 8 healthy subjects (male and female) per cohort have been administered SOL-116 or placebo (6 active and 2 placebo)~~.~~**, up to 6.075 mg/kg single dose.** In Part 2, the enrolment of rheumatoid arthritis (RA)-patients is currently ongoing. **Part 3, with multiple dosing is ongoing.**
Section 6.3.2 – Selection of Dose in Part 2 (RA cohort)	**In Part 1 of the study, doses up to 6.075 mg/kg SOL-116 resulted in an exposure of 12 800 (µg/mL*h) in healthy subjects, with no safety or tolerability issues.** [redacted]
Section 6.3.2 to 6.3.5	**Section numbering updated.**

Section 8.1.3 – Exploratory Endpoints (all parts)	• Change from baseline in inflammatory biomarkers, i.e. serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) for all subjects/patients and S-calprotectin **and high sensitive CRP (hsCRP)** (only RA patients). • **Change form baseline in other exploratory markers (RA patients only), based on flow cytometry panel and whole blood stimulation assay.**
Section 8.2 – Overall Study Design	Part 2 Eligibility will be assessed during a screening period of up to ~~28~~**42** days. In a cohort of up to 8 RA patients (6 active, 2 placebo will be randomized and dosed) (Cohort 7), one of the single doses tested in healthy subjects **was selected, i.e., 2.025 mg/kg** will be tested (see Section 6.1.3 **and Section 6.3.2**). There should be at least ~~48~~**24** hours between administration of SOL-116 and the preceding methotrexate (MTX) dose and at least ~~48~~**24** hours between administration of SOL-116 and the subsequent MTX dose.
Section 8.3.2.2 – RA Medical History, DAS28-CRP, and DAS28-ESR	8.3.2.2 RA Medical History**, DAS28-CRP, and DAS28-ESR** (RA Patients Only) **The disease activity score 28 (DAS28) for RA with CRP (DAS28-CRP) and the DAS-28 for ESR (DAS28-ESR) will be determined on Day -1 (baseline).**
Section 8.3.2.3 – Prior and Concomitant Medications	All relevant medications taken from 2 weeks prior to Screening **(4 weeks for RA cohort)** until end-of-study (EOS) or started during the study will be recorded on the Concomitant Medications page.
Section 8.3.3.3 - Labeling	~~Detailed information will be given in the lab manual.~~
Section 8.3.4.1 – Adverse Events	Adverse events will be recorded according to the ~~QPS Netherlands B.V.~~**local** standard operating procedure (SOP)/Work instruction of the clinic.
Section 8.3.4.2 – Vital Signs	Vital sign assessments will be performed according to the ~~QPS Netherlands B.V.~~**local** SOP **of the clinic** and will include measurements of supine blood pressure, pulse rate, and temporal body temperature. Vital sign measurements will be collected after the subject/patient has been resting for 5 minutes **in a supine position**.
Section 8.3.4.3 – Body Weight and Height	The subject's/patient's body weight will be measured using a validated balance according to the ~~QPS Netherlands B.V.~~**local** SOP **of the clinic**.
Section 8.3.4.4 – 12-lead ECG	Subjects/patients will be in a supine position for 5 minutes prior to the measurements. ECGs will be evaluated and classified as

	normal/abnormal according to the ~~QPS Netherlands B.V.~~**local** SOP **of the clinic**. HR, PR, QRS, and QT will be provided on the print-out of the ECG apparatus~~.~~ **or in the electronic Muse system (RA patients only)**. Bazett (QT/RR1/2)/Fridericia (QT/RR1/3) QTc is automatically calculated by the ECG apparatus and provided on the print-out~~.~~ **or in Muse (RA patients only).** Evaluation of average recordings will be performed according to ~~QPS Netherlands B.V.~~**the local** SOP **of the clinic**.
Section 8.3.4.5 – Physical Examination	Physical examination will be performed consisting of inspection, percussion, palpation, and auscultation according to the ~~QPS Netherlands B.V. SOP~~**.local SOP of the clinic**. **For Part 2, this will also (at baseline) include a 28-joint status (number of swollen joints and number of tender joints).**
Section 8.3.4.6 – Patient Global Health VAS Score (Part 2 Only)	**Section added.** **In Part 2, the patients will be asked (at baseline) to fill in a Patient Global Health VAS score.**
Section 8.3.4.7 – 3-lead ECG (Telemetry)	Telemetry monitoring will be set on alarm and used for evaluation of any cardiac event. It will be performed according to the ~~QPS Netherlands B.V.~~**local** SOP **of the clinic**.
Section 8.3.4.11 – Laboratory Assessments	**At Screening, laboratory assessments may be repeated once, at the discretion of the Investigator.** ~~As a rule, the blood samples will be taken from the subject/patient by puncture of a vein in the cubital or the antebrachial region.~~
Table 8-1: Summary of Clinical Laboraty Tests	Hematology: **Mean corpuscular hemoglobin** **Mean corpuscular hemoglobin concentration** **Erytoblasts** **Red blood cell distribution width (RDW-CV)** Chemistry: **hsCRP (Part 2 only)** Pancreatic lipase[j] Urinalysis: Albumin **or micro albumin** Others: ~~Cytokine/chemokine panel (including but not limited to IFNγ, IL-1β, IL-6, IL-10, IL-12, IL-18, MCP-1, and TNFα)~~ Footnotes: ~~a. Only if urine dipstick is positive and marked as at least '++' for blood or protein.~~ **a. If there is an abnormality in urine in accordance with the clinical laboratory standard procedures.**

	i. Only applicable for Part 2. **j. Not on Day 92 of Part 3**
Section 8.3.4.12 – Drug and Cotinine Screen	For a urine drug screening, the following compounds ~~will~~**may** be assessed: amphetamine, barbiturates, benzodiazepines, cocaine, marijuana (THC), MDMA/ecstasy, methadone, methamphetamine, morphine, opioids, phencyclidine, and tricyclic antidepressants.
Section 8.3.4.13 – Alcohol Breath Test	~~8.3.4.12~~**8.3.4.13** Alcohol ~~Breath~~ Test ~~The~~**An** alcohol **test (**breath test **or urine)** will be performed according to ~~QPS Netherlands B.V.~~**the local** SOP **of the clinic**.
Section 8.3.4.16 – SARS-CoV-2 Test	COVID-19 testing will be performed according to ~~QPS Netherlands B.V.~~ SOP at the time point described in Table 5 1.
Section 8.3.5 - Immunogenicity	~~Information on equipment and further details on the procedures on the sampling are documented in a separate instruction manual.~~
Section 8.3.6 – Exploratory Asessments	Blood samples will be taken to check BSSL concentration, ~~inflammatory biomarkers, and~~ cytokine/chemokine panel **(including but not limited to IFNγ, IL-1β, IL-6, IL-10, IL-12, IL-18, MCP-1, and TNFα), flow cytometry panel (only RA patients), and whole blood stimulation (only RA patients)** at the time points specified in Table 5 1, Table 5 2 and Table 5 3. About ~~4.0~~**2.0** mL **or 4 mL (2 mL for Part 3 and 4 mL for Parts 1 and 2)** blood for the BSSL samples, and about 2 mL for the cytokine/chemokine panel samples will be collected via vena puncture or via an IV catheter placed in a vein in the arm following the local standard procedures. ~~Information on equipment and further details on the procedures on the sampling are documented in a separate instruction manual~~**In Part 2, about 10 mL for the flow cytometry panel and about 10 mL for the whole blood stimulation assay will be collected.**
Section 8.3.6.1 - Exploratory Samples (Future Analysis)	At time points specified in Table 5 1, Table 5 2 and Table 5 3, ~~an~~ extra blood ~~sample~~**samples** (5.5 mL **in total**) will be taken for future exploratory analysis of potential PK and/or PD markers of relevance for SOL-116.
Section 8.3.7 – Order of Assessments	In case several study procedures are scheduled at the same time point, the following sequence should be followed pre-dose: 12-lead ECG, vital signs, asking for AEs, PK blood sampling, blood sampling for immunogenicity, blood sampling for BSSL, blood sampling for cytokine and chemokine panel, blood sampling for **flow cytometry panel (Part 2 only), blood sampling for whole blood stimulation assay (Part 2 only), blood sampling for** future exploratory analysis, and blood sampling for clinical laboratory tests. Post-dose, the following sequence should be followed: PK blood sampling, blood sampling for immunogenicity, blood sampling for BSSL, blood sampling for cytokine and chemokine panel, blood sampling for **flow cytometry panel (Part 2 only), blood sampling for whole blood stimulation assay (Part 2 only), blood sampling for** future

<table>
<tr><td></td><td>exploratory analysis, blood sampling for clinical laboratory tests, 12-lead ECG and 3-lead ECG (telemetry), vital signs, injection site reaction, asking for AEs.</td></tr>
<tr><td>Table 8-4: Blood Volume (Part 2)</td><td>
<table>
<tr><th></th><th>Vol (mL) x Frequency</th><th>Total (mL)</th></tr>
<tr><td>Chemistry</td><td>43.5 x 12</td><td>~~54.0~~42.0</td></tr>
<tr><td>Serology</td><td>~~3.5~~5 x 1</td><td>~~3.0~~5.0</td></tr>
<tr><td>Hematology</td><td>~~3.0~~2.0 x 11</td><td>~~33.0~~22.0</td></tr>
<tr><td>Coagulation</td><td>2.7 x 11</td><td>29.7</td></tr>
<tr><td>SOL-116 PK*</td><td>4.0 x 14</td><td>56.0</td></tr>
<tr><td>Immunogenicity sampling</td><td>3.5 x 6</td><td>21.0</td></tr>
<tr><td>BSSL*</td><td>4.0 x 12</td><td>48.0</td></tr>
<tr><td>QuantiFERON test**</td><td>4.0 x 1</td><td>4.0</td></tr>
<tr><td>Cytokine/chemokine panel</td><td>2.0 x 67</td><td>~~12.0~~14.0</td></tr>
<tr><td>Anti-CCP antibodies</td><td>3.5 x 1</td><td>3.5</td></tr>
<tr><td>α-tocopherol</td><td>6.0 x 3</td><td>18.0</td></tr>
<tr><td>S-calprotectin analysis</td><td>2.0 x ~~6~~7</td><td>~~12.0~~14.0</td></tr>
<tr><td>Flow cytometry panel</td><td>10.0 x 6</td><td>60.0</td></tr>
<tr><td>Whole blood stimulation assay</td><td>10.0 x 6</td><td>60.0</td></tr>
<tr><td>Sample for future exploratory analysis</td><td>5.5 x ~~6~~8</td><td>~~33.0~~44.0</td></tr>
<tr><td>Total blood volume*</td><td></td><td>~~327.7~~441.2</td></tr>
</table>
* If the Day 3 visit does not take place, one less PK of 4.0 mL and one less BSSL sample of 4 mL will be collected. That would decrease the total blood volume to ~~319.7~~433.2 mL.
</td></tr>
<tr><td>Section 8.4.1 – Inclusion Criteria</td><td>3. Normal clinically physical findings, apart from RA specific findings (including deviating laboratory values e.g., mild anaemia or swollen joints) for RA patients, including pulse rate, blood pressure, electrocardiogram (ECG), physical examination, and laboratory values (haematological/clinical chemistry) as judged by the Investigator.

8. • Use of oral glucocorticosteroids is allowed if equivalent to ≤5 mg/day of prednisolone on a stable dose for a least 4 weeks prior to dosing (Day 1) and expected to remain on that dose level for at least 4 weeks after dosing (Day 1).</td></tr>
<tr><td>Section 8.4.2 – Exclusion Criteria</td><td>6. Use of any prescription or non-prescription drugs (excluding paracetamol, hormonal contraceptives), antacids, herbal, and dietary supplements (including St John's Wort) within 14 days (or 28 days if the drug is a potential hepatic enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study drug for healthy subjects and within 4 weeks prior to</td></tr>
</table>

	the first dose of study drug for RA patients, unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise subject/patient safety. In RA patients, MTX and folic acid use are exempted. 7. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≥ 2.0 times upper limit of normal (ULN); alkaline phosphatase and bilirubin ≥ 1.5 times the ULN at Screening or on Day -1. **At Screening, these assessments may be repeated once, at the discretion of the Investigator.** 8. Serum creatinine > 1.5 times the ULN or estimated glomerular filtration rat (eGFR) <60 at Screening or on Day -1 **(for Part 1 and Part 3). Estimated glomerular filtration rat (eGFR) <60 at Screening or on Day -1 (for Part 2). At Screening, these assessments may be repeated once, at the discretion of the Investigator.** 9. Subjects/patients who have experienced surgery within 6 months of the screening visit that could negatively impact on the subject's/patient's participation in the opinion of ~~the~~**a** Principal Investigator or responsible physician. 10. ~~Systolic~~**High** blood pressure ~~of >140 mmHg or a diastolic blood pressure of >90 mmHg, confirmed by a repeat test,~~ at Screening or on Day -1**, judged as clinically relevant by a Principal Investigator or responsible physician. A repeat test may be performed.** 18. Positive urine drug screen or alcohol ~~breath~~ test at Screening or on Day -1. 20. The subject currently smokes or uses nicotine-containing products. Former smokers will be eligible, provided they have not smoked for at least 1 month prior to Screening. Positive cotinine test results at Screening or on Day -1 are reason for exclusion. **Such positive test results can be repeated once to exclude environmental influence on the subject.** 22. Intra-articular or systemic corticosteroid injection ~~and/or oral administration~~ within 4 weeks prior to dosing.
Section 8.4.3.1 – Concomitant Medication	From 2 weeks (or 28 days if the drug is a potential hepatic enzyme inducer) or 5 half-lives (whichever is longer) prior to Screening **(or 4 weeks for RA cohort)** until the EOS, prescribed or over-the-counter medication (including herbal remedies) is only allowed as described in exclusion criterion 6. If there is a medical need, local intra-articular corticosteroid injections are permitted at the discretion of ~~the~~**a** Principal Investigator. The patients in the RA cohort will be treated with MTX. There should be at least ~~48~~**24** hours between administration of SOL-116

	and the preceding MTX dose and at least ~~48~~**24** hours between administration of SOL-116 and the subsequent MTX dose.
Section 8.5.2 – Study Drug Preparation	All study drugs will be prepared (packaged and labeled in individual doses) at QPS Netherlands B.V. **(for Part 1 and Part 3) or the pharmacy of the Leiden University Medical Center (LUMC) (for Part 2)** by an unblinded pharmacist, or his/her designee.
Section 8.5.5 – Study Drug Administration	In Part 2, there should be at least ~~48~~**24** hours between administration of SOL-116 and the preceding MTX dose and at least ~~48~~**24** hours between administration of SOL-116 and the subsequent MTX dose.
Section 8.6 – Safety Review Committee	• Principal Investigator**(s)** or delegate**(s)** (delegation only when ~~the~~**a** Principal Investigator is not available);
Section 8.7.1 – Determination of Dose Escalation/Subsequent Dosing	For ~~Parts~~**Part** 1 and 2: The decision to escalate to the next dose level will not take place until the SRC has reviewed the blinded safety and tolerability data, including but not limited to vital signs, ECG results, clinical laboratory tests, and AEs, up to and including 14 days post-dose of at least 6 evaluable subjects (subject assessed as pharmacokinetically evaluable at Day 14). **For Part 2: The same applies as for Part 1 but will include 21 days data for safety/PK review.** The SRC, Principal Investigator**(s)** or Lipum AB may terminate dose escalation at any time if continuing to a higher dose level would jeopardize the safety of the subjects/patients.
Section 8.10.2 – Treatment Assignment	Individual sealed randomization codes are kept ~~by QPS Netherlands B.V.~~,**at the participating sites**, and these are used for emergency un-blinding only.
Section 8.10.3 – Double-blinding	Therefore, the bioanalytical laboratory will receive the randomization list from the ~~pharmacy~~**biostatistician**.
Section 8.11.4 – Exploratory Parameters	• Inflammatory biomarkers (except BSSL): CRP, ESR for all subjects/patients, and S-calprotectin **and hsCRP** (only RA patients); • Cytokine/chemokine panel (including but not limited to IFNγ, IL-1β, IL-6, IL-10, IL-12, IL-18, MCP-1 and TNFα).); **• Flow cytometry panel (only RA patients);** **• Whole blood stimulation assays (only RA patients).**
Section 9.2.2.4 – Reporting Procedures	All SAEs must be reported by ~~the~~**a** Principal Investigator to QPS SU within 24 hours of the Investigator'sInvestigator's knowledge of the event.
Section 10.9 – Interim Safety Report	Based on the results of the interim analysis (including but not limited to AEs, vital signs, ECGs, and clinical laboratory tests), a decision will be taken by the Principal Investigator**(s)** and Lipum AB whether the next cohort can start with the planned dose. This decision will only be made after discussion between the Principal Investigator**(s)** and the Sponsor and after mutual agreement and

	must be submitted to the IEC/IRB for approval before dosing can proceed.
Section 10.10 – Clinical Study Report	Safety and tolerability parameters as well as PK and exploratory parameters (BSSL, CRP, **hsCRP,** ESR and S-calprotectin) will be evaluated in a Clinical Study Report.
Section 12.1.1 – Protocol Amendments	It should be reviewed by the Principal Investigator**(s)**, Sponsor and other relevant team members, if appropriate.
Section 12.1.3.1 – Data Collection	Data will be collected ~~using paper source, and via eSource. In~~**according to local SOP of the clinic.** ~~the Data Management Plan, a specification will be made for which assessments the data will be collected via eSource.~~ For each randomized subject/patient, regardless of study drug initiation, an eCRF must be completed and signed by ~~the~~**a** Principal Investigator or sub-investigator.
Section 12.1.3.2 – Data Management and Quality Control	The CRA will use ~~the~~ eCRF systems ~~(OpenClinica and ClinSpark)~~ to track the monitoring queries and their resolution by the site.
Section 13 Structured Risk Analysis	~~A risk analysis (TSP603.02) will be made by the Division Clinical of QPS Netherlands B.V.~~ **New section added.**

Amendment 4, dated 29 August 2023, original protocol issued 15 September 2022, Amendment 1 dated 30 November 2020, Amendment 2 dated 24 February 2023 and Amendment 3 dated 28 July 2023. Amendment 4 is identical to Amendment 3 plus that EC's comments were incorporated and minor corrections done.

Section	Update
Header	~~28 July 2023~~ **29 August 2023,** ~~Amendment 3~~ **Amendment 4**
Title Page	Document status/version ~~Amendment 3~~ **Amendment 4** Date ~~28 July 2023~~ **29 August 2023**
Table 5-2: Visit and Assessment Schedules	Footnote 14 was updated: "*~~CRP, ESR and~~ S-calprotectin determined prior to dosing and 4 hours post-dose on Day 1, on Day 2, on Day 4, on Day 49 and on Day 90*." The rest of the footnote remains the same. The update was done to correct a prior mistake.
Table 5-3: Visit and Assessment Schedule for Repeated Dosing Part (every Q4W dosing) – Part 3	**BMI** was added. The update was done to correct a prior mistake.
Table 8-6: Assignment of Study Codes to Subjects/Patients	The clarification: **"Healthy subjects"** was added

Amendment 3, **dated 28 July 2023**, original protocol issued 15 September 2022, Amendment 1 dated 30 November 2020 and Amendment 2 dated 24 February 2023.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20EC of the European Parliament and the Council of the European Union.

In this amendment, updates were made to study design including addition of a multiple dosing part (Part 3), updates of inclusion and exclusion criteria, involved laboratories have been defined, Sponsor's Chief Medical Officer was updated and administrative updates.

Section	Update
Header	~~24 February 2023~~ **28 July 2023,** ~~Amendment 2~~ **Amendment 3**
Title Page	Document status/version ~~Amendment 2~~ **Amendment 3** Date ~~24 February 2023~~ **28 July 2023**
Contact Details	BSSL ANALYSES: **BioAgilytix Europe GmbH**~~Pelago Biosciences~~ **Lademannbogen 10, 22339 Hamburg** **Germany** ~~Scheeles väg 1~~ ~~SE-171 65 Solna~~ ~~Sweden~~ **CYTOKINE ANALYSES:** **TATAA Biocenter AB** **Sofierogatan 3A** **SE-412 51 Gothenburg, Sweden**
Signature Page for Lipum AB	[redacted] Chief Medical Officer
Synopsis - Objectives	**Objectives for single dosing (Parts 1 and 2)** Primary objective: • To evaluate the safety and tolerability of single ascending doses of SOL-116 in healthy subjects and rheumatoid arthritis (RA) patients. Secondary objective: • To determine single dose pharmacokinetic (PK) characteristics of SOL-116 in healthy subjects and RA patients. • To assess the immunogenicity of SOL-116 after single SC doses in healthy subjects and RA patients. Exploratory objectives: • To evaluate the effect of single ascending doses of SOL-116 on bile salt-stimulated lipase (BSSL) concentration in the blood of healthy subjects and RA patients. • To evaluate the pharmacodynamic (PD) effect of single ascending doses of SOL-116 on inflammatory biomarkers in the blood of healthy subjects and RA patients.

	Objectives for multiple dosing (Part 3) **Primary objective:** • **To evaluate the safety and tolerability of multiple dosing of SOL-116 in healthy subjects.** **Secondary objective:** • **To determine multiple dose PK characteristics of SOL-116 in healthy subjects.** • **To assess the immunogenicity of SOL-116 after multiple SC doses in healthy subjects.** **Exploratory objectives:** • **To evaluate the effect of multiple doses of SOL-116 on BSSL concentration in the blood of healthy subjects.** • **To evaluate the PD effect of multiple doses of SOL-116 on inflammatory biomarkers in the blood of healthy subjects.**
Synopsis - Treatments	**Part 3** **Up to two multiple dosing cohorts of 8 healthy subjects (6 active, 2 placebo) (Cohorts MD1 and MD2) are planned, i.e. in total up to 16 subjects will be randomized and dosed.** **The starting dose in Cohort MD1 will be 3.0 mg/kg SOL-116 given as SC injection(s).** [redacted] **Sentinel dosing will be employed in all cohorts. Thus, within each cohort initially 1 subject will receive SOL-116 and 1 subject will receive placebo. The remaining 6 subjects of the cohort may be dosed at least 48 hours after dosing of the initial 2 subjects of the cohort, provided no clinically significant safety issues, as judged by the Investigator, are noted in the 48 hours after dosing of the initial 2 subjects of the cohort.** **After each cohort completes dosing, a dose escalation SRC meeting will take place. Escalation to the next MD dose cohort may occur only after evaluation of the safety/tolerability and available PK data up to and including 28 days post last dose of at least 6 evaluable subjects (subject assessed as pharmacokinetically evaluable at Day 28) and after approval by the IEC. This time point may be adjusted based on the PK data of previous cohorts if the SRC recommends.**
Synopsis – Summary of Study Design	Eligibility will be assessed during a screening period of up to 28 days. For the treatment period, subjects/patients will check into the clinic one day prior to dosing (Day -1). On Day 1, all subjects/patients will receive SOL-116 in a fasted state (after an overnight fast of at least 10 hours). Subjects/patients will be released from the clinic on Day 4 (Part 1) or Day

	2 (Part 2), after all required study procedures are completed and if medically justified. If medically indicated and/or based on emerging data, patients in Part 2 may be asked to return on Day 3 for additional safety assessments (optional visit). Furthermore, in both parts the clinic stay may be extended up to Day 7 if medically indicated and/or based on emerging data. In total, subjects/patients will return to the clinic for 6 (Part 1) or up to 8 (Part 2) ambulant visits up to Day 63. Subjects/patients will return to the clinic on Day 90 for an EOS/follow-up visit. **A multiple dosing part will be performed in healthy subjects where, in the first multiple dosing cohort, each subject will receive a total of four doses every fourth week (Q4W): at baseline (D1) and Days 29, 57 and 85. With a dose interval of 28 days, it is estimated that with the half-life of SOL-116 (assessed in the SAD) concentrations at, or close to, steady state will be reached after the fourth dose. The subjects are followed up until Day 169.**
Synopsis – Study Population	Up to 48 healthy male or female subjects and 8 male or female RA patients (**for Parts 1 and 2, respectively**). Preferably at least 3 out of 8 subjects per cohort should be of the least represented sex (female or male), respectively. **The study also includes up to 16 healthy adult subjects in one or two multiple dosing cohorts (Part 3).**
Synopsis – Inclusion Criteria	2. Males and females aged between 18 and 65 years (inclusive) at Screening. **For patients in the RA cohort, an age interval between 18 and 70 years (inclusive).** 3. Normal clinically physical findings, apart from RA specific findings **(including deviating laboratory values e.g., mild anaemia)** for RA patients, including pulse rate, blood pressure, electrocardiogram (ECG), physical examination, and laboratory values (haematological/clinical chemistry) as judged by the Investigator. Healthy subjects must be negative for anti- cyclic citrullinated peptide (CCP) and have Rheumatoid Factor <1.5 ULN at Screening. 4. **For Parts 1 and 3, b~~B~~**ody mass index (BMI) between 19.0 and 30.0 kg/m^2 and body weight between 50 to 100 kg (inclusive) at Screening. **For Part 2, body weight between 50 to 120 kg (inclusive) at Screening.** 5. *Sexually active male patients* participating in the study must use a barrier method of contraception (condom) and refrain from sperm donation during the study and for 150 days after **last** dosing if their female sexual partner is of childbearing potential. Acceptable methods of birth control for female partners of male subjects are: hormonal contraceptives (oral contraceptives, implant or injection), intrauterine device (placed at least 1 month before the start of the study). Surgical sterilization of male patients can be accepted as a form of birth control if the sterilization procedure took place at least 6 months prior to the start of the study. 8. The following inclusion criterion is only applicable for RA patients:

	Fulfilling the 2010 American College of Rheumatology (ACR)/European Union League Against Rheumatism (EULAR) classification criteria for RA. • Treatment with a stable dose of MTX for at least 12 weeks prior to treatment start and planned to continue with MTX during the study. • Patients naïve to biological disease modifying anti-rheumatic drug (bDMARD) **or who are washed out (at least 5 half-lives) from such therapy before study drug dosing.**
Synopsis – Exclusion Criteria	8. Serum creatinine > 1.5 times the ULN or estimated glomerular filtration rat (eGFR) <~~70~~ **60** at Screening or on Day -1. 10. Systolic blood pressure of ≧ **>140** mmHg or a diastolic blood pressure of ≧ **>90** mmHg, confirmed by a repeat test, at Screening or on Day -1. 13. Subjects/patients who are currently enrolled in or have recently participated in another interventional clinical study defined as having received the last intervention within 90 days or 5 half-lives of the study drug (whichever is longer) prior to dosing ~~of the study drug~~**(Parts 1 and 2) vs. prior to first dosing (Part 3) of the study drug.** 15. Receipt of a vaccine ~~(except COVID-19 vaccine)~~ within 4 weeks **(COVID-19 vaccine within 6 weeks)** prior to dosing and/or the intention to receive a vaccine during the study. **Deviation from this should be judged by the Investigator and in dialogue with the Sponsor.** 16. Recent confirmed COVID-19 infection, with less than 6 weeks between recovery and dosing of study drug~~, and/or receipt of a COVID-19 vaccine within 6 weeks prior to dosing of the study drug or having the intention to receive such a vaccine within 7 weeks post dosing of study drug~~. 20. The subject currently smokes or uses nicotine-containing products. Former smokers will be eligible, provided they have not smoked for at least ~~3~~ **1** month~~s~~ prior to Screening. Positive cotinine test results at Screening or on Day -1 are reason for exclusion. The following exclusion criteria are only applicable for RA patients: 22. Intra-articular or systemic corticosteroid injection **and/or oral administration** within 4 weeks prior to ~~randomization~~ **dosing**. 23. Current or expected need of other immunosuppressant medication except MTX and/or ~~expected need for~~ intra-articular corticosteroid injections.
Synopsis – Pharmacokinetic Parameters	**In multiple dosing part, also:** **Minimum observed serum concentration at steady state (C_{trough}), time to steady state, accumulation ratio.**
Table 5-2: Visit and Assessment Schedules	SARS-CoV-2 test taken out

Table 5-3: Visit and Assessment Schedules	Added Table for Part 3
Section 6.1.3 – Clinical Experience with SOL-116 (current study)	**6.1.3 Clinical Experience with SOL-116 (current study)** **To date, Part 1 has been concluded. Five cohorts with 8 healthy subjects (male and female) per cohort have been administered SOL-116 or placebo (6 active and 2 placebo). There were 25 males and 15 females enrolled, age range 22 to 64 years. No subjects dropped out, few adverse events and no serious adverse event (SAE) were reported. There were no clinically relevant changes from baseline reported on the following: vital signs, ECG parameters, telemetry, clinical laboratory, physical examination. The serum SOL-116 exposure (AUC, C_{max}) increased in an approximately dose-proportional manner.** **In Part 2, the enrolment of rheumatoid arthritis (RA)-patients is currently ongoing.**
Section 6.2.1 – Rationale for Study Design	**In the multiple dosing part in healthy subjects, up to two multiple dosing cohorts (6:2) will be conducted sequentially, but with an overlap, where the 28-day (i.e., T_{max} plus one half-life) safety and PK data post last dose will be assessed by a Safety Review Committee (SRC). The SRC will decide if, and at what dose level, the subsequent cohort may commence. For the first multiple dosing cohort (MD1), the dose and dose interval will be based on all available SAD data and PK modelling data. The subjects will be followed for approximately 90 days post-treatment in order to get an estimate of clearance and elimination half-life after multiple dosing.**
Section 6.3.1 – Selection of Staring dose in Part 1 SAD	Header updated
Section 6.3.2 – Maximum Exposure (SAD)	Header updated
Section 6.3.3 – Selection of Starting Dose and Dose Interval in Multiple Dosing Cohort(s)	**6.3.3 Selection of Starting Dose and Dose Interval in Multiple Dosing Cohort(s)** **The starting dose in the first multiple dosing cohort (MD1) will be 3.0 mg/kg. This dose level is predicted to result in an exposure within the same order of magnitude as the expected therapeutic concentration in humans.** [redacted]

	[redacted] **The subjects will be administered study drug approximately every four weeks for 12 weeks (total of 4 doses). This administration schedule was selected for the first multiple dosing cohort from the projected time to reach steady state, which is based on the half-life of SOL-116 observed in Part 1 of this study (approximately 19 days).** [redacted]
Section 6.3.4 – Maximum Exposure (Multiple Dosing Part)	**6.3.4 Maximum Exposure (Multiple Dosing Part)** [redacted]
Section 7.1 – Study Objectives for Single Dosing (Parts 1 and 2)	Header updated
Section 7.2 – Study Objectives for Multiple Dosing (Part 3)	**<u>Primary objective:</u>** • **To evaluate the safety and tolerability of multiple dosing of SOL-116 in healthy subjects.** **<u>Secondary objective:</u>** • **To determine multiple dose PK characteristics of SOL-116 in healthy subjects.** • **To assess the immunogenicity of SOL-116 after multiple SC doses in healthy subjects.**

	Exploratory objectives: • **To evaluate the effect of multiple doses of SOL-116 on BSSL concentration in the blood of healthy subjects.** • **To evaluate the PD effect of multiple doses of SOL-116 on inflammatory biomarkers in the blood of healthy subjects.**
Section 8.1.1 – Primary Endpoints	Header updated
Section 8.1.2.1 – Secondary Endpoints	• PK of SOL-116 variables **for single dose regimens**: area under the serum concentration-time 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 ($AUC_{0\text{-}t}$), **area under the serum concentration-time from time zero to the end of dosing interval ($AUC_{0\text{-}tau}$) (Part 3)**, maximum observed serum concentration (C_{max}), time to C_{max} (T_{max}), terminal elimination half-life ($T_{1/2}$) **(Parts 1 and 2)**, apparent volume of distribution (V_z/F) **(Parts 1 and 2)**, apparent total body clearance (CL/F) **(Parts 1 and 2)** and dose proportionality after single dose (based on AUC and C_{max}) **(Part 1)**.
Section 8.1.2.2 – Secondary Endpoints Part 3 only	**PK of SOL-116 variables for the last dose: area under the serum concentration-time from time zero to the end of dosing interval ($AUC_{0\text{-}tau}$), maximum observed serum concentration (C_{max}), time to C_{max} (T_{max}), minimum observed serum concentration (C_{trough}), average serum concentration (C_{ave}), apparent total body clearance at steady state (CL_{ss}/F), time to steady state, accumulation ratio in C_{max} and $AUC_{0\text{-}tau}$.**
Section 8.1.3	Header updated
Section 8.2 – Overall Study Design	**This is a randomized, double-blind, placebo-controlled phase I, first-in-human (FIH) study designed to evaluate the safety, tolerability and PK of single SC ascending doses of SOL-116 in healthy subjects and adult RA patients (Parts 1 and 2) and multiple SC doses in healthy subjects (Part 3).** **Part 3** **The multiple dosing part will be in healthy subjects where, in the first multiple dosing cohort, each subject will receive a total of four doses every fourth week (Q4W): at baseline (D1) and Days 29, 57 and 85. With a dose interval of 28 days, it is estimated that with the half-life of SOL-116 (assessed in the SAD) concentrations at, or close to, steady state will be reached after the fourth dose.** **Eligibility will be assessed during a screening period of up to 28 days. For the first dose, subjects will check into the clinic one day prior to dosing (Day -1). On Day 1, all subjects will receive SOL-116 or placebo. Subjects will be released from the clinic on Day 2, after all required study procedures are completed and if medically justified. If medically indicated and/or based on emerging data, the clinic stay**

	may be extended up to Day 7. Subjects will return to the clinic for 15 ambulant visits up to Day 154. Subjects will return to the clinic on Day 169 for an EOS/follow-up visit. After the second and third dose, a phone contact will be made (3 to 7 days after the dose) with the subject to ensure no new adverse events or if new medication has been added. **Up to two multiple dosing cohorts of 8 healthy subjects (6 active, 2 placebo) (Cohorts MD1 and MD2) are planned, i.e. in total up to 16 subjects will be randomized and dosed.** **The starting dose in Cohort MD1 will be 3.0 mg/kg SOL-116 given as SC injection(s) (see Section 6.3.3).** [redacted]**.** **Sentinel dosing will be employed in all cohorts. Thus, within each cohort initially 1 subject will receive SOL-116 and 1 subject will receive placebo. The remaining 6 subjects of the cohort may be dosed at least 48 hours after dosing of the initial 2 subjects of the cohort, provided no clinically significant safety issues, as judged by the Investigator, are noted in the 48 hours after dosing of the initial 2 subjects of the cohort.** **After each cohort completes dosing, a dose escalation SRC meeting will take place (see Section 8.7.1). Escalation to the next MD dose cohort may occur only after evaluation of the safety/tolerability and available PK data up to and including 28 days post last dose of at least 6 evaluable subjects (subject assessed as pharmacokinetically evaluable at Day 28) and after approval by the IEC. This time point may be adjusted based on the PK data of previous cohorts if the SRC recommends.** **Please refer to Table 5-3 for an overview of ambulatory visits and residence in the clinic.**
Section 8.3.3.1 – Timing for Sampling	Table 5-1, ~~and~~ Table 5-2 **and Table 5-3** provide an overview of all PK blood sampling time points.
Section 8.3.4 – Safety and Tolerability Assessments	Table 5-1, ~~and~~ Table 5-2 **and Table 5-3** provide an overview of all time points on which safety assessments will be performed.
Section 8.3.4.10 – Laboratory Assessments	**For Part 1 and 2, t**~~T~~he blood samples will be taken under fasted conditions at time points specified in Table 5-1 and Table 5-2 (due to fasting glucose and/or lipid and α-tocopherol status). On these days, subjects/patients will not be allowed to eat or drink (except water) for a period of 4 hours (Screening) or 10 hours (other time points as specified in Table 5-1 and Table 5-2) prior to blood sampling. **For Part 3, fasting glucose will be determined at Screening only. Moreover, lipid status**

	will be determined only at Screening and Day 169 (10 hours' fasting at both occasions), see Table 5-3.
Table 8-1 – Summary of Clinical Laboratory Tests	f. Only at Screening, pre-dose on Day 1, Day 14 and Day 35 **(Parts 1 and 2). For Part 3 at Screening and Day 169 (EOS).** g. A SARS-CoV-2 rapid test will be performed on Day -1 **(Part 1 only)**. At the discretion of the Investigator, a SARS-CoV-2 PCR or rapid test may be performed at other time points during the study. h. Only pre-dose on Day 1, Day 14 and Day 35 **(Parts 1 and 2). For Part 3 at Screening and Day 169 (EOS)**.
Section 8.3.4.13 – Pregnancy Test	A serum pregnancy test will be performed at Screening. A urine pregnancy test will be performed on Day -1, Visit 7 (Parts 1 **and 3), Visit 8 (Part 3)** ~~or~~ **and** Visit 9 (Parts 2 **and 3**) and at the EOS examination (or at early termination) **(all parts)**. The results must be available prior to dosing.
Section 8.3.4.15 – SARS-CoV-2 Test	COVID-19 testing will be performed according to QPS Netherlands B.V. SOP at the time point described in Table 5-1~~and Table 5-2~~. A check on health status will be performed and body temperature will be measured before the subject/patient enters the clinic on Day -1 **(Part 1). For Parts 2 and 3, COVID-19 testing is not mandatory as recommendations have changed since the study started. Testing for COVID-19 will be done at the discretion of the investigator, based on clinical symptoms.**
Section 8.3.5 - Immunogenicity	Blood samples will be taken to check for the presence of ADA at time points specified in Table 5-1, ~~and~~ Table 5-2 **and Table 5-3.**
Section 8.3.5 – Exploratory Assessments	Blood samples will be taken to check BSSL concentration, inflammatory biomarkers, and cytokine/chemokine panel at the time points specified in Table 5-1, ~~and~~ Table 5-2 **and Table 5-3.**
Section 8.3.6.1 – Exploratory Samples (Future Analysis)	At time points specified in Table 5-1, ~~and~~ Table 5-2 **and Table 5-3**, an extra blood sample (5.5 mL) will be taken for future exploratory analysis of potential PK and/or PD markers of relevance for SOL-116. The samples will be discarded at the latest 10 years after the sampling occasion.
Section 8.3.9 – Total Blood Volume	Table 8-5: Blood Volume (Part 3): Added due to a Part 3 added
Section 8.4 – Study Population	The subject population will include healthy adult subjects (Cohort 1-6 **of Part 1 and multiple dosing cohorts of Part 3**) and patients (Cohort 7, **Part 2**) who satisfy all entry criteria.
Section 8.4.1 – Inclusion criteria	2. Males and females aged between 18 and 65 years (inclusive) at Screening. **For patients in the RA cohort, an age interval between 18 and 70 years (inclusive).** 3. Normal clinically physical findings, apart from RA specific findings **(including deviating laboratory values e.g., mild anaemia)** for RA patients, including pulse rate, blood pressure, electrocardiogram (ECG), physical examination, and laboratory values (haematological/clinical

	chemistry) as judged by the Investigator. Healthy subjects must be negative for anti- cyclic citrullinated peptide (CCP) and have Rheumatoid Factor <1.5 ULN at Screening. 4. **For Parts 1 and 3, b**~~B~~ody mass index (BMI) between 19.0 and 30.0 kg/m^2 and body weight between 50 to 100 kg (inclusive) at Screening. **For Part 2, body weight between 50 to 120 kg (inclusive) at Screening.** 5. *Sexually active male patients* participating in the study must use a barrier method of contraception (condom) and refrain from sperm donation during the study and for 150 days after **last** dosing if their female sexual partner is of childbearing potential. Acceptable methods of birth control for female partners of male subjects are: hormonal contraceptives (oral contraceptives, implant or injection), intrauterine device (placed at least 1 month before the start of the study). Surgical sterilization of male patients can be accepted as a form of birth control if the sterilization procedure took place at least 6 months prior to the start of the study. 8. The following inclusion criterion is only applicable for RA patients: Fulfilling the 2010 American College of Rheumatology (ACR)/European Union League Against Rheumatism (EULAR) classification criteria for RA. • Treatment with a stable dose of MTX for at least 12 weeks prior to treatment start and planned to continue with MTX during the study. Patients naïve to biological disease modifying anti-rheumatic drug (bDMARD) **or who are washed out (at least 5 half-lives) from such therapy before study drug dosing.**
Section 8.4.2 – Exclusion criteria	8. Serum creatinine > 1.5 times the ULN or estimated glomerular filtration rat (eGFR) <~~70~~ **60** at Screening or on Day -1. 10. Systolic blood pressure of ≧ **>140** mmHg or a diastolic blood pressure of ≧ **>90** mmHg, confirmed by a repeat test, at Screening or on Day -1. **For** 13. Subjects/patients who are currently enrolled in or have recently participated in another interventional clinical study defined as having received the last intervention within 90 days or 5 half-lives of the study drug (whichever is longer) prior to dosing ~~of the study drug~~**(Parts 1 and 2) vs. prior to first dosing (Part 3) of the study drug.** 15. Receipt of a vaccine ~~(except COVID-19 vaccine)~~ within 4 weeks **(COVID-19 vaccine within 6 weeks)** prior to dosing and/or the intention to receive a vaccine during the study. **Deviation from this should be judged by the Investigator and in dialogue with the Sponsor.** 16. Recent confirmed COVID-19 infection, with less than 6 weeks between recovery and dosing of study drug~~, and/or receipt of a COVID-19 vaccine within 6 weeks prior to dosing of the study drug or having the intention to receive such a vaccine within 7 weeks post dosing of study drug~~.

	20. The subject currently smokes or uses nicotine-containing products. Former smokers will be eligible, provided they have not smoked for at least ~~3~~ **1** month~~s~~ prior to Screening. Positive cotinine test results at Screening or on Day -1 are reason for exclusion. The following exclusion criteria are only applicable for RA patients: 22. Intra-articular or systemic corticosteroid injection **and/or oral administration** within 4 weeks prior to ~~randomization~~ **dosing**. 24. Current or expected need of other immunosuppressant medication except MTX and/or ~~expected need for~~ intra-articular corticosteroid injections.
Section 8.4.3.1 – Concomitant Medication	From 2 weeks (or 28 days if the drug is a potential hepatic enzyme inducer) or 5 half-lives (whichever is longer) prior to Screening until the EOS prescribed or over-the-counter medication (including herbal remedies) ~~is not allowed, except for medication that is required for the treatment of AEs~~ **is only allowed as described in exclusion criterion 6. Any new concomitant medication for treatment of AEs should preferably be discussed beforehand with the Investigator.** The occasional use of paracetamol is allowed. Female subjects/patients are allowed to use oral contraception, a hormonal implant or hormonal intra-uterine devices as contraception. ~~Oral corticosteroids are not allowed during study~~. **RA patients only (Part 2)**: If there is a medical need, local intra-articular corticosteroid injections are permitted at the discretion of the Principal Investigator. **Part 3 only: Medications for incidental use (e.g., hay fever) may, at the Investigator's discretion, be allowed during the study.**
Section 8.4.3.2 – COVID-19	Section was removed
Section 8.4.3.2 - Alcohol	Drinking of alcoholic beverages is not permitted from 48 hours prior to each clinic visit ~~or stay~~ **or while in the clinic** ~~until clinic discharge~~.
Section 8.4.3.3 – Physical Activities	From ~~Screening until the Day 14 visit as well as 48~~ **24** hours prior to each clinic visit ~~thereafter~~, the subjects/patients should refrain from excessive physical exercise and strenuous sports activities (endurance sports).
Section 8.4.3.4 – Dietary Aspects	Consumption of food containing poppy seeds is not allowed from 24 hours prior to **Screening and prior to** Day -1.
Section 8.4.3.5 - Smoking	Smoking is not permitted from ~~three~~ **one** month~~s~~ prior to Screening up to and including the EOS visit.
Section 8.4.3.6 Participation in Other Clinical Studies	Study subjects are not allowed to participate in any other **interventional** clinical **drug** study during the study period.
Section 8.5.5 – Study Drug Administration	**In Part 3, the same applies but 4 dose administrations (with maximum 4 injections per occasion) will be administered with 28 days' interval (in MD1).**

Section 8.6 – Safety Review Committee	**For Part 3, the same applies but data up to 28 days post last dose will be collected and assessed at the SRC.**
Section 8.7.1 – Determination of Dose Escalation/Subsequent Dosing	**For Parts 1 and 2:** The decision to escalate to the next dose level will not take place until the SRC has reviewed the blinded safety and tolerability data, including but not limited to vital signs, ECG results, clinical laboratory tests, and AEs, up to and including 14 days post-dose of at least 6 evaluable subjects (subject assessed as pharmacokinetically evaluable at Day 14). **For Part 3: The decision to escalate to the next dose level will not take place until the SRC has reviewed the blinded safety and tolerability data, including but not limited to vital signs, ECG results, clinical laboratory tests, and AEs, up to and including 28 days (i.e., T_{max} plus one half-life) post last dose of at least 6 evaluable subjects (subject assessed as pharmacokinetically evaluable at Day 28 post last dose).** Additionally, **for all parts,** an interim PK analysis of available serum SOL-116 concentration data will be reviewed as part of the dose escalation assessment. Any available blood PK data will be reviewed as part of the dose escalation assessment.
Table 8-6 – Assignment of Study Codes to Subjects/Patients	Cohorts MD1 and MD2 added
Section 8.11.1 - Pharmacokinetic Parameters	**In multiple dosing part, C_{trough}, time to steady state and accumulation ratio will also be assessed.** Attainment of steady-state conditions will be determined by visual inspection of the ~~trough~~ **pre-dose** serum concentrations.
Section 10.2 – Analysis Sets	~~Three~~ **Five** different analysis sets are defined. Subjects/patients who withdraw from the study, or who have missing data, will be included in the statistical analyses provided that they are eligible for inclusion in the analysis population as described below.
10.3.1 – Pharmacokinetic Statistical Analysis	Attainment of steady-state conditions will be determined by visual inspection of the ~~trough~~ **pre-dose** serum concentrations.
10.8 – Exploratory Analyses	A definition of the exploratory parameters is described in Section 8.11.4. Exploratory parameters will be listed individually, displayed in appropriate graphics and summarized using descriptive statistics. **The PD (exploratory) set will be used. Also, the PP set and the "all-treated set" will be used.**
10.9 – Interim Safety Report	**For Parts 1 and 2, the i**~~I~~nterim safety analysis will be conducted by the SRC on safety/tolerability and available PK data up to and including 14 days post-dose after completion of at least 6 evaluable subjects per treatment group (subject assessed as pharmacokinetically evaluable at Day 14). **For Part 3, the interim safety analysis will be conducted by**

	the SRC on safety/tolerability and available PK data up to and including 28 days post last dose after completion of at least 6 evaluable subjects per treatment group (subject assessed as pharmacokinetically evaluable at Day 28 post last dose.
10.10 – Clinical Study Report	Safety and tolerability parameters as well as PK and exploratory parameters **(BSSL, CRP, ESR and S-calprotectin)** will be evaluated in a Clinical Study Report. **Certain exploratory parameters may be reported separately.**

Amendment 2, **dated 24 February 2023**, original protocol issued 15 September 2022 and Amendment 1 dated 30 November 2020.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20EC of the European Parliament and the Council of the European Union.

In this amendment, updates were made to the maximum number of study drug injections and maximum volume per injection. In addition, the duration of residence in the clinic and the number of ambulant visits for patients' participation in Part 2 of the study has been changed and some additional updates have been made.

Section	Update
Header	~~30 November 2022~~ **24 February 2023**, ~~Amendment 1~~ **Amendment 2**
Title Page	Document status/version ~~Amendment 1~~ **Amendment 2** Date ~~30 November 2022~~ **24 February 2023**
Synopsis - Treatments	The actual dose for Cohort 2 to Cohort 5 and the dose regimen for the optional additional cohort of healthy subjects (Cohort 6) will be based on the safety and PK results of all preceding cohorts. Furthermore, based on the safety and PK results of all preceding cohorts the number of SC injections given to administer the single dose in Cohort 2 to Cohort 6 may be increased to ~~2 or 3~~**up to 4** injections. In ~~1~~**a** cohort of up to 8 RA patients (6 active and 2 placebo will be randomized and dosed) (Cohort 7), one of the single doses tested in healthy subjects will be tested. There should be at least 48 hours between administration of SOL-116 and the ~~proceeding~~**preceding** methotrexate (MTX) dose and at least 48 hours between administration of SOL-116 and the subsequent MTX dose.
Synopsis – Summary of Study Design	On Day 1, all subjects/patients will receive SOL-116 in a fasted state (after an overnight fast of at least 10 hours). Subjects/patients will be released from the clinic on Day 4~~,~~ **(Part 1) or Day 2 (Part 2),** after all required study procedures are completed and if medically justified. If medically indicated and/or based on emerging data, **patients in Part 2 may be asked to return on Day 3 for additional safety assessments (optional visit). Furthermore, in both parts** the clinic stay may be extended up to Day 7~~. Subjects~~ **if medically indicated and/or based on emerging data. In total, subjects**/patients will return to the clinic for 6 **(Part 1) or up to 8 (Part 2)** ambulant visits up to Day 63. Subjects/patients will return to the clinic on Day 90 for an EOS/follow-up visit.
Table 5-2 Visit and Assessment Schedule – Part 2	Residence in the clinic was reduced to 3 days (discharge on Day 2), so visit numbers were updated and footnote 2 was added. 2. **Day 3 (Visit 3) is optional. In case of safety concerns after discharge on Day 2, patients may be asked to return on Day 3 for the assessments as presented.**

<table>
<tr><td></td><td>7. There should be at least 48 hours between administration of SOL-116 and the ~~proceeding~~preceding MTX dose and at least 48 hours between administration of SOL-116 and the subsequent MTX dose.

12. On Day 1 prior to dosing, and at 1, 4, 8, 24 (Day 2), 48 (Day 3, optional) and 72 hours (Day 4) post-dose.</td></tr>
<tr><td>Section 8.2 – Overall Study Design</td><td>The actual dose for Cohort 2 to Cohort 5 and the dose regimen for the optional additional cohort of healthy subjects (Cohort 6) will be based on the safety and PK results of all preceding cohorts. Furthermore, based on the safety and PK results of all preceding cohorts the number of SC injections given to administer the single dose in Cohort 2 to Cohort 6 may be increased to ~~2 or 3~~up to 4 injections.

Patients will be released from the clinic on Day ~~4~~2, after all required study procedures are completed and if medically justified. If medically indicated and/or based on emerging data, patients may be asked to return on Day 3 for additional safety assessments (optional visit). Furthermore, the clinic stay may be extended up to Day 7~~. Patients~~, if medically indicated and/or based on emerging data. In total, patients will return to the clinic for ~~6~~up to 8 ambulant visits up to Day 63. Patients will return to the clinic on Day 90 for an EOS/follow-up visit.

In ~~1~~a cohort of up to 8 RA patients (6 active, 2 placebo will be randomized and dosed) (Cohort 7), one of the single doses tested in healthy subjects will be tested.

There should be at least 48 hours between administration of SOL-116 and the ~~proceeding~~preceding MTX dose and at least 48 hours between administration of SOL-116 and the subsequent MTX dose.</td></tr>
<tr><td>Section 8.3.4.13 – Pregnancy Test</td><td>A serum pregnancy test will be performed at Screening. A urine pregnancy test will be performed on Day -1, Visit 7 (Part 1) or Visit 9 (Part 2) and at the EOS examination (or at early termination). The results must be available prior to dosing.</td></tr>
<tr><td>Table 8-2 – Allowed Time Windows for PK, PD and Safety Assessments</td><td>
<table>
<tr><td>≤ 4 hours after study drug administration</td><td>± 2 min*</td></tr>
</table>
* On Day 1, 4 hour post-dose samples have an allowed time deviation of ± 10 min.
</td></tr>
<tr><td>Table 8-4 – Blood Volume (Part 2)</td><td>
<table>
<tr><th></th><th>Vol (mL) x Frequency</th><th>Total (mL)</th></tr>
<tr><td>Chemistry</td><td>4.5 x 12</td><td>54.0</td></tr>
<tr><td>Serology</td><td>3.5 x 1</td><td>3.5</td></tr>
<tr><td>Hematology</td><td>3.0 x 11</td><td>33.0</td></tr>
<tr><td>Coagulation</td><td>2.7 x 11</td><td>29.7</td></tr>
<tr><td>SOL-116 PK*</td><td>4.0 x 14</td><td>56.0</td></tr>
<tr><td>Immunogenicity sampling</td><td>3.5 x 6</td><td>21.0</td></tr>
<tr><td>BSSL*</td><td>4.0 x 12</td><td>48.0</td></tr>
</table>
</td></tr>
</table>

	<table><tr><td>QuantiFERON test***</td><td>4.0 x 1</td><td>4.0</td></tr><tr><td>Cytokine/chemokine panel</td><td>2.0 x 6</td><td>12.0</td></tr><tr><td>Anti-CCP antibodies</td><td>3.5 x 1</td><td>3.5</td></tr><tr><td>α-tocopherol</td><td>6.0 x 3</td><td>18.0</td></tr><tr><td>S-calprotectin analysis</td><td>2.0 x 6</td><td>12.0</td></tr><tr><td>Sample for future exploratory analysis</td><td>5.5 x 6</td><td>33.0</td></tr><tr><td>**Total blood volume***</td><td></td><td>**327.7**</td></tr><tr><td></td><td></td><td></td></tr></table> *** If the Day 3 visit does not take place, one less PK of 4.0 mL and one less BSSL sample of 4 mL will be collected. That would decrease the total blood volume to 319.7 mL.**
Section 8.4.3.1 – Concomitant Medication	There should be at least 48 hours between administration of SOL-116 and the ~~proceeding~~**preceding** MTX dose and at least 48 hours between administration of SOL-116 and the subsequent MTX dose.
Section 8.5.5 – Study Drug Administration	SOL-116 will be administered as abdominal SC injection(s). The injection volume will be no more than ~~1~~**2**.0 mL per injection. The number of SC injections given to administer the single dose in Cohort 2 to Cohort 7 may be increased to ~~2 or 3~~ **up to 4** injections. In Part 2, there should be at least 48 hours between administration of SOL-116 and the ~~proceeding~~**preceding** MTX dose and at least 48 hours between administration of SOL-116 and the subsequent MTX dose.

Amendment 1, **dated 30 November 2022**, original protocol issued 15 September 2022.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20EC of the European Parliament and the Council of the European Union.

In this amendment updates were made to existing in- and exclusion criteria and two exclusion criteria were added, the sample volumes for PK, BSSL and future exploratory analysis samples were increased, the separate mention of sampling for inflammatory biomarkers (except BSSL) has been removed throughout the protocol as the analysis is already performed with safety lab samples, a clarification was made to the physical examination section, time points for α-tocopherol status determination were updated and the sample matrix for the PK analysis was changed from plasma to serum.

Section	Update
Header	~~15 September 2022~~ **30 November 2022**, ~~Version 2~~ **Amendment 1**
Title Page	Document status/version ~~Version 2~~ **Amendment 1** Date ~~15 September 2022~~ **30 November 2022**
Section 4 List of Abbreviations	C_{max} Maximum observed ~~plasma~~ **serum** concentration
Synopsis – Center / Country	~~2 centers:~~ QPS Netherlands B.V., Groningen, The Netherlands. ~~QPS Netherlands B.V., Leeuwarden, The Netherlands.~~
Synopsis – Inclusion Criteria	3. Normal clinically physical findings, apart from RA specific findings for RA patients, including pulse rate, blood pressure, electrocardiogram (ECG), physical examination, and laboratory values (haematological/clinical chemistry) as judged by the Investigator. **Healthy subjects must be negative for anti-cyclic citrullinated peptide (CCP) and have Rheumatoid Factor <1.5 ULN at Screening.** 8. Fulfilling the 2010 American College of Rheumatology (ACR)/European Union League Against Rheumatism (EULAR) classification criteria for RA. • Treatment with a stable dose of MTX for at least 12 weeks prior to treatment start and planned to continue with MTX during the study. • Patients naïve to biological disease modifying anti-rheumatic drug (bDMARD). • Patients naïve to conventional/targeted synthetic disease modifying anti-rheumatic drug (csDMARD/tsDMARD), except for MTX, or who are washed out since at least 12 weeks from such therapy ~~that gave inadequate response or stopped due to other medical reason.~~**before study drug dosing**.
Synopsis – Exclusion Criteria	13. Subjects/patients who **are currently enrolled in or** have **recently** participated in ~~other investigational studies~~ **another interventional clinical study defined as having received the last intervention** within

	90 days ~~of Screening~~ or 5 half-lives of the study drug (whichever is longer~~).~~**) prior to dosing of the study drug.** 15. Receipt of a vaccine **(except COVID-19 vaccine)** within 4 weeks prior to dosing and/or the intention to receive a vaccine during the study. 16. **Recent confirmed COVID-19 infection, with less than 6 weeks between recovery and dosing of study drug, and/or receipt of a COVID-19 vaccine within 6 weeks prior to dosing of the study drug or having the intention to receive such a vaccine within 7 weeks post dosing of study drug.** 18. Positive urine drug screen or alcohol breath test at Screening ~~and~~**or** on Day -1. 24. **Known Gilbert's syndrome or Screening laboratory values indicating Gilbert's syndrome.**
Synopsis – Pharmacokinetic Parameters	The following will be reported as ~~plasma~~**serum** PK parameters for SOL-116: • Area under the concentration-time curve from time zero to infinity (AUC0-inf); • Maximum observed ~~plasma~~**serum** concentration (C_{max});
Synopsis – Statistical Methodology	Pharmacokinetic ~~Plasma~~**Serum** concentrations and PK parameters of SOL-116 will be listed by dose level and summarized by time point.
Table 5-1 – Visit and Assessment Schedule Part 1	Row Blood sampling inflammatory biomarkers (except BSSL) was removed. Footnotes 10. Fasting glucose**, and** lipid status ~~and α tocopherol status~~ determined at Screening, pre-dose on Day 1, Day 14 and Day 35 only. **α-tocopherol status determined pre-dose on Day 1, Day 14 and Day 35 only. CRP and ESR determined prior to dosing and 4 hours post-dose on Day 1, on Day 2, on Day 4, on Day 49 and on Day 90.** Subjects should be fasting for at least 4 hours prior to blood sampling at Screening, and 10 hours prior to blood sampling on Day 1, Day 14 and Day 35. Rheumatoid factor and anti-CCP antibodies only at Screening.
Table 5-2 – Visit and Assessment Schedule Part 2	Row Blood sampling inflammatory biomarkers (except BSSL) was removed. Footnotes 10. Fasting glucose**, and** lipid status ~~and α tocopherol status~~ determined at Screening, pre-dose on Day 1, Day 14 and Day 35 only. **α-tocopherol status determined pre-dose on Day 1, Day 14 and Day 35 only. CRP, ESR and S-calprotectin determined prior to dosing and 4 hours post-dose on Day 1, on Day 2, on Day 4, on Day 49 and on Day 90.** Subjects should be fasting for at least 4 hours prior to blood sampling

	at Screening, and 10 hours prior to blood sampling on Day 1, Day 14 and Day 35. Rheumatoid factor and anti-CCP antibodies only at Screening.
Section 8.1.2 – Secondary Endpoints	• PK of SOL-116 variables: area under the ~~plasma~~**serum** concentration-time from time zero to infinity (AUC_{0-inf}), AUC from time zero to time t of the last measured concentration above the limit of quantification (AUC_{0-t}), maximum observed ~~plasma~~**serum** concentration (C_{max}), time to C_{max} (T_{max}), terminal elimination half-life ($T_{1/2}$), apparent volume of distribution (V_z/F), apparent total body clearance (CL/F) and dose proportionality after single dose (based on AUC and C_{max}).
Section 8.3.3.2 – Procedures for Sampling	About ~~3.5~~**4.0** mL blood for the PK samples will be collected via vena puncture or via an intravenous (IV) catheter placed in a vein in the arm following the local standard procedures.
Section 8.3.3.5 - Bioanalysis	The concentrations of SOL-116 in ~~plasma~~**serum** will be determined in the range 1-500 ng/mL (preliminary) using a validated ligand binding assay.
Section 8.3.4.5 – Physical Examination	Physical examination will be performed consisting of inspection, percussion, palpation, and auscultation according to the QPS Netherlands B.V. SOP. Clinically relevant findings that are observed after the screening assessment **but before dosing** must be recorded on **the** specific ~~AE pages~~**medical history page** of the eCRF. Clinically relevant findings found after~~ signing the informed consent form~~**dosing** and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded on an AE page of the eCRF.
Table 8-1 – Summary of Clinical Laboratory Tests	Chemistry: α-~~tocopherol~~[f] **tocopherol**[h] f. Only at Screening, pre-dose on Day 1, ~~on~~ Day 14 and ~~on~~ Day 35. h. **Only pre-dose on Day 1, Day 14 and Day 35.**
Section 8.3.6 – Exploratory Assessments	About ~~3.5~~**4.0** mL blood for the BSSL samples~~, about 3.5 mL for the inflammatory biomarker~~, and about 2 mL for the cytokine/chemokine panel samples will be collected via vena puncture or via an IV catheter placed in a vein in the arm following the local standard procedures.
Section 8.3.6.1 Exploratory Samples (Future Analysis)	At time points specified in Table 5 1 and Table 5 2, an extra blood sample (5**.5** mL) will be taken for future exploratory analysis of potential PK and/or PD markers of relevance for SOL-116. The samples will be discarded at the latest 10 years after the sampling occasion.
Section 8.3.7 – Order of Assessments	In case several study procedures are scheduled at the same time point, the following sequence should be followed pre-dose: 12-lead ECG, vital signs, asking for AEs, PK blood sampling, blood sampling for immunogenicity, blood sampling for BSSL, blood sampling for ~~inflammatory biomarkers (except BSSL), blood sampling for~~ cytokine and chemokine panel, blood sampling for future exploratory analysis, and blood sampling for clinical laboratory tests. Post-dose, the following sequence should be followed: PK blood sampling, blood sampling for

<table>
<tr><td></td><td>immunogenicity, blood sampling for BSSL, blood sampling for ~~inflammatory biomarkers (except BSSL), blood sampling for~~ cytokine and chemokine panel, blood sampling for future exploratory analysis, blood sampling for clinical laboratory tests, 12-lead ECG and 3-lead ECG (telemetry), vital signs, injection site reaction, asking for AEs.</td></tr>
<tr><td>Table 8-2 – Allowed Time Windows</td><td>Scheduled time for ECGs, vital signs, injection site reaction</td></tr>
<tr><td>Table 8-3 – Blood Volume (Part 1)</td><td>
<table>
<tr><th></th><th>Vol (mL) x Frequency</th><th>Total (mL)</th></tr>
<tr><td>Chemistry</td><td>4.5 x 12</td><td>54.0</td></tr>
<tr><td>Serology</td><td>3.5 x 1</td><td>3.5</td></tr>
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<tr><td>Coagulation</td><td>2.7 x 11</td><td>29.7</td></tr>
<tr><td>SOL-116 PK</td><td>~~3.5~~4.0 x 14</td><td>~~49~~56.0</td></tr>
<tr><td>Immunogenicity sampling</td><td>3.5 x 6</td><td>21.0</td></tr>
<tr><td>BSSL</td><td>~~3.5~~4.0 x 12</td><td>~~42~~48.0</td></tr>
<tr><td>QuantiFERON test*</td><td>4.0 x 1</td><td>4.0</td></tr>
<tr><td>~~Inflammatory biomarkers (except BSSL)~~</td><td>~~3.5 x 6~~</td><td>~~21.0~~</td></tr>
<tr><td>Cytokine/chemokine panel</td><td>2.0 x 6</td><td>12.0</td></tr>
<tr><td>Anti-CCP antibodies</td><td>3.5 x 1</td><td>3.5</td></tr>
<tr><td>α-tocopherol</td><td>6.0 x ~~4~~3</td><td>~~24~~18.0</td></tr>
<tr><td>Sample for future exploratory analysis</td><td>5.~~0~~5 x 6</td><td>~~30~~33.0</td></tr>
<tr><td>Total blood volume</td><td></td><td>~~326~~315.7</td></tr>
</table>
</td></tr>
<tr><td>Table 8-4 – Blood Volume (Part 2)</td><td>
<table>
<tr><th></th><th>Vol (mL) x Frequency</th><th>Total (mL)</th></tr>
<tr><td>Chemistry</td><td>4.5 x 12</td><td>54.0</td></tr>
<tr><td>Serology</td><td>3.5 x 1</td><td>3.5</td></tr>
<tr><td>Hematology</td><td>3.0 x 11</td><td>33.0</td></tr>
<tr><td>Coagulation</td><td>2.7 x 11</td><td>29.7</td></tr>
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</table>
</td></tr>
</table>

	<table><tr><td>S-calprotectin analysis</td><td>2.0 x 6</td><td>12.0</td></tr><tr><td>Sample for future exploratory analysis</td><td>5.~~0~~**5** x 6</td><td>~~30~~**33**.0</td></tr><tr><td>**Total blood volume**</td><td></td><td>~~**338**~~**327.7**</td></tr><tr><td colspan="3">~~**Includes S-Calprotectin~~</td></tr></table>
Section 8.4.1 – Inclusion Criteria	3. Normal clinically physical findings, apart from RA specific findings for RA patients, including pulse rate, blood pressure, electrocardiogram (ECG), physical examination, and laboratory values (haematological/clinical chemistry) as judged by the Investigator. **Healthy subjects must be negative for anti- cyclic citrullinated peptide (CCP) and have Rheumatoid Factor <1.5 ULN at Screening.** 8. Fulfilling the 2010 American College of Rheumatology (ACR)/European Union League Against Rheumatism (EULAR) classification criteria for RA. • Treatment with a stable dose of MTX for at least 12 weeks prior to treatment start and planned to continue with MTX during the study. • Patients naïve to biological disease modifying anti-rheumatic drug (bDMARD). • Patients naïve to conventional/targeted synthetic disease modifying anti-rheumatic drug (csDMARD/tsDMARD), except for MTX, or who are washed out since at least 12 weeks from such therapy ~~that gave inadequate response or stopped due to other medical reason.~~**before study drug dosing**.
Section 8.4.2 – Exclusion Criteria	13. Subjects/patients who **are currently enrolled in or** have **recently** participated in ~~other investigational studies~~ **another interventional clinical study defined as having received the last intervention** within 90 days ~~of Screening~~ or 5 half-lives of the study drug (whichever is longer~~).~~**) prior to dosing of the study drug.** 15. Receipt of a vaccine **(except COVID-19 vaccine)** within 4 weeks prior to dosing and/or the intention to receive a vaccine during the study. 16. **Recent confirmed COVID-19 infection, with less than 6 weeks between recovery and dosing of study drug, and/or receipt of a COVID-19 vaccine within 6 weeks prior to dosing of the study drug or having the intention to receive such a vaccine within 7 weeks post dosing of study drug.** 18. Positive urine drug screen or alcohol breath test at Screening ~~and~~**or** on Day -1. 24. **Known Gilbert's syndrome or Screening laboratory values indicating Gilbert's syndrome.**
Section 8.7.1 – Determination of Dose	Additionally, an interim PK analysis of available ~~plasma~~**serum** SOL-116 concentration data will be reviewed as part of the dose escalation assessment. Any available blood PK data will be reviewed as part of the dose escalation assessment.

Escalation/Subsequent Dosing	The SRC, Principal Investigator or Lipum AB may terminate dose escalation at any time if continuing to a higher dose level would jeopardize the safety of the subjects/patients. SRC reports will be submitted to the Independent Ethics Committee (IEC) for approval of **the planned** dose escalation and for approval to proceed to the ~~patient~~**next** cohort.
Section 8.11.1 – Pharmacokinetic Parameters	The ~~plasma~~**serum** PK parameters for SOL-116 will be derived by non-compartmental analysis of the ~~plasma~~**serum** concentration-time profiles. The following PK parameters have been defined: • Area under the concentration-time curve from time zero to infinity (AUC_{0-inf}); • Maximum observed ~~plasma~~**serum** concentration (C_{max}); Attainment of steady-state conditions will be determined by visual inspection of the trough ~~plasma~~**serum** concentrations.
Section 8.11.1.1 – Calculation of Pharmacokinetic Parameters and Assumption	The measured individual ~~plasma~~**serum** concentrations of SOL-116 will be used to directly obtain C_{max} and T_{max}. AUC_{0-t} will be calculated according to the linear up/log down trapezoidal method using the measured concentration-time values above the lower limit of quantification (LLOQ). AUC_{0-inf} will be calculated by combining AUC_{0-t} and AUC_{extra}. AUC_{extra} represents an extrapolated value obtained by C_t/λ, where C_t is the last ~~plasma~~**serum** concentration measured above the LLOQ and λ represents the terminal elimination rate constant determined by log-linear regression analysis of the measured ~~plasma~~**serum** concentrations of the terminal elimination phase. The half-life of SOL-116 will be calculated as follows: $T_{1/2} = \ln 2 / \lambda$.
Section 10.3.1 – Pharmacokinetic Statistical Analysis	The Per-protocol analysis set will be used for all PK analyses. Individual subject/patient listings will be provided. Mean and individual ~~plasma~~**serum** concentration-time profiles for SOL-116 will be presented graphically for each group. Attainment of steady-state conditions will be determined by visual inspection of the trough ~~plasma~~**serum** concentrations.

3 TABLE OF CONTENTS

List of tables

4 LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADA	Anti-drug antibodies
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC	Area under the concentration-time curve
$AUC_{0\text{-}inf}$	AUC from time zero to infinity
$AUC_{0\text{-}t}$	AUC from time zero to time t of the last measured concentration above the limit of quantification
$AUC_{0\text{-}tau}$	AUC from time zero to the ending of the dosing interval
bDMARD	Biological disease modifying anti-rheumatic drug
BMI	Body mass index
BSSL	Bile salt-stimulated lipase
CAIA	Collagen antibody induced arthritis
CCP	Cyclic citrullinated peptide
CIA	Collagen induced arthritis
CL/F	Clearance
C_{max}	Maximum observed serum concentration
COVID-19	Coronavirus disease 2019
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRP	C-reactive protein
csDMARD	Conventional synthetic disease modifying anti-rheumatic drug
$C_{max,\ ss}$	Maximum plasma concentration at steady state concentration
C_{ss}	Concentration at steady state
C_t	Last concentration measured above LLOQ
CV%	Coefficient of variation
DA	Dark Agouti
DAS28	Disease activity score 28
DAS28-CRP	DAS28 with CRP

DAS28-ESR	DAS28 with ESR
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End-of-study
ESR	Erythrocyte sedimentation rate
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EULAR	European Alliance of Associations for Rheumatology
FDA	Food and Drug Administration
FIH	First-in-human
FSH	Follicle stimulating hormone
FU	Follow-up
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
hsCRP	High sensitive C-reactive protein
ICH	International Council for Harmonization (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	Independent ethics committee
IFNγ	Interferon gamma
IL	Interleukin
INR	International normalized ratio
IP-10	Interferon gamma inducible protein 10
IRB	Institutional review board
ISF	Investigator Site File
IU	International Unit
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IP	Intraperitoneal

IV	Intravenous(ly)
KO	Knockout
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LH	Luteinizing hormone
LLOQ	Lower limit of quantification
MABEL	Minimum anticipated biological effect level
MedDRA	Medical Dictionary for Regulatory Activities
MD	Multiple dosing
MP	Monitoring plan
MCP	Monocyte chemoattractant protein
MTX	Methotrexate
N	Number of subjects/patients
NHP	Non-human primate
NOAEL	No observed adverse effect level
PCV	Packed cell volume
PD	Pharmacodynamic(s)
PIA	Pristane induced arthritis
PK	Pharmacokinetic(s)
PKAP	Pharmacokinetic analysis plan
PR	PR interval of the ECG
PT	Prothrombin time
Q4W	Every fourth week
QA	Quality assurance
QRS	QRS interval of the ECG
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia's formula
RA	Rheumatoid arthritis
RBC	Red blood cell
RDW-CV	Red blood cell distribution width
RR	RR interval of the ECG
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan

SARS-CoV-2	Severe acute respiratory syndrome-coronavirus-2
SC	Subcutaneous(ly)
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
SRC	Safety review committee
SU	Safety unit
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Terminal elimination half-life
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
THC	Tetrahydrocannabinol
T_{max}	Time to reach C_{max}
TNFα	Tumor necrosis factor alpha
tsDMARD	Targeted synthetic disease modifying anti-rheumatic drug
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
V_z/F	Apparent volume of distribution
WBC	White blood cell
WHO	World Health Organization
WT	Wild type

5 PROTOCOL SYNOPSIS

TITLE	A Randomized, Double-Blind, Placebo-Controlled, First-in-Human Phase I Study Evaluating Safety, Tolerability and Pharmacokinetics of Single Ascending Doses of SOL-116 (a Humanized Monoclonal Anti-BSSL Antibody) in Healthy Subjects and Patients with Rheumatoid Arthritis
PHASE	I
CENTERS / COUNTRY	QPS Netherlands B.V., Groningen, The Netherlands CHDR, Leiden, The Netherlands ICON, Groningen, The Netherlands
INVESTIGATIONAL DRUG AND DOSAGE FORM	SOL-116 for subcutaneous (SC) administration
ROUTE OF ADMINISTRATION	SC injection
OBJECTIVES	Objectives for single dosing (Parts 1 and 2) Primary objective: • To evaluate the safety and tolerability of single ascending doses of SOL-116 in healthy subjects and rheumatoid arthritis (RA) patients. Secondary objective: • To determine single dose pharmacokinetic (PK) characteristics of SOL-116 in healthy subjects and RA patients. • To assess the immunogenicity of SOL-116 after single SC doses in healthy subjects and RA patients. Exploratory objectives: • To evaluate the effect of single ascending doses of SOL-116 on bile salt-stimulated lipase (BSSL) concentration in the blood of healthy subjects and RA patients. • To evaluate the pharmacodynamic (PD) effect of single ascending doses of SOL-116 on inflammatory biomarkers in the blood of healthy subjects and RA patients. Objectives for multiple dosing (Part 3) Primary objective: • To evaluate the safety and tolerability of multiple dosing of SOL-116 in healthy subjects.

	Secondary objective: • To determine multiple dose PK characteristics of SOL-116 in healthy subjects. • To assess the immunogenicity of SOL-116 after multiple SC doses in healthy subjects. Exploratory objectives: • To evaluate the effect of multiple doses of SOL-116 on BSSL concentration in the blood of healthy subjects. • To evaluate the PD effect of multiple doses of SOL-116 on inflammatory biomarkers in the blood of healthy subjects.
DESIGN	This is a randomized, double-blind, placebo-controlled Phase I, first-in-human (FIH) study.
TREATMENTS	**Part 1** Up to 5 single doses are planned to be tested in 5 cohorts of 8 healthy subjects (6 active, 2 placebo) (Cohort 1 to Cohort 5). One additional cohort (Cohort 6) of 8 healthy subjects (6 active, 2 placebo) may be added based on emerging data, i.e. in total 40 or 48 subjects will be randomized and dosed. The starting dose in Cohort 1 will be 0.075 mg/kg SOL-116 given as a single SC injection. The actual dose for Cohort 2 to Cohort 5 and the dose regimen for the optional additional cohort of healthy subjects (Cohort 6) will be based on the safety and PK results of all preceding cohorts. Furthermore, based on the safety and PK results of all preceding cohorts the number of SC injections given to administer the single dose in Cohort 2 to Cohort 6 may be increased to up to 4 injections. The maximum dose increment will be 3. The highest dose to be tested in man will not exceed a dose predicted to generate exposures above those at NOAEL in the monkey (plasma concentrations of 1240 µg/mL (C_{max}) or an $AUC_{0\text{-}168h}$ of 164000 µg/mL*h). Sentinel dosing will be employed in all cohorts. Thus, within each cohort initially 1 subject will receive SOL-116 and 1 subject will receive placebo. The remaining 6 subjects of the cohort may be dosed at least 48 hours after dosing of the initial 2 subjects of the cohort, provided no clinically significant safety issues, as judged by the Investigator, are noted in the 48 hours after dosing of the initial 2 subjects of the cohort. After each cohort completes dosing, a dose escalation Safety Review Committee (SRC) meeting will take place. Escalation to the next higher dose level may occur only after evaluation of the safety/tolerability and available PK data

	up to and including 14 days post-dose of at least 6 evaluable subjects (subject assessed as pharmacokinetically evaluable at Day 14) and after approval by the independent ethics committee (IEC). This time point may be adjusted based on the PK data of previous cohorts if the SRC recommends. **Part 2** In a cohort of up to 8 RA patients (6 active and 2 placebo will be randomized and dosed) (Cohort 7), one of the single doses tested in healthy subjects will be tested. The cohort with RA patients (Cohort 7) will be run after the completion of all cohorts with healthy subjects. The dose level of Cohort 7 will be determined based on the safety and PK results of all preceding cohorts and will not exceed that of the already given dose levels in healthy subjects. There should be at least 24 hours between administration of SOL-116 and the preceding methotrexate (MTX) dose and at least 24 hours between administration of SOL-116 and the subsequent MTX dose. Sentinel dosing will be employed. Thus, initially 1 patient will receive SOL-116 and 1 patient will receive placebo. The remaining 6 subjects of the cohort can be dosed at least 48 hours after dosing, provided no clinically significant safety issues, as judged by the Investigator, are noted in the 48 hours after dosing of the initial 2 patients of the cohort. **Part 3** Up to two multiple dosing cohorts of 8 healthy subjects (6 active, 2 placebo) (Cohorts MD1 and MD2) are planned, i.e. in total up to 16 subjects will be randomized and dosed. The starting dose in Cohort MD1 will be 3.0 mg/kg SOL-116 given as SC injection(s). [redacted] The dosing period will not exceed 12 weeks, but dosing frequency may be altered (higher or lower) compared to the first multiple dosing cohort. Sentinel dosing will be employed in all cohorts. Thus, within each cohort initially 1 subject will receive SOL-116 and 1 subject will receive placebo. The remaining 6 subjects of the cohort may be dosed at least 48 hours after dosing of the initial 2 subjects of the cohort, provided no clinically significant safety issues, as judged by the Investigator, are noted in the 48 hours after dosing of the initial 2 subjects of the cohort. After each cohort completes dosing, a dose escalation SRC meeting will take place. Escalation to the next MD dose

	cohort may occur only after evaluation of the safety/tolerability and available PK data up to and including 28 days post last dose of at least 6 evaluable subjects (subject assessed as pharmacokinetically evaluable at Day 28) and after approval by the IEC. This time point may be adjusted based on the PK data of previous cohorts if the SRC recommends.
SUMMARY OF STUDY DESIGN	The study will be monitored by a SRC. The intent of the SRC is to ensure that treatment does not pose undue risk to subjects/patients. Safety, tolerability and available PK data will be assessed by the SRC after each cohort before ascending to the next dose level. Eligibility will be assessed during a screening period of up to 42 days. For the treatment period, subjects/patients will check into the clinic one day prior to dosing (Day -1). On Day 1, all subjects/patients will receive SOL-116 in a fasted state (after an overnight fast of at least 10 hours). Subjects/patients will be released from the clinic on Day 4 (Part 1) or Day 2 (Part 2), after all required study procedures are completed and if medically justified. If medically indicated and/or based on emerging data, patients in Part 2 may be asked to return on Day 3 for additional safety assessments (optional visit). Furthermore, in both parts the clinic stay may be extended up to Day 7 if medically indicated and/or based on emerging data. In total, subjects/patients will return to the clinic for 6 (Part 1) or up to 8 (Part 2) ambulant visits up to Day 63. Subjects/patients will return to the clinic on Day 90 for an EOS/follow-up visit. A multiple dosing part will be performed in healthy subjects where, in the first multiple dosing cohort, each subject will receive a total of four doses every fourth week (Q4W): at baseline (D1) and Days 29, 57 and 85. With a dose interval of 28 days, it is estimated that with the half-life of SOL-116 (assessed in the SAD) concentrations at, or close to, steady state will be reached after the fourth dose. The subjects are followed up until Day 169. Based on SRC recommendation, the visit schedule may be adjusted.
STUDY POPULATION	Up to 48 healthy male or female subjects and 8 male or female RA patients (for Parts 1 and 2, respectively). Preferably at least 3 out of 8 subjects per cohort should be of the least represented sex (female or male), respectively. The study also includes up to 16 healthy adult subjects in one or two multiple dosing cohorts (Part 3).

INCLUSION CRITERIA	The following criteria must be met by all subjects/patients considered for study participation: 1. Willing and able to give written informed consent for participation in the study and is willing and able to abide by the study restrictions. 2. Males and females aged between 18 and 65 years (inclusive) at Screening. For patients in the RA cohort, an age interval between 18 and 70 years (inclusive). 3. Normal clinically physical findings, apart from RA specific findings (including deviating laboratory values e.g., mild anaemia or swollen joints) for RA patients, including pulse rate, blood pressure, electrocardiogram (ECG), physical examination, and laboratory values (haematological/clinical chemistry) as judged by the Investigator. Healthy subjects must be negative for anti-cyclic citrullinated peptide (CCP) and have Rheumatoid Factor <1.5 ULN at Screening. 4. For Parts 1 and 3, body mass index (BMI) between 19.0 and 30.0 kg/m^2 and body weight between 50 to 100 kg (inclusive) at Screening. For Part 2, body weight between 50 to 120 kg (inclusive) at Screening. 5. *Sexually active male patients* participating in the study must use a barrier method of contraception (condom) and refrain from sperm donation during the study and for 150 days after last dosing if their female sexual partner is of childbearing potential. Acceptable methods of birth control for female partners of male subjects are: hormonal contraceptives (oral contraceptives, implant or injection), intrauterine device (placed at least 1 month before the start of the study). Surgical sterilization of male patients can be accepted as a form of birth control if the sterilization procedure took place at least 6 months prior to the start of the study. 6. *Females of childbearing potential* must during the study and for at least 230 days after dosing utilise a method of contraception that can achieve a failure rate of less than 1% per year when used consistently and correctly. Such highly effective birth control methods include: • combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: i. oral ii. intravaginal iii. transdermal • progestogen-only hormonal contraception associated with inhibition of ovulation: i. oral ii. injectable

	iii. implantable • intrauterine device (IUD) • intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion • vasectomized partner • sexual abstinence 7. *Females of non-childbearing potential* must fulfil one of the following: • Irreversibly surgically sterile i.e., hysterectomy, bilateral salpingectomy, the fallopian tubes have been blocked or sealed (sterilisation), and bilateral oophorectomy. • Spontaneous amenorrhoea during the last 12 months prior to enrolment, and having follicle stimulating hormone (FSH) levels in the postmenopausal range (i.e. ≥ 30 mIU/mL) at Screening. The following inclusion criterion is only applicable for RA patients: 8. Fulfilling the 2010 American College of Rheumatology (ACR)/European Union League Against Rheumatism (EULAR) classification criteria for RA. • Treatment with MTX for at least 12 weeks prior to treatment start and planned to continue with MTX during the study; if the MTX dose was changed during the 12-week period, such a patient may be included in the study based on Investigator judgement. • Patients naïve to biological disease modifying anti-rheumatic drug (bDMARD) or who are washed out (at least 5 half-lives) from such therapy before study drug dosing. • Patients naïve to conventional/targeted synthetic disease modifying anti-rheumatic drug (csDMARD/tsDMARD), except for MTX, or who are washed out since at least 12 weeks from such therapy before study drug dosing. • Use of oral glucocorticosteroids is allowed if equivalent to ≤5 mg/day of prednisolone on a stable dose for a least 4 weeks prior to dosing (Day 1) and expected to remain on that dose level for at least 4 weeks after dosing (Day 1).
EXCLUSION CRITERIA	Subjects/Patients will be excluded if they meet any of the following criteria: 1. History of any clinically significant acute inflammatory joint disease (for the RA cohort; other than RA). 2. Any chronic or long-lasting disease which may interfere with the study objectives or jeopardise the

	safety of the subjects/patients as judged by the Investigator or responsible physician (for the RA cohort; other than RA). 3. Ongoing infection on Day-1. 4. Serious infection treated with antibiotics and evaluated by physician in the past 14 days prior to Day -1. 5. Current treatment with heparin products. 6. Use of any prescription or non-prescription drugs (excluding paracetamol, hormonal contraceptives), antacids, herbal, and dietary supplements (including St John's Wort) within 14 days (or 28 days if the drug is a potential hepatic enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study drug for healthy subjects and within 4 weeks prior to the first dose of study drug for RA patients, unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise subject/patient safety. In RA patients, MTX and folic acid use are exempted. 7. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≥ 2.0 times upper limit of normal (ULN); alkaline phosphatase and bilirubin ≥ 1.5 times the ULN at Screening or on Day -1. At Screening, these assessments may be repeated once, at the discretion of the Investigator. 8. Serum creatinine > 1.5 times the ULN or estimated glomerular filtration rat (eGFR) <60 at Screening or on Day -1 (for Part 1 and Part 3). Estimated glomerular filtration rat (eGFR) <60 at Screening or on Day -1 (for Part 2). At Screening, these assessments may be repeated once, at the discretion of the Investigator. 9. Subjects/patients who have experienced surgery within 6 months of the screening visit that could negatively impact on the subject's/patient's participation in the opinion of a Principal Investigator or responsible physician. 10. High blood pressure at Screening or on Day -1, judged as clinically relevant by a Principal Investigator or responsible physician. A repeat test may be performed. 11. Positive test for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (anti-HCV) at Screening. 12. Having evidence of active tuberculosis (TB) or latent TB at Screening as assessed by chest X-ray (RA patients only) and/or by QuantiFERON®-test. Applicable for RA patients only: in case of rescreening within three months after Screening, negative results from the initial chest X-ray and/or QuantiFERON®-test performed during Screening do not need to be repeated.

	13. Subjects/patients who are currently enrolled in or have recently participated in another interventional clinical study defined as having received the last intervention within 90 days or 5 half-lives of the study drug (whichever is longer) prior to dosing (Parts 1 and 2) vs. prior to first dosing (Part 3) of the study drug. 14. History or known hypersensitivity or allergy, or any form of allergic reactions to any excipients in the study drug or to humanized or murine monoclonal antibodies (or immunoglobulins). 15. Receipt of a vaccine within 4 weeks (COVID-19 vaccine within 6 weeks) prior to dosing and/or the intention to receive a vaccine during the study. Deviation from this should be judged by the Investigator and in dialogue with the Sponsor. 16. Recent confirmed COVID-19 infection, with less than 6 weeks between recovery and dosing of study drug. 17. Blood or plasma donation within 3 months of enrolment. 18. Positive urine drug screen or alcohol test at Screening or on Day -1. 19. History of drug or alcohol abuse, at the discretion of the Investigator, within past 12 months prior to Screening. 20. The subject currently smokes or uses nicotine-containing products. Former smokers will be eligible, provided they have not smoked for at least 1 month prior to Screening. Positive cotinine test results at Screening or on Day -1 are reason for exclusion. Such positive test results can be repeated once to exclude environmental influence on the subject. 21. A positive pregnancy test or lactation at Screening or on Day -1. The following exclusion criteria are only applicable for RA patients: 22. Intra-articular or systemic corticosteroid injection within 4 weeks prior to dosing. 23. Current or expected need of other immunosuppressant medication except MTX and/or intra-articular corticosteroid injections. 24. Known Gilbert's syndrome or Screening laboratory values indicating Gilbert's syndrome.
SAFETY / TOLERABILITY PARAMETERS	The following are defined as safety/tolerability parameters: • Clinical laboratory evaluations; • Injection site reactions; • Adverse events (AEs); • Immune reactions (e.g. hypersensitivity, cytokine release syndrome, immunogenicity); • Vital signs;

	• Physical examination; • ECGs (3-lead telemetry and 12-lead ECGs); • Concomitant medications/therapy.
PHARMACOKINETIC PARAMETERS	The following will be reported as serum PK parameters for SOL-116: • Area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$); • Maximum observed serum concentration (C_{max}); • Time to C_{max} (T_{max}); • 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); • Apparent total body clearance (CL/F). In multiple dosing part, also: • Minimum observed serum concentration at steady state (C_{trough}), time to steady state, accumulation ratio.

IMMUNOGENICITY PARAMETERS	The following are defined as immunogenicity parameters:
	• Development of anti-drug antibodies (ADA). If a subject is confirmed ADA-positive, the following may be determined:
	  ○ Estimation of ADA titers
	  ○ Neutralizing capacity
	  ○ Isotype
	  ○ Epitope map

EXPLORATORY PARAMETERS	The following are defined as exploratory parameters: • BSSL concentration; • Inflammatory biomarkers (except BSSL): C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) for all subjects/patients, and S-calprotectin and high sensitive CRP (hsCRP) (only RA patients); • Cytokine/chemokine panel (including but not limited to IFNγ, IL-1β, IL-6, IL-10, IL-12, IL-18, MCP-1 and TNFα); • Flow cytometry panel (only RA patients); • Whole blood stimulation assays (only RA patients).
STATISTICAL METHODOLOGY	**Safety and tolerability** AEs will be coded with MedDRA and a summary frequency table of AEs will be provided. The severity and relationship of AEs to study drug will also be summarized. Furthermore,

	if any serious adverse events (SAEs) occur, a summary of SAEs will be described and listed in a table. ECG variables (3-lead (telemetry) and 12-lead ECG), vital sign measurements and laboratory measurements will be summarized at each time point using mean, median, standard deviation, min, max, number of available observations, and change from baseline. Individual subject listings of ECG data, vital signs data, physical examination data, immune reactions, injection site reactions, concomitant medication/therapy and laboratory measurements will be provided. **Pharmacokinetic** Serum concentrations and PK parameters of SOL-116 will be listed by dose level and summarized by time point. The following descriptive statistics will be calculated: number of subjects (N), arithmetic mean, standard deviation, geometric mean, median, minimum, maximum, and coefficient of variation (CV%). Nominal blood sampling times will be used in the summary. Dose proportionality will be assessed for SOL-116. **Immunogenicity and exploratory** Immunogenicity and exploratory parameters will be listed individually, displayed in appropriate graphics and summarized using descriptive statistics.

Table 5-1: Visit and Assessment Schedule – Part 1

Study Period	**Screening**	**Treatment Period**											**FU/EOS**
Visit	**Visit 1**	**Visit 2**					**Visit 3[1]**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**
Assessments / Study days (visit windows)	Day -28 to Day -2	Day -1[17]	Day 1	Day 2	Day 3	Day 4	Day 8 (±1)	Day 14 (±1)	Day 21 (±3)	Day 35 (±3)	Day 49 (±3)	Day 63 (±3)	Day 90 (±3)
Informed consent	X												
Eligibility criteria	X	X											
Randomization			X										
Demographics	X												
Height	X												
Weight	X	X											
BMI	X	X											
QuantiFERON® test[2]	X												
Vital signs (blood pressure, pulse rate, temperature)[3]	X	X	X	X	X	X		X	X		X		X
General medical history	X												
Prior and concomitant medications	X	<----------Continuously---------->											
Physical examination	X	X			X								X
SOL-116 administration			X										
Injection site reactions[4]			X	X		X	X						
12-lead ECG[5]	X	X	X	X	X	X							X
3-lead ECG (telemetry)[6]			X										
Pregnancy testing[7]	X	X									X		X
Serology	X												
Serum FSH (postmenopausal women only)	X												
Blood sampling for SOL-116 PK[8]			X	X	X	X	X	X	X	X	X	X	X
Blood sampling for immunogenicity			X[14]				X		X		X		X
Blood sampling for BSSL			X[14]	X	X	X	X	X	X	X	X	X	X
Blood sampling for cytokine and chemokine panel			X[14]	X		X					X		X

Study Period	**Screening**	**Treatment Period**											**FU/EOS**
Visit	**Visit 1**	**Visit 2**					**Visit 3[1]**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**
Assessments / Study days (visit windows)	Day -28 to Day -2	Day -1[17]	Day 1	Day 2	Day 3	Day 4	Day 8 (±1)	Day 14 (±1)	Day 21 (±3)	Day 35 (±3)	Day 49 (±3)	Day 63 (±3)	Day 90 (±3)
Blood sampling for future exploratory analysis[9]			X[14]	X		X					X		X
Urine drugs of abuse and cotinine screen	X	X											
Alcohol breath test	X	X											
Serum biochemistry, lipid status, hematology, coagulation, urinalysis[10]	X	X	X[15]	X		X	X	X	X	X	X		X
SARS-CoV-2 test[11]		X											
Baseline symptoms	X	X	X[16]										
Ambulant visit	X						X	X	X	X	X	X	X
Residence in clinic[12]		<-----Continuously----->											
AEs/SAEs reported/questions[13]			<----------Continuously---------->										

Abbreviation: ADA, anti-drug antibodies; AEs, adverse events; BSSL, bile salt-stimulated lipase; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; FSH, follicle stimulating hormone; PK, pharmacokinetics; RA, rheumatoid arthritis; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

1. If the clinic visit is extended up to and including Day 7, Visit 3 will not take place. In that case, all blood sampling scheduled for Day 8 will be performed on Day 6 or Day 7, at the discretion of the Investigator.
2. Not to be performed when this assessment was done within 3 weeks prior to dosing and result is available.
3. On Day 1: Prior to dosing and 1 and 4 hours post-dose.
4. Four (4) hours after the (last) injection on Day 1, on Day 2, Day 4, Day 8 and thereafter as needed.
5. Triplicate at Screening and on Day- 1. On Day 1: 1 and 4 hours post-dose.
6. From 1 hour pre-dose until 6 hours post-dose.
7. Serum at Screening, urine at all other timepoints.
8. On Day 1 prior to dosing, and at 1, 4, 8, 24 (Day 2), 48 (Day 3) and 72 hours (Day 4) post-dose.
9. Only collected and analysed when the subject has given consent for the collection and future analysis of this sample in the informed consent form.
10. Fasting glucose and lipid status determined at Screening, pre-dose on Day 1, Day 14 and Day 35 only. α-tocopherol status determined pre-dose on Day 1, Day 14 and Day 35 only. CRP and ESR determined prior to dosing and 4 hours post-dose on Day 1, on Day 2, on Day 4, on Day 49 and on Day 90. Subjects should be fasting for at least 4 hours prior to blood sampling at Screening, and 10 hours prior to blood sampling on Day 1, Day 14 and Day 35. Rheumatoid factor and anti-CCP antibodies only at Screening.
11. A SARS-CoV-2 rapid test will be performed on Day -1. At the discretion of the Investigator, a SARS-CoV-2 PCR or rapid test may be performed at other time points during the study.
12. If medically indicated and/or based on emerging data, the clinic stay may be extended up to Day 7.
13. Starting from study drug administration.
14. Prior to dosing and 4 hours post-dose.
15. 4 hours post-dose.

16. Up until study drug administration.
17. Spare subjects not immediately included in the study may be kept in the clinic until it is decided whether these subjects are to be included. If subjects are included > 48 hours after admission in the clinic on Day -1, the Day -1 assessments have to be repeated.

Table 5-2: Visit and Assessment Schedule – Part 2

Study Period	**Screening**	**Treatment Period**											**FU/EOS**
Visit	**Visit 1[1]**	**Visit 2**			**Visit 3[2]**	**Visit 4**	**Visit 5[3]**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**
Assessments / Study days (visit windows)	Day -42 to Day -2	Day -1[22]	Day 1	Day 2	Day 3	Day 4	Day 8 (±1)	Day 14 (±1)	Day 21 (±3)	Day 35 (±3)	Day 49 (±3)	Day 63 (±3)	Day 90 (±3)
Informed consent	X												
Eligibility criteria	X	X											
Randomization			X										
Demographics	X												
Height	X												
Weight	X	X											
BMI	X	X											
QuantiFERON® test[4]	X												
Chest X-ray[5]	X												
Vital signs (blood pressure, pulse rate, temperature)[6]	X	X	X	X	X	X		X	X		X		X
General medical history	X												
RA medical history	X												
Prior and concomitant medications incl. RA medication	X	<----------Continuously---------->											
Physical examination[7]	X	X			X								X
Patient Global Health VAS Score		X											
DAS28-CRP and DAS28-ESR		X											
SOL-116 administration[8]			X										
Injection site reactions[9]			X	X		X	X						
12-lead ECG[10]	X	X	X	X	X	X							X
3-lead ECG (telemetry)[11]			X										
Pregnancy testing[12]	X	X									X		X
Serology	X												

Study Period	**Screening**	**Treatment Period**											**FU/EOS**
Visit	**Visit 1[1]**	**Visit 2**			**Visit 3[2]**	**Visit 4**	**Visit 5[3]**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**
Assessments / Study days (visit windows)	Day -42 to Day -2	Day -1[22]	Day 1	Day 2	Day 3	Day 4	Day 8 (±1)	Day 14 (±1)	Day 21 (±3)	Day 35 (±3)	Day 49 (±3)	Day 63 (±3)	Day 90 (±3)
Serum FSH (postmenopausal women only)	X												
Blood sampling for SOL-116 PK[13]			X	X	X	X	X	X	X	X	X	X	X
Blood sampling for immunogenicity			X[19]				X		X		X		X
Blood sampling for BSSL			X[19]	X	X	X	X	X	X	X	X	X	X
Blood sampling for cytokine and chemokine panel			X[19]	X		X			X		X		X
Blood sampling for flow cytometry and whole blood stimulation assay[14]			X	X		X	X		X		X		
Blood sampling for future exploratory analysis[15]			X[19]	X		X	X		X		X		X
Urine drugs of abuse and cotinine screen	X	X											
Alcohol test	X	X											
Serum biochemistry, lipid status, hematology, coagulation, urinalysis[16]	X	X	X[20]	X		X	X	X	X	X	X		X
Baseline symptoms	X	X	X[21]										
Ambulant visit	X				X	X	X	X	X	X	X	X	X
Residence in clinic[17]		<-----Continuously----->											
AEs/SAEs reported/questions[18]			<----------Continuously---------->										

Abbreviation: ADA, anti-drug antibodies; AEs, adverse events; BSSL, bile salt-stimulated lipase; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS28-CRP, disease activity score 28 with C-reactive protein; DAS28-ESR, disease activity score 28 with erythrocyte sedimentation rate; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; FSH, follicle stimulating hormone; hsCRP, high sensitive C-reactive protein; MTX, methotrexate; PK, pharmacokinetics; RA, rheumatoid arthritis; SAE, serious adverse event; VAS, visual analogue scale.

1. Screening can be divided over 2 visits.

2. Day 3 (Visit 3) is optional. In case of safety concerns after discharge on Day 2, patients may be asked to return on Day 3 for the assessments as presented.
3. If the clinic visit is extended up to and including Day 7, Visit 5 will not take place. In that case, all blood sampling scheduled for Day 8 will be performed on Day 6 or Day 7, at the discretion of the Investigator.
4. Not to be performed when this assessment was done within 3 weeks prior to dosing and result is available. In case of rescreening within three months after Screening, negative results from the initial QuantiFERON® test performed during Screening do not need to be repeated.
5. If a chest X-ray was performed within the past three weeks prior to dosing and documentation is available, it is not necessary to repeat the chest X-ray. In case of rescreening within three months after Screening, negative results from the initial chest X-ray performed during Screening do not need to be repeated.
6. On Day 1: Prior to dosing and 1 and 4 hours post-dose.
7. The 28-joint assessment will only be performed on Day -1 (baseline).
8. There should be at least 24 hours between administration of SOL-116 and the preceding MTX dose and at least 24 hours between administration of SOL-116 and the subsequent MTX dose.
9. Four (4) hours after the (last) injection on Day 1, on Day 2, Day 4, Day 8 and thereafter as needed.
10. Triplicate at Screening and on Day- 1. On Day 1: 1 and 4 hours post-dose.
11. From 1 hour pre-dose until 6 hours post-dose.
12. Serum at Screening, urine at all other timepoints.
13. On Day 1 prior to dosing, and at 1, 4, 8, 24 (Day 2), 48 (Day 3, optional) and 72 hours (Day 4) post-dose.
14. On Day 1 prior to dosing. Based on emerging data, collection time points may be updated.
15. Only collected and analysed when the patient has given consent for the collection and future analysis of this sample in the informed consent form.
16. Fasting glucose and lipid status determined at Screening, pre-dose on Day 1, Day 14 and Day 35. α-tocopherol status determined pre-dose on Day 1, Day 14 and Day 35 only. S-calprotectin and hsCRP determined prior to dosing and 4 hours post-dose on Day 1, on Day 2, on Day 4, on Day 21, on Day 49 and on Day 90. Subjects should be fasting for at least 4 hours prior to blood sampling at Screening, and 10 hours prior to blood sampling on Day 1, Day 14 and Day 35. Rheumatoid factor and anti-CCP antibodies only at Screening. Urinalysis only at Screening, on Day -1, on Day 2, on Day 8, on Day 14, on Day 21, and on Day 90. At Screening, laboratory assessments may be repeated once, at the discretion of the Investigator.
17. If medically indicated and/or based on emerging data, the clinic stay may be extended up to Day 7.
18. Starting from study drug administration.
19. Prior to dosing and 4 hours post-dose.
20. 4 hours post-dose.
21. Up until study drug administration.
22. Spare patients not immediately included in the study may be kept in the clinic until it is decided whether these patients are to be included. If subjects are included > 48 hours after admission in the clinic on Day -1, the Day -1 assessments have to be repeated.

Table 5-3: Visit and Assessment Schedule for Repeated Dosing Part (every Q4W dosing) – Part 3

Study Period	**Screening**	**Treatment period**											**FU/EOS**
Visit	**Visit 1[1]**	**Visit 2[2]**			**Visit 3**	**Visit 4[3]**	**Visits 5-6**	**Visit 7 (dosing day)[4]**	**Visit 8 (dosing day)[4]**	**Visit 9 (dosing day)**	**Visits 10-11**	**Visits 12-17**	**Visit 18**
Assessments / Study days (visit windows in days)	Day -28 to Day -2	Day -1	Day 1	Day 2	Day 4 (72 hrs) (±1)	Day 8 (±1)	Days 11 and 15 (±1)	Day 29 (±1)	Day 57 (±3)	Day 85 (±3)	Day 86 and 88	Days 92, 95, 99, 113, 140, 154 (±3)	Day 169 (±5)
Informed consent	X												
Eligibility criteria	X	X											
Randomization			X										
Demographics	X												
Height	X												
Weight	X	X						X	X	X			
BMI	X												
QuantiFERON® test[5]	X												
Vital signs (blood pressure, pulse rate, temperature)	X		X[14]	X	X	X		X[14]	X[14]	X[14]	X	X[15]	X
General medical history	X	X[24]	X[24]										
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X											X
SOL-116 administration[6]			X					X	X	X			
Injection site reactions			X[16]	X	X			X[16]	X[16]	X[16]			
12-lead ECG[7]	X	X	X					X[17]	X[17]	X[17]			X
3-lead ECG (telemetry)[8]			X										
Pregnancy testing[9]	X	X						X	X	X			X
Serology	X												
Serum FSH (postmenopausal women only)	X												
Blood sampling for SOL-116 PK			X[18]	X	X	X	X	X[19]	X[19]	X[20]	X	X	X
Blood sampling for immunogenicity			X[19]					X[19]	X[19]	X[19]		X[21]	X
Blood sampling for BSSL			X[18]	X	X	X	X	X[19]	X[19]	X[20]	X	X	X

Study Period	**Screening**	**Treatment period**											**FU/EOS**
Visit	**Visit 1[1]**	**Visit 2[2]**			**Visit 3**	**Visit 4[3]**	**Visits 5-6**	**Visit 7 (dosing day)[4]**	**Visit 8 (dosing day)[4]**	**Visit 9 (dosing day)**	**Visits 10-11**	**Visits 12-17**	**Visit 18**
Assessments / Study days (visit windows in days)	Day -28 to Day -2	Day -1	Day 1	Day 2	Day 4 (72 hrs) (±1)	Day 8 (±1)	Days 11 and 15 (±1)	Day 29 (±1)	Day 57 (±3)	Day 85 (±3)	Day 86 and 88	Days 92, 95, 99, 113, 140, 154 (±3)	Day 169 (±5)
Blood sampling for cytokine and chemokine panel			X[19]		X	X		X[19]	X[19]	X[19]	X[22]	X[23]	X
Blood sampling for future exploratory analysis[10]			X[19]							X		X[15]	X
Urine drugs of abuse and cotinine screen	X	X[19]											
Alcohol test	X	X[19]						X[19]	X[19]	X[19]			
Serum biochemistry, lipid status, hematology, coagulation, urinalysis[11]	X	X[19]			X	X		X[19]	X[19]	X[19]	X[22]	X[15]	X
Baseline symptoms	X	X[24]	X[24]										
Ambulant visit	X				X	X	X	X	X	X	X	X	X
Residence in clinic[12]		X	X	X									
AEs/SAEs reported/questions[13]			X	X	X	X	X	X	X	X	X	X	X

Abbreviation: ADA, anti-drug antibodies; AEs, adverse events; BSSL, bile salt-stimulated lipase; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; FSH, follicle stimulating hormone; PK, pharmacokinetics.

1. Screening can be divided over 2 visits.
2. Spare subjects not immediately included in the study may be kept in the clinic until it is decided whether these subjects are to be included. If subjects are included > 48 hours after admission in the clinic on Day -1, the Day -1 assessments have to be repeated.
3. If the clinic visit is extended up to and including Day 6, Visit 4 will not take place. In that case, all assessments including blood sampling scheduled for Visit 4 will be performed on Day 6, at the discretion of the Investigator.
4. Study site should make **a phone follow-up with subject approximately 3 to 7 days after dose** to follow up adverse events and/or medication.
5. Not to be performed when this assessment was done within 3 weeks prior to dosing and result is available.
6. The PI must review Day -1 safety lab results prior to dosing.
7. Triplicate at Screening and on Day -1. On Day 1: 1 and 4 hours post-dose.
8. From 1 hour pre-dose until 6 hours post-dose.
9. Serum at Screening, urine at all other timepoints.
10. Only collected and analysed when the subject has given consent for the collection and future analysis of this sample in the informed consent form. Pre-dose on Day 1 and Days 85, 92 and 169.
11. Fasting glucose determined at Screening only. Lipid status determined only at Screening and Day 169 only (10 hours' fasting at both occasions). No pancreatic lipase on Day 92.

12. If medically indicated and/or based on emerging data, the clinic stay may be extended up to Day 7.
13. Starting from first study drug administration.
14. On Day 1: Prior to dosing and 1 and 4 hours post-dose. After the other doses: Prior to dosing and 4 hours post-dose.
15. Day 92 only
16. Assessed for four (4) hours after each injection and thereafter as needed.
17. Prior to dosing and 4 hours post-dose.
18. Pre-dose, 4 and 24 hours post-dose
19. Pre-dose only.
20. Pre-dose and 4 hours post dose.
21. Day 113 only.
22. Day 88 only
23. Days 92 and 113 only.
24. Up until first study drug administration.

6 INTRODUCTION AND RATIONALE

6.1 Background

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory joint disease characterized by varying numbers of swollen, stiff and painful joints typically in hands and feet, but any joint may be affected. With time, erosion of joints and bone results in varying degree of disability and loss of quality of life. RA may also have systemic manifestations affecting other organs, e.g., skin, heart, lungs and/or eyes causing severe complications. The etiology of the disease is not fully understood but the expert opinion is that a combination of genetic predisposition and environmental factors as trigger is needed. Examples of triggers are cigarette smoking, infections, and trauma. The global prevalence of RA is 0.3% to 1% with significant variation between populations and the disease is threefold more common among women than men [1]. It affects all age groups but the most common age at onset is 40-60 years [2]. RA is a heterogeneous disease with substantial variation between individuals both with respect to number of joints and organs affected and the activity of the disease, something that is also reflected on the cellular and molecular level. This in turn is likely part of the explanation why a substantial proportion of the RA patients do not respond satisfactorily to current treatment alternatives, and why there is still a great medical need for new treatment alternatives [3].

6.1.1 Product Characteristics

The intended product SOL-116 is a humanized monoclonal anti-Bile Salt-Stimulated Lipase (BSSL) antibody of the IgG4 S228P subclass [redacted]

The therapeutic approach for the antibody SOL-116 is to block the function of BSSL in chronic inflammatory conditions with a lead indication to prevent inflammation and joint destruction in patients diagnosed with RA.

6.1.2 Mechanism of Action

[redacted]

For more details on the pre-clinical studies conducted with SOL-116, please see the Investigator's Brochure [6].

6.1.3 Clinical Experience with SOL-116 (current study)

To date, Part 1 has been concluded. Five cohorts with 8 healthy subjects (male and female) per cohort have been administered SOL-116 or placebo (6 active and 2 placebo), up to 6.075 mg/kg single dose. There were 25 males and 15 females enrolled, age range 22 to 64 years. No subjects dropped out, few adverse events and no serious adverse event (SAE) were reported. There were no clinically relevant changes from baseline reported on the following: vital signs, ECG parameters, telemetry, clinical laboratory, physical examination. The serum SOL-116 exposure (AUC, C_{max}) increased in an approximately dose-proportional manner.

In Part 2, the enrolment of rheumatoid arthritis (RA)-patients is currently ongoing. Part 3, with multiple dosing is ongoing.

6.2 Study Rationale

SOL-116 is a new monoclonal antibody targeting BSSL that is developed for the treatment of RA. There are preliminary data showing increased concentration of serum BSSL in patients with inflammatory conditions compared to healthy individuals [7].

The aim of the study is to achieve safety, tolerability and PK data to support continued development of the candidate drug.

This clinical study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

6.2.1 Rationale for Study Design

The design of the SAD study is based on the aim to study safety, tolerability and pharmacokinetics (PK) of selected doses of SOL-116 in a limited number of healthy subjects and in a cohort of RA patients.

Fertile women are allowed to enter the study. SOL-116 has not been investigated with regards to reproductive toxicology, hence sexually active male subjects must use a barrier method of contraception and female subjects of childbearing potential must utilize a method that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods.

The adaptive study design allows for flexible dose escalation and involves careful monitoring of the subject's well-being. The study will provide important PK data to support the design of further studies. The time points for PK blood sampling were selected based on data obtained from previous studies with other monoclonal antibodies.

A placebo control will be used to establish the frequency and magnitude of changes in endpoints that may occur in the absence of active treatment. Randomization will be used to minimize bias in the assignment of subjects to dose groups and to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

One cohort with RA patients will be enrolled to obtain safety and PK data and to observe any difference in PK parameters between healthy subjects and RA patients. This information is important for future clinical studies.

In the multiple dosing part in healthy subjects, up to two multiple dosing cohorts (6:2) will be conducted sequentially, but with an overlap, where the 28-day (i.e., T_{max} plus one half-life) safety and PK data post last dose will be assessed by a Safety Review Committee (SRC). The

SRC will decide if, and at what dose level, the subsequent cohort may commence. For the first multiple dosing cohort (MD1), the dose and dose interval will be based on all available SAD data and PK modelling data. The subjects will be followed for approximately 90 days post-treatment in order to get an estimate of clearance and elimination half-life after multiple dosing.

6.3 Dose Selection

6.3.1 Selection of Starting Dose in Part 1 SAD

[redacted]

6.3.2 Selection of Dose in Part 2 (RA cohort)

In Part 1 of the study, doses up to 6.075 mg/kg SOL-116 resulted in an exposure of 12 800 (µg/mL*h) in healthy subjects, with no safety or tolerability issues.

To allow for a direct comparison of plasma SOL-116 PK in healthy subjects versus RA patients, a previously used dose was selected for the RA patient cohort. The planned SC dose for the RA SAD-cohort is 2.025 mg/kg SOL-116, i.e., 3-fold lower than the highest dose tested in healthy subjects but believed to result in an exposure within the predicted therapeutic concentration range in humans.

[redacted]

6.3.3 Maximum Exposure (SAD)

[redacted]

6.3.4 Selection of Starting Dose and Dose Interval in Multiple Dosing Cohort(s)

The starting dose in the first multiple dosing cohort (MD1) will be 3.0 mg/kg. This dose level is predicted to result in an exposure within the same order of magnitude as the expected therapeutic concentration in humans. [redacted]

[redacted]

The subjects will be administered study drug approximately every four weeks for 12 weeks (total of 4 doses). This administration schedule was selected for the first multiple dosing

cohort from the projected time to reach steady state, which is based on the half-life of SOL-116 observed in Part 1 of this study (approximately 19 days).

[redacted]

[redacted]

6.3.5 Maximum Exposure (Multiple Dosing Part)

[redacted]

7 STUDY OBJECTIVES

7.1 Study Objectives for Single Dosing (Parts 1 and 2)

Primary objective:

- To evaluate the safety and tolerability of single ascending doses of SOL-116 in healthy subjects and RA patients.

Secondary objective:

- To determine single dose PK characteristics of SOL-116 in healthy subjects and RA patients.
- To assess the immunogenicity of SOL-116 after single SC doses in healthy subjects and RA patients.

Exploratory objectives:

- To evaluate the effect of single ascending doses of SOL-116 on BSSL concentration in the blood of healthy subjects and RA patients.
- To evaluate the PD effect of single ascending doses of SOL-116 on inflammatory biomarkers in the blood of healthy subjects and RA patients.

7.2 Study Objectives for Multiple Dosing (Part 3)

Primary objective:

- To evaluate the safety and tolerability of multiple dosing of SOL-116 in healthy subjects.

Secondary objective:

- To determine multiple dose PK characteristics of SOL-116 in healthy subjects.
- To assess the immunogenicity of SOL-116 after multiple SC doses in healthy subjects.

Exploratory objectives:

- To evaluate the effect of multiple doses of SOL-116 on BSSL concentration in the blood of healthy subjects.
- To evaluate the PD effect of multiple doses of SOL-116 on inflammatory biomarkers in the blood of healthy subjects.

8 STUDY DESIGN

8.1 Endpoints

8.1.1 Primary Endpoints (all parts)

- Adverse events (type, frequency, severity, and relationship of adverse events (AEs) to study drug treatment), clinical laboratory evaluations (including blood haematology/plasma biochemistry analyses and urinalyses), immune reactions, vital signs, electrocardiogram (ECG) and injection site reactions.

8.1.2 Secondary Endpoints

8.1.2.1 Secondary Endpoints

- PK of SOL-116 variables for single dose regimens: area under the serum concentration-time 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 ($AUC_{0\text{-}t}$), area under the serum concentration-time from time zero to the end of dosing interval ($AUC_{0\text{-}tau}$) (Part 3), maximum observed serum concentration (C_{max}), time to C_{max} (T_{max}), terminal elimination half-life ($T_{1/2}$) (Parts 1 and 2), apparent volume of distribution (V_z/F) (Parts 1 and 2), apparent total body clearance (CL/F) (Parts 1 and 2) and dose proportionality after single dose (based on AUC and C_{max}) (Part 1).
- Incidence and titre of anti-drug antibodies (ADA) to SOL-116.

8.1.2.2 Secondary Endpoints Part 3 only

PK of SOL-116 variables for the last dose: area under the serum concentration-time from time zero to the end of dosing interval ($AUC_{0\text{-}tau}$), maximum observed serum concentration (C_{max}), time to C_{max} (T_{max}), minimum observed serum concentration (C_{trough}), average serum concentration (C_{ave}), apparent total body clearance at steady state (CL_{ss}/F), time to steady state, accumulation ratio in C_{max} and $AUC_{0\text{-}tau}$.

8.1.3 Exploratory Endpoints (all parts)

- Change from baseline in BSSL concentration in blood.
- Change from baseline in inflammatory biomarkers, i.e. serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) for all subjects/patients and S-calprotectin and high sensitive CRP (hsCRP) (only RA patients).
- Change from baseline in plasma concentration of cytokine/chemokine panel (including but not limited to IFNγ, IL-1β, IL-6, IL-10, IL-12, IL-18, MCP-1 and TNFα).
- Change form baseline in other exploratory markers (RA patients only), based on flow cytometry panel and whole blood stimulation assay.

8.2 Overall Study Design

This is a randomized, double-blind, placebo-controlled phase I, first-in-human (FIH) study designed to evaluate the safety, tolerability and PK of single SC ascending doses of SOL-116 in healthy subjects and adult RA patients (Parts 1 and 2) and multiple SC doses in healthy subjects (Part 3).

The study will be monitored by a Safety Review Committee (SRC). The intent of the SRC is to ensure that treatment does not pose undue risk to subjects/patients. Safety, tolerability and

available PK data will be assessed by the SRC after each cohort before ascending to the next dose level. Based on SRC recommendation, the visit schedule may be adjusted.

Part 1

Eligibility will be assessed during a screening period of up to 28 days. For the treatment period, subjects will check into the clinic one day prior to dosing (Day -1). On Day 1, all subjects will receive SOL-116 in a fasted state (after an overnight fast of at least 10 hours). Subjects will be released from the clinic on Day 4, after all required study procedures are completed and if medically justified. If medically indicated and/or based on emerging data, the clinic stay may be extended up to Day 7. Subjects will return to the clinic for 6 ambulant visits up to Day 63. Subjects will return to the clinic on Day 90 for an EOS/follow-up visit.

Up to 5 single doses are planned to be tested in 5 cohorts of 8 healthy subjects (6 active, 2 placebo) (Cohort 1 to Cohort 5). One additional[1] cohort (Cohort 6) of 8 healthy subjects (6 active, 2 placebo) may be added based on emerging data, i.e. in total 40 or 48 subjects will be randomized and dosed.

The starting dose in Cohort 1 will be 0.075 mg/kg SOL-116 given as a single SC injection. The actual dose for Cohort 2 to Cohort 5 and the dose regimen for the optional additional cohort of healthy subjects (Cohort 6) will be based on the safety and PK results of all preceding cohorts. Furthermore, based on the safety and PK results of all preceding cohorts the number of SC injections given to administer the single dose in Cohort 2 to Cohort 6 may be increased to up to 4 injections. The maximum dose increment will be 3. The highest dose to be tested in man will not exceed a dose predicted to generate exposures above those at NOAEL in the monkey (plasma concentrations of 1240 µg/mL (C_{max}) or an $AUC_{0\text{-}168h}$ of 164000 µg/mL*h).

Sentinel dosing will be employed in all cohorts. Thus, within each cohort initially 1 subject will receive SOL-116 and 1 subject will receive placebo. The remaining 6 subjects of the cohort may be dosed at least 48 hours after dosing of the initial 2 subjects of the cohort, provided no clinically significant safety issues, as judged by the Investigator, are noted in the 48 hours after dosing of the initial 2 subjects of the cohort.

After each cohort completes dosing, a dose escalation SRC meeting will take place. Escalation to the next higher dose level may occur only after evaluation of the safety/tolerability and available PK data up to and including 14 days post-dose of at least 6 evaluable subjects (subject assessed as pharmacokinetically evaluable at Day 14) and after approval by the IEC. This time point may be adjusted based on the PK data of previous cohorts if the SRC recommends.

Please refer to Table 5-1 for an overview of ambulatory visits and residence in the clinic.

Part 2

Eligibility will be assessed during a screening period of up to 42 days. For the treatment period, patients will check into the clinic one day prior to dosing (Day -1). On Day 1, all patients will receive SOL-116 in a fasted state (after an overnight fast of at least 10 hours). Patients will be released from the clinic on Day 2, after all required study procedures are completed and if medically justified. If medically indicated and/or based on emerging data, patients may be asked to return on Day 3 for additional safety assessments (optional visit). Furthermore, the clinic stay may be extended up to Day 7, if medically indicated and/or based on emerging data.

[1] The optional 6th cohort in healthy subjects was not run

In total, patients will return to the clinic for up to 8 ambulant visits up to Day 63. Patients will return to the clinic on Day 90 for an EOS/follow-up visit.

In a cohort of up to 8 RA patients (6 active, 2 placebo will be randomized and dosed) (Cohort 7), one of the single doses tested in healthy subjects was selected, i.e., 2.025 mg/kg will be tested (see Section 6.1.3 and Section 6.3.2).

The cohort with RA patients (Cohort 7) will be run after the completion of all cohorts with healthy subjects. The dose level of Cohort 7 will be determined based on the safety and PK results of all preceding cohorts and will not exceed that of the already given dose levels in healthy subjects. There should be at least 24 hours between administration of SOL-116 and the preceding methotrexate (MTX) dose and at least 24 hours between administration of SOL-116 and the subsequent MTX dose.

Sentinel dosing will be employed. Thus, initially 1 patient will receive SOL-116 and 1 patient will receive placebo. The remaining 6 subjects of the cohort can be dosed at least 48 hours after dosing, provided no clinically significant safety issues, as judged by the Investigator, are noted in the 48 hours after dosing of the initial 2 patients of the cohort.

Please refer to Table 5-2 for an overview of ambulatory visits and residence in the clinic.

Part 3

The multiple dosing part will be in healthy subjects where, in the first multiple dosing cohort, each subject will receive a total of four doses every fourth week (Q4W): at baseline (D1) and Days 29, 57 and 85. With a dose interval of 28 days, it is estimated that with the half-life of SOL-116 (assessed in the SAD) concentrations at, or close to, steady state will be reached after the fourth dose.

Eligibility will be assessed during a screening period of up to 28 days. For the first dose, subjects will check into the clinic one day prior to dosing (Day -1). On Day 1, all subjects will receive SOL-116 or placebo. Subjects will be released from the clinic on Day 2, after all required study procedures are completed and if medically justified. If medically indicated and/or based on emerging data, the clinic stay may be extended up to Day 7. Subjects will return to the clinic for 15 ambulant visits up to Day 154. Subjects will return to the clinic on Day 169 for an EOS/follow-up visit. After the second and third dose, a phone contact will be made (3 to 7 days after the dose) with the subject to ensure no new adverse events or if new medication has been added.

Up to two multiple dosing cohorts of 8 healthy subjects (6 active, 2 placebo) (Cohorts MD1 and MD2) are planned, i.e. in total up to 16 subjects will be randomized and dosed.

The starting dose in Cohort MD1 will be 3.0 mg/kg SOL-116 given as SC injection(s) (see Section 0). The actual dose and dose interval for the potential Cohort MD2 will be based on the safety and PK results of all preceding SAD and MD cohort (see Section 6.3.5). The dosing period will not exceed 12 weeks, but dosing frequency may be altered (higher or lower) compared to the first multiple dosing cohort.

Sentinel dosing will be employed in all cohorts. Thus, within each cohort initially 1 subject will receive SOL-116 and 1 subject will receive placebo. The remaining 6 subjects of the cohort may be dosed at least 48 hours after dosing of the initial 2 subjects of the cohort, provided no clinically significant safety issues, as judged by the Investigator, are noted in the 48 hours after dosing of the initial 2 subjects of the cohort.

After each cohort completes dosing, a dose escalation SRC meeting will take place (see Section 8.7.1). Escalation to the next MD dose cohort may occur only after evaluation of the safety/tolerability and available PK data up to and including 28 days post last dose of at least 6 evaluable subjects (subject assessed as pharmacokinetically evaluable at Day 28) and after approval by the IEC. This time point may be adjusted based on the PK data of previous cohorts if the SRC recommends.

Please refer to Table 5-3 for an overview of ambulatory visits and residence in the clinic.

8.3 Study Assessments

8.3.1 Informed Consent

After adequate explanation of the aims, methods, objectives of the study and potential hazards of the study drug and after the subject/patient has had ample time to consider their participation, a written informed consent from each individual participating in this study will be obtained.

8.3.2 Medical History and Baseline Demographics

All relevant medical history will be documented.

Baseline demographics including sex, age, race and ethnicity will be recorded.

8.3.2.1 Baseline Symptoms

A baseline symptom is defined as an event that occurs between subject's signing of the informed consent form until the first administration of the study drug. Such events are not AEs and will be recorded as baseline symptoms in the Medical History Log in the eCRF.

8.3.2.2 RA Medical History, DAS28-CRP, and DAS28-ESR (RA Patients Only)

The following information will be noted at Screening: Year of diagnosis, joints affected at diagnosis and present, rheumatoid factor and anti-cyclic citrullinated peptide (CCP) antibodies positivity (positive or negative), disease activity at diagnosis and at screening (mild, moderate, severe), other organs affected by RA, surgery needed (joints or other), previous RA treatment (since diagnosis).

The disease activity score 28 (DAS28) for RA with CRP (DAS28-CRP) and the DAS-28 for ESR (DAS28-ESR) will be determined on Day -1 (baseline).

8.3.2.3 Prior and Concomitant Medications

All relevant medications taken from 2 weeks prior to Screening (4 weeks for RA cohort) until end-of-study (EOS) or started during the study will be recorded on the Concomitant Medications page. For RA cohort, see also Section 8.3.2.2.

Concomitant Medications initiated, stopped, up-titrated or down-titrated for an AE will be recorded on the Concomitant Medications page. This includes concomitant medication for RA (if applicable).

8.3.3 Pharmacokinetic Assessments

8.3.3.1 Timing for Sampling

Table 5-1, Table 5-2 and Table 5-3 provide an overview of all PK blood sampling time points.

8.3.3.2 Procedures for Sampling

About 4.0 mL blood for the PK samples will be collected via vena puncture or via an intravenous (IV) catheter placed in a vein in the arm following the local standard procedures.

Information on equipment and further details on the procedures on the sampling are documented in a separate instruction manual.

8.3.3.3 Labeling

PK tubes will be pre-labeled.

8.3.3.4 Shipping Procedures

The site staff will take care of the shipment of the samples. Samples must be sent to QPS Netherlands B.V. laboratory at time intervals agreed with the Sponsor. The samples must be packed securely together with completed shipment forms in polystyrene-insulated shipping containers together with enough dry ice to last for 48 hours.

8.3.3.5 Bioanalysis

The concentrations of SOL-116 in serum will be determined in the range 1-500 ng/mL (preliminary) using a validated ligand binding assay. Concentrations will be calculated by interpolation from a calibration curve. Quality control samples will be analyzed throughout the study. Their measured concentrations will be used to determine overall precision and accuracy of the analyses.

8.3.4 Safety and Tolerability Assessments

The definitions, reporting, and follow-up of AEs and serious adverse events (SAEs) are described in Section 9. Table 5-1, Table 5-2 and Table 5-3 provide an overview of all time points on which safety assessments will be performed.

8.3.4.1 Adverse Events

Adverse events will be recorded according to the local standard operating procedure (SOP)/Work instruction of the clinic.

8.3.4.2 Vital Signs

Vital sign assessments will be performed according to the local SOP of the clinic and will include measurements of supine blood pressure, pulse rate, and body temperature. Vital sign measurements will be collected after the subject/patient has been resting for 5 minutes in a supine position.

8.3.4.3 Body Weight and Height

The subject's/patient's body weight will be measured using a validated balance according to the local SOP of the clinic. Body weight will be recorded with 1 decimal. The subject's/patient's height is measured without wearing shoes. The body mass index (BMI) will be calculated from the weight and height recorded at Screening. BMI (kg/m^2) = weight (kg)/height^2 (m^2).

8.3.4.4 12-lead ECG

Subjects/patients will be in a supine position for 5 minutes prior to the measurements. ECGs will be evaluated and classified as normal/abnormal according to the local SOP of the clinic. In case of "abnormal", the abnormality has to be described. The Investigator will judge if the abnormal ECG findings are considered clinically significant. Clinically significant abnormal findings (as judged by the Investigator) will be recorded as AE.

HR, PR, QRS, and QT will be provided on the print-out of the ECG apparatus or in the electronic Muse system (RA patients only). Bazett ($QT/RR^{1/2}$)/Fridericia ($QT/RR^{1/3}$) QTc is automatically calculated by the ECG apparatus and provided on the print-out or in Muse (RA

patients only). For the screening ECG and the Day -1 ECG, three recordings will be made with an interval of approximately 1 minute between recordings. Evaluation of average recordings will be performed according to the local SOP of the clinic. Any repeat measurement will also be done in triplicate. All other recordings will be single (one recording of at least 3 complexes).

8.3.4.5 Physical Examination

Physical examination will be performed consisting of inspection, percussion, palpation, and auscultation according to the local SOP of the clinic. For Part 2, this will also (at baseline) include a 28-joint status (number of swollen joints and number of tender joints). Clinically relevant findings that are observed after the screening assessment but before dosing must be recorded on the specific medical history page of the eCRF. Clinically relevant findings found after dosing and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded on an AE page of the eCRF.

8.3.4.6 Patient Global Health VAS Score (Part 2 Only)

In Part 2, the patients will be asked (at baseline) to fill in a Patient Global Health VAS score.

8.3.4.7 3-lead ECG (Telemetry)

Telemetry monitoring will be set on alarm and used for evaluation of any cardiac event. It will be performed according to the local SOP of the clinic. Results will be analyzed by the Investigator and significant findings will be reported. Clinically significant abnormal findings (as judged by the Investigator) will be recorded as AE.

8.3.4.8 QuantiFERON® Test

The QuantiFERON® test will be performed at Screening to test for active tuberculosis (TB) or latent TB unless this assessment was done within 3 weeks prior to dosing and results are available. Applicable for RA patients only: in case of rescreening within three months after Screening, negative results from the initial QuantiFERON®-test performed during Screening do not need to be repeated. For this test 4 tubes of 1 mL blood each will be taken.

8.3.4.9 Chest X-ray (RA Patients Only)

Only for RA patients, a chest X-ray will be taken at Screening to test for active TB or latent TB. If a chest X-ray was performed within the past three weeks prior to dosing and documentation is available, it is not necessary to repeat the chest X-ray. In case of rescreening within three months after Screening, negative results from the initial chest X-ray performed during Screening do not need to be repeated.

8.3.4.10 Injection Site Reactions

Injection site reactions (dryness, redness, swelling, pain/tenderness and itching) will be assessed by the Investigator at specific time points (see Table 5-1, Table 5-2 and Table 5-3). Clinically significant abnormal findings (as judged by the Investigator) will be recorded as AE.

8.3.4.11 Laboratory Assessments

Clinically significant laboratory abnormalities must be reported by the Investigator as AE or SAE as appropriate (see Section 9). At Screening, laboratory assessments may be repeated once, at the discretion of the Investigator.

For Part 1 and 2, the blood samples will be taken under fasted conditions at time points specified in Table 5-1 and Table 5-2 (due to fasting glucose and/or lipid and α-tocopherol status). On these days, subjects/patients will not be allowed to eat or drink (except water) for a period of 4 hours (Screening) or 10 hours (other time points as specified in Table 5-1 and Table

5-2) prior to blood sampling. For Part 3, fasting glucose will be determined at Screening only. Moreover, lipid status will be determined only at Screening and Day 169 (10 hours' fasting at both occasions), see Table 5-3.

The samples will be sent to the local certified laboratory in accordance with specifications.

Table 8-1: Summary of Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis	Others
Hemoglobin	Creatinine and eGFR	Nitrite	Serum pregnancy test[b]
Hematocrit (packed cell volume [PCV])	Fasting glucose[f]	pH	FSH[c]
RBC count	Sodium	Glucose	Serology (HIV, hepatitis B and hepatitis C)[d]
Platelet count	Potassium	Albumin or micro albumin	SARS-CoV-2 PCR or rapid test[g]
WBC count	ALT	Erythrocytes	Coagulation (PT (sec), PT (INR), aPTT)
Neutrophils	AST	Leukocytes	Urine drug and cotinine screen
Eosinophils	GGT	Ketones	S-calprotectin[e]
Monocytes	Bilirubin (total, direct and indirect)	Microscopy[a]	Anti-CCP antibodies[d]
Basophils	Alkaline phosphatase	Specific gravity	
Lymphocytes	Albumin	Creatinine	
Mean corpuscular volume	Cholesterol (total) – *lipid status*[f]	Protein	
Mean corpuscular hemoglobin[i]	LDL – *lipid status*[f]		
Mean corpuscular hemoglobin concentration[i]	HDL – *lipid status*[f]		
Erytoblasts[i]	Triglycerides – *lipid status*[f]		
Red blood cell distribution width (RDW-CV)[i]	LDH – *lipid status*[f]		
ESR	α-tocopherol[h]		
	Rheumatoid factor[d]		
	Chloride		
	CRP		
	hsCRP (Part 2 only)		
	Calcium (corrected)		
	Inorganic phosphate		
	Uric acid		
	Blood urea nitrogen		
	Pancreatic lipase[j]		

a. If there is an abnormality in urine in accordance with the clinical laboratory standard procedures.
b. Only during Screening, other pregnancy tests will be done with urine.
c. Required of postmenopausal females only during Screening.
d. Only at Screening.
e. Only RA patients.
f. Only at Screening, pre-dose on Day 1, Day 14 and Day 35 (Parts 1 and 2). For Part 3 at Screening and Day 169 (EOS).
g. A SARS-CoV-2 rapid test will be performed on Day -1 (Part 1 only). At the discretion of the Investigator, a SARS-CoV-2 PCR or rapid test may be performed at other time points during the study.
h. Only pre-dose on Day 1, Day 14 and Day 35 (Parts 1 and 2). For Part 3 at Screening and Day 169 (EOS).
i. Only applicable for Part 2.
j. Not on Day 92 of Part 3.

8.3.4.12 Drug and Cotinine Screen

For a urine drug screening, the following compounds may be assessed: amphetamine, barbiturates, benzodiazepines, cocaine, marijuana (THC), MDMA/ecstasy, methadone, methamphetamine, morphine, opioids, phencyclidine, and tricyclic antidepressants.

To check if a subject/patient has been smoking, cotinine will be assessed in urine.

8.3.4.13 Alcohol Test

An alcohol test (breath test or urine) will be performed according to the local SOP of the clinic.

8.3.4.14 Pregnancy Test

A serum pregnancy test will be performed at Screening. A urine pregnancy test will be performed on Day -1, Visit 7 (Parts 1 and 3), Visit 8 (Part 3) and Visit 9 (Parts 2 and 3) and at the EOS examination (or at early termination) (all parts). The results must be available prior to dosing.

8.3.4.15 Serology

At Screening, virus serology will be assessed (HIV, hepatitis B and hepatitis C).

8.3.4.16 SARS-CoV-2 Test

COVID-19 testing will be performed at the time point described in Table 5-1. A check on health status will be performed and body temperature will be measured before the subject/patient enters the clinic on Day -1 (Part 1). For Parts 2 and 3, COVID-19 testing is not mandatory as recommendations have changed since the study started. Testing for COVID-19 will be done at the discretion of the investigator, based on clinical symptoms.

8.3.5 Immunogenicity

Blood samples will be taken to check for the presence of ADA at time points specified in Table 5-1, Table 5-2 and Table 5-3.

About 3.5 mL blood for the ADA samples will be collected via vena puncture or via an IV catheter placed in a vein in the arm following the local standard procedures.

8.3.6 Exploratory Assessments

Blood samples will be taken to check BSSL concentration, cytokine/chemokine panel (including but not limited to IFNγ, IL-1β, IL-6, IL-10, IL-12, IL-18, MCP-1, and TNFα), flow cytometry panel (only RA patients), and whole blood stimulation (only RA patients) at the time points specified in Table 5-1, Table 5-2 and Table 5-3.

About 2 mL or 4 mL (2 mL for Part 3 and 4 mL for Parts 1 and 2) blood for the BSSL samples, and about 2 mL for the cytokine/chemokine panel samples will be collected via vena puncture or via an IV catheter placed in a vein in the arm following the local standard procedures. In Part 2, about 10 mL for the flow cytometry panel and about 10 mL for the whole blood stimulation assay will be collected.

8.3.6.1 Exploratory Samples (Future Analysis)

At time points specified in Table 5-1, Table 5-2 and Table 5-3, extra blood samples (5.5 mL in total) will be taken for future exploratory analysis of potential PK and/or PD markers of relevance for SOL-116. The samples will be discarded at the latest 10 years after the sampling occasion.

8.3.7 Order of Assessments

In case several study procedures are scheduled at the same time point, the following sequence should be followed pre-dose: 12-lead ECG, vital signs, asking for AEs, PK blood sampling, blood sampling for immunogenicity, blood sampling for BSSL, blood sampling for cytokine and chemokine panel, blood sampling for flow cytometry panel (Part 2 only), blood sampling for whole blood stimulation assay (Part 2 only), blood sampling for future exploratory analysis, and blood sampling for clinical laboratory tests. Post-dose, the following sequence should be followed: PK blood sampling, blood sampling for immunogenicity, blood sampling for BSSL, blood sampling for cytokine and chemokine panel, blood sampling for flow cytometry panel

(Part 2 only), blood sampling for whole blood stimulation assay (Part 2 only), blood sampling for future exploratory analysis, blood sampling for clinical laboratory tests, 12-lead ECG and 3-lead ECG (telemetry), vital signs, injection site reaction, asking for AEs. Enough time should be reserved for all assessments to be performed so that the administration of study drug and the PK blood sampling is done at the scheduled time point.

8.3.8 Allowed Time Windows for PK, PD and Safety Assessments

Allowed time windows are provided in Table 8-2.

Table 8-2: Allowed Time Windows

Scheduled time for blood sample collection for PK, PD (inflammatory biomarkers), exploratory, and safety	Allowed time deviation
≤ 4 hours after study drug administration	± 2 min*
> 4 hours and ≤24 hours after study drug administration	± 10 min
> 24 hours after study drug administration	± 60 min
Scheduled time for ECGs, vital signs, injection site reaction	Allowed time deviation
≤ 4 hours after study drug administration	± 15 min
> 4 hours and ≤24 hours after study drug administration	± 30 min
> 24 hours after study drug administration	± 60 min

* On Day 1, 4 hour post-dose samples have an allowed time deviation of ± 10 min.

8.3.9 Total Blood Volume

The total volume of blood to be taken per subject/patient during the entire course of the study will be as follows:

Table 8-3: Blood Volume (Part 1)

	Vol (mL) x Frequency	Total (mL)
Chemistry	4.5 x 12	54.0
Serology	3.5 x 1	3.5
Hematology	3.0 x 11	33.0
Coagulation	2.7 x 11	29.7
SOL-116 PK	4.0 x 14	56.0
Immunogenicity sampling	3.5 x 6	21.0
BSSL	4.0 x 12	48.0
QuantiFERON test*	4.0 x 1	4.0
Cytokine/chemokine panel	2.0 x 6	12.0
Anti-CCP antibodies	3.5 x 1	3.5
α-tocopherol	6.0 x 3	18.0
Sample for future exploratory analysis	5.5 x 6	33.0
Total blood volume		**315.7**

* Unless this assessment was done within 3 weeks prior to dosing and result is available.

Table 8-4: Blood Volume (Part 2)

	Vol (mL) x Frequency	Total (mL)
Chemistry	3.5 x 12	42.0
Serology	5 x 1	5.0
Hematology	2.0 x 11	22.0
Coagulation	2.7 x 11	29.7
SOL-116 PK*	4.0 x 14	56.0
Immunogenicity sampling	3.5 x 6	21.0
BSSL*	4.0 x 12	48.0
QuantiFERON test**	4.0 x 1	4.0
Cytokine/chemokine panel	2.0 x 7	14.0
Anti-CCP antibodies	3.5 x 1	3.5
α-tocopherol	6.0 x 3	18.0
S-calprotectin analysis	2.0 x 7	14.0
Flow cytometry panel	10.0 x 6	60.0
Whole blood stimulation assay	10.0 x 6	60.0
Sample for future exploratory analysis	5.5 x 8	44.0
Total blood volume*		**441.2**

* If the Day 3 visit does not take place, one less PK of 4.0 mL and one less BSSL sample of 4 mL will be collected. That would decrease the total blood volume to 433.2 mL.

** Unless this assessment was done within 3 weeks prior to dosing and result is available. In case of rescreening within three months after Screening, negative results from the initial QuantiFERON® test performed during Screening do not need to be repeated.

Table 8-5: Blood Volume (Part 3)

	Vol (mL) x Frequency	Total (mL)
Chemistry	4.5 x 11	49.5
Serology	3.5 x 1	3.5
Hematology	3.0 x 10	30.0
Coagulation	2.7 x 10	27.0
SOL-116 PK	4.0 x 20	80.0
Immunogenicity sampling	3.5 x 6	21.0
BSSL	2.0 x 20	40.0
QuantiFERON test*	4.0 x 1	4.0
Cytokine/chemokine panel	2.0 x 10	20.0
Anti-CCP antibodies	3.5 x 1	3.5
α-tocopherol	6.0 x 2	12.0
Sample for future exploratory analysis	5.5 x 4	22.0
Total blood volume		312.50

* Unless this assessment was done within 3 weeks prior to dosing and result is available.

8.4 Study Population

The subject population will include healthy adult subjects (Cohort 1-6[2] of Part 1 and multiple dosing cohorts in Part 3) and patients (Cohort 7, Part 2) who satisfy all entry criteria.

8.4.1 Inclusion Criteria

The following criteria must be met by all subjects/patients considered for study participation:

1. Willing and able to give written informed consent for participation in the study and is willing and able to abide by the study restrictions.
2. Males and females aged between 18 and 65 years (inclusive) at Screening. For patients in the RA cohort, an age interval between 18 and 70 years (inclusive).
3. Normal clinically physical findings, apart from RA specific findings (including deviating laboratory values e.g., mild anaemia or swollen joints) for RA patients, including pulse rate, blood pressure, electrocardiogram (ECG), physical examination, and laboratory values (haematological/clinical chemistry) as judged by the Investigator. Healthy subjects must be negative for anti-CCP and have Rheumatoid Factor <1.5 ULN at Screening.
4. For Parts 1 and 3, body mass index (BMI) between 19.0 and 30.0 kg/m^2 and body weight between 50 to 100 kg (inclusive) at Screening. For Part 2, body weight between 50 to 120 kg (inclusive) at Screening.
5. *Sexually active male patients* participating in the study must use a barrier method of contraception (condom) and refrain from sperm donation during the study and for at least 150 days after last dosing if their female sexual partner is of childbearing potential. Acceptable methods of birth control for female partners of male subjects are: hormonal contraceptives (oral contraceptives, implant or injection), intrauterine device (placed at least 1 month before the start of the study). Surgical sterilization of male patients can be

[2] The optional 6th cohort in healthy subjects was not run

accepted as a form of birth control if the sterilization procedure took place at least 6 months prior to the start of the study.

6. *Females of childbearing potential* must during the study and for at least 230 days after last dosing utilise a method of contraception that can achieve a failure rate of less than 1% per year when used consistently and correctly. Such highly effective birth control methods include:
   - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
     - oral
     - intravaginal
     - transdermal
   - progestogen-only hormonal contraception associated with inhibition of ovulation:
     - oral
     - injectable
     - implantable
   - intrauterine device (IUD)
   - intrauterine hormone-releasing system (IUS)
   - bilateral tubal occlusion
   - vasectomized partner
   - sexual abstinence
7. *Females of non-childbearing potential* must fulfil one of the following:
   - Irreversibly surgically sterile i.e., hysterectomy, bilateral salpingectomy, the fallopian tubes have been blocked or sealed (sterilization), and bilateral oophorectomy.
   - Spontaneous amenorrhoea during the last 12 months prior to enrolment, and having follicle stimulating hormone (FSH) levels in the postmenopausal range (i.e. ≥ 30 mIU/mL) at Screening.

The following inclusion criterion is only applicable for RA patients:

8. Fulfilling the 2010 American College of Rheumatology (ACR)/European Union League Against Rheumatism (EULAR) classification criteria for RA [8].
   - Treatment with MTX for at least 12 weeks prior to treatment start and planned to continue with MTX during the study; if the MTX dose was changed during the 12-week period, such a patient may be included in the study based on Investigator judgement.
   - Patients naïve to biological disease modifying anti-rheumatic drug (bDMARD) or who are washed out (at least 5 half-lives) from such therapy before study drug dosing.
   - Patients naïve to conventional/targeted synthetic disease modifying anti-rheumatic drug (csDMARD/tsDMARD), except for MTX, or who are washed out since at least 12 weeks from such therapy before study drug dosing.
   - Use of oral glucocorticosteroids is allowed if equivalent to ≤5 mg/day of prednisolone on a stable dose for a least 4 weeks prior to dosing (Day 1) and expected to remain on that dose level for at least 4 weeks after dosing (Day 1).

8.4.2 Exclusion Criteria

Subjects/Patients will be excluded if they meet any of the following criteria:

1. History of any clinically significant acute inflammatory joint disease (for the RA cohort; other than RA).
2. Any chronic or long-lasting disease which may interfere with the study objectives or jeopardise the safety of the subjects/patients as judged by the Investigator or responsible physician (for the RA cohort; other than RA).

3. Ongoing infection on Day-1.
4. Serious infection treated with antibiotics and evaluated by physician in the past 14 days prior to Day -1.
5. Current treatment with heparin products.
6. Use of any prescription or non-prescription drugs (excluding paracetamol, hormonal contraceptives), antacids, herbal, and dietary supplements (including St John's Wort) within 14 days (or 28 days if the drug is a potential hepatic enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study drug for healthy subjects and within 4 weeks prior to the first dose of study drug for RA patients, unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise subject/patient safety. In RA patients, MTX and folic acid use are exempted.
7. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≥ 2.0 times upper limit of normal (ULN); alkaline phosphatase and bilirubin ≥ 1.5 times the ULN at Screening or on Day -1. At Screening, these assessments may be repeated once, at the discretion of the Investigator.
8. Serum creatinine > 1.5 times the ULN or estimated glomerular filtration rat (eGFR) <60 at Screening or on Day -1 (for Part 1 and Part 3). Estimated glomerular filtration rat (eGFR) <60 at Screening or on Day -1 (for Part 2). At Screening, these assessments may be repeated once, at the discretion of the Investigator.
9. Subjects/patients who have experienced surgery within 6 months of the screening visit that could negatively impact on the subject's/patient's participation in the opinion of a Principal Investigator or responsible physician.
10. High blood pressure at Screening or on Day -1, judged as clinically relevant by a Principal Investigator or responsible physician. A repeat test may be performed.
11. Positive test for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (anti-HCV) at Screening.
12. Having evidence of active TB or latent TB at Screening as assessed by chest X-ray (RA patients only) and/or by QuantiFERON®-test. Applicable for RA patients only: in case of rescreening within three months after Screening, negative results from the initial chest X-ray and/or QuantiFERON®-test performed during Screening do not need to be repeated.
13. Subjects/patients who are currently enrolled in or have recently participated in another interventional clinical study defined as having received the last intervention within 90 days or 5 half-lives of the study drug (whichever is longer) prior to dosing (Parts 1 and 2) vs. prior to first dosing (Part 3) of the study drug.
14. History or known hypersensitivity or allergy, or any form of allergic reactions to any excipients in the study drug or to humanized or murine monoclonal antibodies (or immunoglobulins).
15. Receipt of a vaccine within 4 weeks (COVID-19 vaccine within 6 weeks) prior to dosing and/or the intention to receive a vaccine during the study. Deviation from this should be judged by the Investigator and in dialogue with the Sponsor.
16. Recent confirmed COVID-19 infection, with less than 6 weeks between recovery and dosing of study drug.
17. Blood or plasma donation within 3 months of enrolment.
18. Positive urine drug screen or alcohol test at Screening or on Day -1.
19. History of drug or alcohol abuse, at the discretion of the Investigator, within past 12 months prior to Screening.
20. The subject currently smokes or uses nicotine-containing products. Former smokers will be eligible, provided they have not smoked for at least 1 month prior to Screening. Positive

cotinine test results at Screening or on Day -1 are reason for exclusion. Such positive test results can be repeated once to exclude environmental influence on the subject.

21. A positive pregnancy test or lactation at Screening or on Day -1.

The following exclusion criteria are only applicable for RA patients:

22. Intra-articular or systemic corticosteroid injection within 4 weeks prior to dosing.
23. Current or expected need of other immunosuppressant medication except MTX and/or intra-articular corticosteroid injections.
24. Known Gilbert's syndrome or Screening laboratory values indicating Gilbert's syndrome.

8.4.3 Diet, Activities, and Other Restrictions

8.4.3.1 Concomitant Medication

From 2 weeks (or 28 days if the drug is a potential hepatic enzyme inducer) or 5 half-lives (whichever is longer) prior to Screening (or 4 weeks for RA cohort) until the EOS, prescribed or over-the-counter medication (including herbal remedies) is only allowed as described in exclusion criterion 6. Any new concomitant medication for treatment of AEs should preferably be discussed beforehand with the Investigator. The occasional use of paracetamol is allowed. Female subjects/patients are allowed to use oral contraception, a hormonal implant or hormonal intra-uterine devices as contraception. RA patients only (Part 2): If there is a medical need, local intra-articular corticosteroid injections are permitted at the discretion of a Principal Investigator.

If concomitant medication is needed during the study, this medication must be recorded on the eCRF, stating its generic name, time of administration, dose, route, frequency and duration, as well as the reason for administration.

The patients in the RA cohort will be treated with MTX. There should be at least 24 hours between administration of SOL-116 and the preceding MTX dose and at least 24 hours between administration of SOL-116 and the subsequent MTX dose. The patients in the RA cohort are allowed to use folic acid.

Part 3 only: Medications for incidental use (e.g., hay fever) may, at the Investigator's discretion, be allowed during the study.

8.4.3.2 Alcohol

Drinking of alcoholic beverages is not permitted from 48 hours prior to each clinic visit or while in the clinic.

8.4.3.3 Physical Activities

From 24 hours prior to each clinic visit, the subjects/patients should refrain from excessive physical exercise and strenuous sports activities (endurance sports).

8.4.3.4 Dietary Aspects

Consumption of food containing poppy seeds is not allowed from 24 hours prior to Screening and prior to Day -1.

8.4.3.5 Smoking

Smoking is not permitted from one month prior to Screening up to and including the EOS visit.

8.4.3.6 Participation in Other Clinical Studies

Study subjects are not allowed to participate in any other interventional clinical drug study during the study period.

8.5 Study Drugs

Study drugs include the investigational drug SOL-116 and matching placebo administered during the study.

8.5.1 Investigational Drug and Matching Placebo

Lipum AB will provide SOL-116 and matching placebo. SOL-116 is available for clinical study use in the form of a solution for SC injection. Placebo is available as matching solution for SC administration.

8.5.2 Study Drug Preparation

All study drugs will be prepared (packaged and labeled in individual doses) at QPS Netherlands B.V. (for Part 1 and Part 3) or the pharmacy of the Leiden University Medical Center (LUMC) (for Part 2) by an unblinded pharmacist, or his/her designee. In order to minimize the risks of unblinding, the pharmacist/designee is not involved in any other aspect of the study.

8.5.3 Study Drug Packaging

Lipum AB will be responsible for the supply of the following drugs:

- Solution containing 100 mg/mL of SOL-116.
- Matching placebo.

The study drug will be packed and dispatched in containers. A batch release certificate will be provided, stating that the batches have been manufactured according to good manufacturing practice (GMP). Study drugs are provided as a solution and supplied to the study center as a bulk shipment. Under the supervision of the pharmacist, the study drug will be packed per subject/patient for each dosing occasion, according to the randomization list.

8.5.4 Study Drug Labeling

The labeling complies with the applicable (local) laws and regulations. At the minimum, the following information will be stated on the labels:

- Study number (LPM-116-001)
- SOL-116 (strength) or placebo
- Name, address of Sponsor
- Name of the Investigator and CRO
- Batch number
- Subject/patient identification/treatment number
- Quantity of dosage units
- Route of administration (SC) and pharmaceutical dosage form
- Directions for use
- Storage conditions
- Expiry date
- “For clinical study use only” or similar wording

8.5.5 Study Drug Administration

SOL-116 will be administered as abdominal SC injection(s). The injection volume will be no more than 2.0 mL per injection. The number of SC injections given to administer the single dose in Cohort 2 to Cohort 7 may be increased to up to 4 injections.

Subjects/patients will not be allowed to eat or drink (except water) from 10 hours prior to the administration of study drug or placebo.

All study drugs will be dispensed by the Investigator or a person supervised by the Investigator. The time of administration of SOL-116 or placebo will be recorded in the eCRF.

In Part 3, the same applies but 4 dose administrations (with maximum 4 injections per occasion) will be administered with 28 days' interval (in MD1).

In Part 2, there should be at least 24 hours between administration of SOL-116 and the preceding MTX dose and at least 24 hours between administration of SOL-116 and the subsequent MTX dose.

8.5.6 Storage and Return of Study Drug

Upon receipt of the study drugs, the responsible pharmacist or her designee will inspect all study drugs for completeness. Subsequently, he/she must immediately return the enclosed acknowledgement of receipt form; duly completed and signed (the date of receipt must be noted).

The pharmacist is responsible for storage of the study drug at the study site in an appropriate lockable room at 2–8 °C. The drug will be stored according to the instructions provided by the Sponsor. Only the pharmacist or his/her designee, who are otherwise not involved in the study, will handle the study drug.

A Drug Preparation Protocol as well as a Drug Accountability Record must be kept current and should at least contain the following information:

- Subject/patient number for whom the drug was prepared
- Initials and date of the person who prepared the study drug
- Date(s) on which drug was prepared and quantity of the drug prepared

The inventory must be available for verification by the clinical research associate (CRA)/monitor.

After Sponsor confirmation, all unused investigational material (drugs and packaging) must be returned to the Sponsor or destroyed by the site on termination of the study and after a drug accountability check by the CRA/monitor, listing the following:

- All SOL-116 administered
- All unused SOL-116
- All SOL-116 returned at the end of the study, and the date of return/destroyed by the site

The pharmacist will be responsible for the inventory and accountability of all Clinical Trial Material, exercising accepted pharmaceutical practices. An accurate, timely record of the Clinical Trial Material will be maintained. Only after completion of the study (to avoid breaking the blind), the Clinical Trial Material and the inventory will be available for inspection by the designated representatives of Lipum AB upon request. The original Drug Preparation Protocol and Drug Accountability Record are considered as source data and will be archived at the site.

8.6 Safety Review Committee

The study will be monitored by an SRC. The SRC is intended to ensure that the study drug does not pose undue risk to subjects/patients. Safety, tolerability and available PK data up to 14 days post-dose of at least 6 evaluable subjects (subject assessed as pharmacokinetically evaluable at Day 14) will be assessed by the SRC prior to ascending from one dose-level cohort to the next-higher dose-level cohort. For Cohort 2 onwards, cumulative PK data will also be considered. Key PK parameters for dose escalation are C_{max} (µg/mL) and AUC (µg/mL*h). A

dose increment of 3 will never be exceeded in selecting the next dose level. Prior to Cohort 3 and thereafter, the SRC will also consider dose linearity.

For Part 3, the same applies but data up to 28 days post last dose will be collected and assessed at the SRC.

The SRC will be composed of the following core individuals:

- Principal Investigator(s) or delegate(s) (delegation only when a Principal Investigator is not available);
- Lipum AB chief medical officer or delegate (must be a physician);
- QPS pharmacokineticist;
- Other internal or external experts may be invited to participate in the review or may be consulted.

8.7 Dose Escalation Strategy

8.7.1 Determination of Dose Escalation/Subsequent Dosing

For Part 1: The decision to escalate to the next dose level will not take place until the SRC has reviewed the blinded safety and tolerability data, including but not limited to vital signs, ECG results, clinical laboratory tests, and AEs, up to and including 14 days post-dose of at least 6 evaluable subjects (subject assessed as pharmacokinetically evaluable at Day 14). For Part 2: The same applies as for Part 1 but will include 21 days data for safety/PK review.

For Part 3: The decision to escalate to the next dose level will not take place until the SRC has reviewed the blinded safety and tolerability data, including but not limited to vital signs, ECG results, clinical laboratory tests, and AEs, up to and including 28 days (i.e., T_{max} plus one half-life) post last dose of at least 6 evaluable subjects (subject assessed as pharmacokinetically evaluable at Day 28 post last dose).

Additionally, for all parts, an interim PK analysis of available serum SOL-116 concentration data will be reviewed as part of the dose escalation assessment. Any available blood PK data will be reviewed as part of the dose escalation assessment.

After the review of each dose level, the SRC will make one of the following determinations:

- To continue with the study as planned. The SRC agrees that adequate safety and tolerability have been demonstrated in accordance with the dose-escalation and stopping criteria).
- To continue with the study as planned and evaluate additional or alternate time points for safety evaluations. Additional time points for existing safety procedures requiring blood collection may be added, provided that the additional time points do not result in the additional collection of more than 15 mL of blood. For the addition of safety procedures that would require blood collection more than 15 mL, an EC-approved protocol amendment and Informed Consent Form is required.
- To continue with the study by:
  - Repeating a dose level.
  - Selecting an alternative dose level between the current dose level and the next planned dose level.
  - Selecting an alternative dose level between the current dose level and any previous lower dose level.

The SRC, Principal Investigator(s) or Lipum AB may terminate dose escalation at any time if continuing to a higher dose level would jeopardize the safety of the subjects/patients. SRC

reports will be submitted to the Independent Ethics Committee (IEC) for approval of the planned dose escalation and for approval to proceed to the next cohort. After completion of all healthy subject cohorts, the report to the IEC on proceeding to the patient cohort will also include a cumulative interim report and a revised structured risk analysis, as applicable.

8.7.2 Dose Escalation Stopping Criteria

- One (1) or more subjects who receive SOL-116 experience a SAE which is considered to be related to the study medication.
- Two (2) or more subjects who receive SOL-116 have QTc prolongation, defined as an average absolute (regardless of baseline value) QTcF >500 msec or an increase of QTcF >60 msec above baseline, confirmed by repeated ECG after at least 5 minutes, and determined post-dose.
- Two (2) or more subjects who receive SOL-116 exhibit hypotension, defined as resting supine diastolic blood pressure <40 mmHg, an asymptomatic or symptomatic fall in systolic blood pressure to below 80 mmHg, persisting for at least 10 minutes on repeated assessment.
- Two (2) or more subjects who receive SOL-116 exhibit hypertension, defined as an increase in resting systolic blood pressure to above 180 mmHg, persisting for at least 10 minutes, or an increase in resting diastolic blood pressure to above 105 mmHg, persisting for at least 10 minutes.
- Two (2) or more subjects who receive SOL-116 exhibit tachycardia, defined as resting supine heart rate >130 beats per minute, persisting for at least 10 minutes.
- Two (2) or more subjects who receive SOL-116 exhibit symptomatic bradycardia, defined as heart rate <40 beats per minute, or asymptomatic bradycardia, defined as resting supine heart rate <30 beats per minute while awake, persisting for at least 10 minutes.
- One (1) or more subjects who receive SOL-116 fulfills Hy's law, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 x upper limit of normal (ULN) and total bilirubin ≥2 x ULN, in the absence of a significant increase in alkaline phosphatase (ALP) and in the absence of an alternative diagnosis that explains the increase in total bilirubin (confirmed by repeating within 24 hours).
- Two (2) or more subjects who receive SOL-116 exhibit ALT, total bilirubin, or ALP >3 x ULN accompanied by significant increase in other liver function test (confirmed by repeating within 24 hours).
- Two (2) or more subjects who receive SOL-116 exhibit renal toxicity, defined as serum creatinine ≥1.5 x ULN (confirmed by repeating within 24 hours).
- Two (2) or more subjects who receive SOL-116 exhibit hematologic toxicity, defined as one or more of the following (confirmed by repeating within 24 hours):
  - Leukocyte count <2.5 x 10^9/L
  - Neutrophil count <1.0 x 10^9/L
  - Platelet count <75 x 10^9/L

In addition, the SRC may stop dose escalation at any time if the SRC determines that dose escalation would pose undue risk to subjects. If dose escalation is not stopped, the SRC may recommend ascending to the planned next-higher dose level cohort, ascending to a dose level

lower than the planned next-higher dose level cohort, or a repeat dosing at the current dose level.

The safety and available PK data will be reviewed by the SRC. For the PK results, this will be done in a blinded manner (e.g., without subject identifiers or using reblinded subject numbers), but if the SRC considers it necessary due to a safety concern, individual subject data or an entire cohort's data may be unblinded to the SRC to enable decision-making. Before any such unblinding, the reason for unblinding will be documented.

SRC reports will be submitted to the IEC for approval of dose escalation.

8.7.3 Re-initiation of Dose Escalation

If dose escalation is terminated due to the criteria noted above, reduced and/or repeat dose levels (as allowed per protocol) may be administered to provide additional data regarding the frequency and/or severity of AEs.

If the SRC agrees that these additional data suggest that the observations that initially resulted in a termination of dose escalation were not attributable to study medication, then dose escalation may be allowed to continue.

8.8 Study Termination or Withdrawal of Subject/Patient from Study

8.8.1 Study Termination

If the Sponsor terminates or suspends the study, the Investigator or his/her designee should promptly inform the IEC (and/or regulatory authorities where required) of a temporary halt including the reason for such an action (see also Section 12.1.10).

8.8.2 Subject/Patient Discontinuation or Withdrawal

Subjects/patients may withdraw from the study at any time without prejudice to their future medical care by the physician or at the institution. Furthermore, a subject/patient may also be discontinued at any time should they meet the criteria defined in Section 12.1.9.

The withdrawal of a subject/patient from the study should be discussed where possible with the Medical Monitor prior to withdrawal. If the subject is discontinued or withdraws from the study, the final evaluations are to be performed as completely as possible.

8.8.3 Subject's/Patient's Follow-up after Study Discontinuation or Withdrawal

The subjects/patients will be advised that participation in these investigations is voluntary. Furthermore, the subjects/patients may request that from the time point of withdrawal no more data will be recorded and that all biological samples collected during the study will be destroyed.

In the case of premature discontinuation or withdrawal, the safety assessments scheduled for the EOS examination will be performed as soon as possible after study drug administration, as per Investigator judgement, unless the subject/patient withdrew informed consent. A safety follow-up visit will be performed as per Investigator judgement, unless the subject/patient withdrew informed consent. PK and PD assessments after early discontinuation will be performed upon mutual agreement between the Investigator and the Sponsor.

8.8.4 Subject/Patient Replacement

Drop-outs might be replaced but only upon mutual agreement between the Investigator and the Sponsor, unless withdrawal is due to a drug-related AE. The replacing subject/patient will receive the same treatment as assigned to the subject/patient whom he/she replaces.

8.9 Treatment Exposure and Compliance

Records of study drug used, dosages administered, are kept during the study. Study drug accountability is performed on an ongoing basis by the study staff and checked by the CRA/monitor during site visits and at the completion of the study.

All drug administrations will be done under direct medical supervision.

8.10 Treatment Assignment and Blinding

8.10.1 Assignment of Subject/Patient Numbers

Subjects/Patients will receive a 4-digit number on Day 1 before study drug administration (Table 8-6). The assignment of number and code for subject/patient identification is based on the obligation for anonymity.

Table 8-6: Assignment of Study Codes to Subjects/Patients

Cohort	Subject/Patient numbers	Replacement numbers
Healthy subjects		
Cohort 1	0001 – 0008	1001 – 1008
Cohort 2	0009 – 0016	1009 – 1016
Cohort 3	0017 – 0024	1017 – 1024
Cohort 4	0025 – 0032	1025 – 1032
Cohort 5	0033 – 0040	1033 – 1040
Cohort 6 (optional)*	0041 – 0048	1041 – 1048
RA patients		
Cohort 7	0101 – 0108	1101 - 1108
Healthy subjects		
Cohort MD1	0201 - 0208	1201 - 1208
Cohort MD2	0301 - 0308	1301 - 1308

*Optional 6th cohort not run

Subjects/patients who replace discontinuing subjects/patients after randomization on Day 1 will receive the number of this subject/patient +1000, e.g., subject/patient 1006 will replace subject/patient 0006, subject/patient 2006 will replace subject/patient 1006, etc. The substitute subject/patient will receive the treatment assigned to the withdrawn subject/patient.

In the case of discontinuation of a subject/patient before randomization, the substitute subject/patient will receive the same number as the subject/patient he/she replaces.

8.10.2 Treatment Assignment

Subjects/patients will be randomized to any of the treatments assigned for that cohort. The randomization code is stored securely. It is accessible only to authorized persons who are not involved in the conduct and analysis of the study, until time of un-blinding. Individual sealed randomization codes are kept at the participating sites, and these are used for emergency un-blinding only.

Unused sealed code envelopes will be archived.

Randomization is controlled by the study drug packaging. The number on the subject/patient packaging equals the randomization number. Subjects/patients must be randomized in a consecutive order starting with the lowest subject number.

Randomization will be performed by the Biostatistics department of QPS Qualitix Taiwan, according to Qualitix Taiwan SOPs. The randomization code and the randomization list will be generated using SAS version *9.4* or the last available version at time of randomization.

The randomization code will be un-blinded and made available for data analysis only after study closure, i.e., when the study has been completed, the protocol deviations determined and the clinical database declared complete, accurate, and locked.

8.10.3 Double-blinding

The study is performed in a double-blind fashion. The Investigator and study staff (including processing lab personnel), the subjects/patients, the CRAs/monitors and the Sponsor's staff will remain blinded to the treatment until study closure. The investigational drug and its matching placebo are indistinguishable. The labels of the syringes will be double blind and the packaging of the placebo/active syringes identical. Only after preparation of the syringe is completed, it will be handed over by pharmacy staff to the staff of the clinic.

The randomization code will be kept strictly confidential. It is accessible only to the pharmacist on site, who is not involved in the conduct and analysis of the study, and will keep the randomization scheme strictly confidential.

The bioanalytical laboratory will only analyze the samples of subjects/patients receiving SOL-116, and not the samples of subjects/patients receiving placebo. Therefore, the bioanalytical laboratory will receive the randomization list from the biostatistician. The bioanalytical laboratory will not share this list with other parties and will blind all PK results before sending these to other team members.

8.10.4 Emergency Procedure for Unblinding

The Investigator receives emergency envelopes for each subject/patient containing the identity of the study drug dispensed. The Investigator and the study staff must remain blinded to the subject's/patient's treatment assignment, even if the subject/patient refuses to participate in any study procedures or experiences an AE. The identity of the study drug may be revealed only if the subject/patient experiences a medical emergency whose management would be improved by the knowledge of the blinded treatment assignment.

The occurrence of any code break during the study must be clearly justified and explained by the Investigator. Before opening the emergency envelope, every attempt must be made by the Investigator to discuss the intended code break with Lipum AB. In all cases, the Sponsor must be informed as soon as possible before or after the code break.

Any code break must be documented on the emergency envelope and in a detailed report with the date and time of the code break and signed by the Investigator. This report is to be attached to the source documents and the date and time of code break will be documented in the eCRF.

The CRA/monitor checks the emergency envelopes according to the Monitoring Plan (MP).

8.11 Study Parameters

8.11.1 Pharmacokinetic Parameters

The serum PK parameters for SOL-116 will be derived by non-compartmental analysis of the serum concentration-time profiles.

The following PK parameters have been defined:

- Area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$);
- Maximum observed serum concentration (C_{max});

- Time to C_{max} (T_{max});
- AUC from time zero to time t of the last measured concentration above the limit of quantification (AUC_{0-t});
- Terminal elimination half-life ($T_{1/2}$);
- Apparent volume of distribution (V_z/F);
- Apparent total body clearance (CL/F).

In multiple dosing part, C_{trough}, time to steady state and accumulation ratio will also be assessed.

Attainment of steady-state conditions will be determined by visual inspection of the pre-dose serum concentrations.

8.11.1.1 Calculation of Pharmacokinetic Parameters and Assumptions

The measured individual serum concentrations of SOL-116 will be used to directly obtain C_{max} and T_{max}.

AUC_{0-t} will be calculated according to the linear up/log down trapezoidal method using the measured concentration-time values above the lower limit of quantification (LLOQ). AUC_{0-inf} will be calculated by combining AUC_{0-t} and AUC_{extra}. AUC_{extra} represents an extrapolated value obtained by C_t/λ, where C_t is the last serum concentration measured above the LLOQ and λ represents the terminal elimination rate constant determined by log-linear regression analysis of the measured serum concentrations of the terminal elimination phase. The half-life of SOL-116 will be calculated as follows: $T_{1/2} = \ln 2 / \lambda$.

The PK parameters will be based on actual blood sampling times [h] (relative to the corresponding administration time) rounded to two digits and negative pre-dose times will be set to zero.

Please refer to Section 10 for more information on statistical methodology.

8.11.2 Safety and Tolerability Parameters

Baseline is defined as the last value measured prior to SOL-116 administration (vital signs, ECG, laboratory parameters), unless otherwise specified.

The following parameters have been defined as parameters regarding safety and tolerability:

- Clinical laboratory evaluations;
- Injection site reactions;
- AEs;
- Immune reactions (e.g. hypersensitivity, cytokine release syndrome, immunogenicity);
- Vital signs;
- Physical examination;
- ECGs (3-lead telemetry and 12-lead ECGs);
- Concomitant medications/therapy.

8.11.3 Immunogenicity Parameters

The following are defined as immunogenicity parameters:

- Development of ADA. If confirmed ADA positive, the following may be determined:
  - Estimation of ADA titers
  - Neutralizing capacity
  - Isotype
  - Epitope map

8.11.4 Exploratory Parameters

The following are defined as exploratory parameters:

- BSSL concentration;
- Inflammatory biomarkers (except BSSL): CRP, ESR for all subjects/patients, and S-calprotectin and hsCRP (only RA patients);
- Cytokine/chemokine panel (including but not limited to IFNγ, IL-1β, IL-6, IL-10, IL-12, IL-18, MCP-1 and TNFα);
- Flow cytometry panel (only RA patients);
- Whole blood stimulation assays (only RA patients).

9 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

9.1 Adverse Events

9.1.1 Definitions of Adverse Events

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (International Council for Harmonization (ICH) E6; Section 1.2).

A treatment-emergent AE is any AE temporally associated with the use of a study drug, whether or not considered related to the study drug.

Adverse events include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.
- Lack of efficacy in the acute treatment of a life-threatening disease.
- Events considered by the Investigator to be related to study-mandated procedures.
- Abnormal assessments, e.g., ECG, vital signs or physical examination findings, must be reported as AEs if they represent a clinically significant finding that was not present at baseline or worsened during the course of the study.
- Laboratory test abnormalities must be reported as AEs if they represent a clinically significant finding, symptomatic or not, which was not present at baseline or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study drug.

Adverse events do not include:

- Medical or surgical procedure, e.g., surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE narrative.
- Pre-existing disease or medical condition that does not worsen.
- Situations in which an adverse change has not occurred, e.g., hospitalizations for cosmetic elective surgery or for social and/or convenience reasons.
- Overdose of either study drug or concomitant medication without any signs or symptoms. However, overdose must be mentioned in the Study Drug Log.

9.1.2 Intensity of Adverse Events

The intensity of clinical AEs is graded on a three-point scale: mild, moderate, severe, and reported on specific AE pages of the eCRF.

If the intensity of an AE worsens during study drug administration, the AE will be closed and a new AE with enhanced severity will be generated in the eCRF. If the AE lessens in intensity, no change in the severity is required.

If an AE occurs during a washout or placebo run-in phase and afterwards worsens during the treatment phase, a new AE page must be filled in with the intensity observed during study drug administration.

Mild: Event may be noticeable to subject/patient; does not influence daily activities; usually does not require intervention.

Moderate: Event may make subject/patient uncomfortable; performance of daily activities may be influenced; intervention may be needed.

Severe: Event may cause noticeable discomfort; usually interferes with daily activities; subject/patient may not be able to continue in the study; treatment or intervention is usually needed.

A mild, moderate or severe AE may or may not be serious. These terms are used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction). However, a severe event may be of relatively minor medical significance (such as severe headache) and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not be clinically serious. Fever of 39 °C that is not considered severe may become serious if it prolongs hospital discharge by a day (see Section 9.2.1.2). Seriousness rather than severity serves as a guide for defining regulatory reporting obligations.

9.1.3 Relationship to Study Drug

Adverse events should be assessed by the investigators as to whether or not there is a reasonable possibility of causal relationship to the study drug and reported as either related or unrelated.

Related to study drug: This category applies to any AE (serious or not) that appears to have a reasonable possibility of causal relationship to the use of the study drug (i.e., a relationship cannot be ruled out). Guidelines to determine whether an event might be considered related include (but are not limited to) the following:

- The event occurred in close temporal relationship to study drug administration.
- The event abated (diminished) or disappeared when treatment with the study drug was down-titrated, interrupted, or discontinued.
- The event re-occurred when treatment was re-introduced.
- Environmental factors such as clinical state and other treatments could equally have caused the event.

Related AEs should be considered as one of the following categories:

Definite	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be

explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unrelated to study drug: This category applies to any AE (serious or not) that does not appear to have a reasonable relationship to the use of study drug (see above guidelines).

Unrelated AEs should be considered as one of the following categories:

Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Unrelated	A clinical event, including laboratory test abnormality, which is clearly not related to drug administration.

9.1.4 Reporting of Adverse Events

All AEs occurring from the (first) dose administration and up to Follow-Up must be recorded on specific AE pages of the eCRF (note: only AEs for randomized subjects/patients will be recorded in the eCRF) see also Section 8.3.2.1.

9.1.5 Follow-up of Adverse Events

Adverse events must be followed until resolution, stabilization or up to EOS. Adverse events assessed as related must be followed until resolution, stabilization or to a maximum of 28 days after the EOS.

9.2 Serious Adverse Events

9.2.1 Definitions

9.2.1.1 Serious Adverse Events

A SAE is defined by the ICH guidelines as any AE fulfilling at least one of the following criteria:

- Results in death.
- Is life-threatening. Life-threatening refers to an event in which the subject/patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires subject's/patient's hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is medically significant or requires intervention to prevent at least one of the outcomes listed above.

Important medical events that may not immediately result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The reference safety document to assess whether or not an SAE should be reported by the Sponsor to Health Authorities, IECs/institutional review boards (IRBs) and investigators in an expedited fashion is the Investigator's Brochure.

9.2.1.2 Pregnancy

All initial reports of pregnancy, including pregnancy outcome (follow-up) in female subjects/patients or in partners of male subjects/patients, must be reported to QPS safety unit (QPS SU) by the Investigator within 24 hours of his/her knowledge of the event using a Pregnancy Form.

The Investigator will contact the subject/patient at the expected time of delivery for follow-up. Abnormal pregnancy outcomes (e.g., induced abortion, stillbirth, neonatal death, congenital abnormality, birth defect) are considered SAEs and must be reported using the Serious Adverse Event Form.

9.2.1.3 Hospitalization – Prolongation of Existing Hospitalization

Hospitalization is defined as an overnight stay in a hospital unit and/or emergency room.

An additional overnight stay defines a prolongation of existing hospitalization.

The following is not considered an SAE and should be reported as an AE only:

- Treatment on an emergency or outpatient basis for an event not fulfilling the definition of seriousness given above and not resulting in hospitalization.

The following reasons for hospitalizations are not considered AEs, and therefore not SAEs:

- Hospitalizations for cosmetic elective surgery, social and/or convenience reasons.
- Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a patient with stable angina pectoris.
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for chemotherapy for cancer, elective hip replacement for arthritis.

9.2.1.4 Serious Adverse Events Related to Study-mandated Procedures

Such SAEs are defined as SAEs that appear to have a reasonable possibility of causal relationship (i.e., a relationship cannot be ruled out) to study-mandated procedures (excluding administration of study drug) such as discontinuation of subject's/patient's previous treatment during a washout period, complication of a mandated invasive procedure (e.g., blood sampling, heart catheterization), car accident on the way to the hospital for a study visit, etc.

9.2.2 Reporting of Serious Adverse Events

9.2.2.1 Before Study Drug Initiation

Serious adverse events occurring after signature of the Informed Consent and up to study drug initiation must be reported to the QPS SU.

9.2.2.2 During Study Drug Administration

All SAEs regardless of causal relationship must be reported, including those related to study-mandated procedures. These SAEs occurring during study drug administration, i.e., between study drug initiation and EOS, are defined as treatment emergent SAEs.

These SAEs are reported on SAE forms and also on AE pages in the eCRF. Therefore, they are entered both in the drug safety and clinical databases, and must be reconciled before study closure.

9.2.2.3 After Study Drug Administration

New SAEs, including those related to study-mandated procedures, occurring after study drug administration, i.e., until EOS, must be reported.

All SAEs occurring after study drug administration until Follow-Up must be recorded on an SAE form and as AEs in the eCRF. Therefore, these treatment-emergent SAEs are entered both in the QPS drug safety and clinical databases, and must be reconciled before study closure.

9.2.2.4 Reporting Procedures

All SAEs must be reported by a Principal Investigator to QPS SU within 24 hours of the Investigator's knowledge of the event.

All SAEs must be recorded on SAE forms, irrespective of the study drug received by the subject/patient, whether or not this event is considered by the Investigator to be related to study drug.

These SAE forms must be sent to QPS SU. The Investigator must complete the SAE form in English (unless otherwise specified) and assess the relationship to study drug.

Such preliminary reports will be followed by detailed descriptions that should include copies of hospital case reports, autopsy reports, hospital discharge summaries and other documents when requested and applicable. Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. QPS SU may contact the Investigator to obtain further information.

Suspected (considered related to the study drug) and Unexpected (not previously described in the reference safety information), Serious Adverse Reactions (SUSARs) will be expedited by QPS SU to Health Authorities, IEC/IRB and investigators, as appropriate. SUSARs will not be subject to systematic unblinding.

9.2.3 Follow-up of Serious Adverse Events

Serious adverse events still ongoing at the EOS visit must be followed until resolution or stabilization or until the event is otherwise explained or referral to appropriate medical care.

New SAEs occurring at any time after the EOS or after the 28-day follow-up period after study drug discontinuation (whichever comes first) may be reported to QPS SU within 24 hours of the Investigator's knowledge of the event, if felt appropriate by the investigators.

Such information will only be entered into the drug safety database and hence will not affect study closure.

10 STATISTICAL METHODOLOGY AND ANALYSES

10.1 Statistical Analysis Plan

A statistical analysis plan (SAP) will be written and finalized before the study closure, i.e., database closure and unblinding of the randomization code of the study, if applicable. The SAP will provide full details of the analyses, the data displays and the algorithms to be used for data derivations. An SAP for safety and tolerability will be written by QPS Qualitix Taiwan. An SAP for the PK analyses (PKAP) will be written by QPS LLC.

Any deviations from the original statistical plan will be described and justified in the final report.

10.2 Analysis Sets

Five different analysis sets are defined. Subjects/patients who withdraw from the study, or who have missing data, will be included in the statistical analyses provided that they are eligible for inclusion in the analysis population as described below.

All-treated set: This analysis set includes all randomized subjects/patients who received study drug (at least one dose).

Safety set: This analysis set includes subjects/patients from the All-treated set who had at least one safety assessment post-baseline. The safety set will be employed in the analysis of tolerability and safety variables.

Immunogenicity set: This analysis set includes all subjects/patients who received the study treatment and had at least 1 post-dose immunogenicity sample collected.

Per-protocol set: This analysis set comprises all subjects/patients included in the All-treated set who did not violate the protocol in a way that might affect the evaluation of the effect of the study drug(s) on the primary endpoint, i.e., without major protocol violations or deviations. The Per-protocol set will be employed in the analysis of PK and exploratory variables.

PD (exploratory) set: This analysis set comprises all subjects/patients included in the All-treated set who did not violate the protocol in a way that might significantly affect the ability to analyze exploratory endpoints (i.e. RA patients who received more than 2 intra-articular injections in large joints and/or 6 intra-articular injections in small joints during the study are excluded).

10.2.1 Sample Size

No formal sample size calculation has been performed. The proposed sample size is considered sufficient to provide adequate information for the study objectives.

A statistical analysis plan will be prepared prior to database lock for each part of the study (see Section 10.1).

10.2.2 Procedure for Accounting for Missing, Unused, and Spurious Data

All analyses will be performed on data available at the time point considered. In summary tables, the number of subjects/patients with missing data will be presented unless otherwise specified. In calculation of percentages, subjects/patients with missing data will not be considered in numerator or denominator unless otherwise specified.

10.3 Pharmacokinetic Parameters

The PK parameters will be calculated on the basis of the actual blood sampling time points. Please refer to Section 8.3.3.1 for details on the timing of sampling.

10.3.1 Pharmacokinetic Statistical Analysis

A definition of the PK parameters is described in Section 8.11.1. PK parameters will be described descriptively.

The Per-protocol analysis set will be used for all PK analyses. Individual subject/patient listings will be provided. Mean and individual serum concentration-time profiles for SOL-116 will be presented graphically for each group.

PK variables will be summarized using arithmetic mean, standard deviation, geometric mean, median, minimum, maximum, and coefficient of variation (CV%).

Attainment of steady-state conditions will be determined by visual inspection of the pre-dose serum concentrations.

10.4 Safety and Tolerability Parameters

Definitions of the safety and tolerability parameters are described in Section 8.11.2.

The safety set is used to perform all safety analyses.

The medical history is coded using the latest version of MedDRA and listed.

All AEs and SAEs are coded using the latest version of MedDRA.

The treatment-emergent AEs are tabulated by system organ class (SOC), and individual preferred terms within each SOC by treatment group. The number and percentage of subjects/patients who experienced AEs coded with the same preferred term and SOC will be summarized by treatment group (in descending order according to the incidence in the investigational study drug group). Adverse events will also be tabulated by severity and by relationship to study drug. Summary tables will be accompanied by individual subject/patient listings broken down by treatment group, including pre-dose events.

SAEs will be listed and summarized similarly to AEs.

Reasons for death will only be listed.

Reasons for premature discontinuation of study drug will be listed and summarized by frequency tables.

ECG variables, vital sign measurements and laboratory measurements will be summarized at each time point using mean, median, standard deviation, min, max, number of available observations, and change from baseline. Individual subject/patient listings of physical examination data, ECG data, vital signs data, physical examination data, immune reactions, injection site reactions, concomitant medication/therapy and laboratory measurements will be provided.

Standard numeric laboratory parameters are presented in the units supplied. If needed, a conversion will be made to standard units.

10.5 Immunogenicity Parameters

A definition of the immunogenicity parameters is described in Section 8.11.3.

Immunogenicity and exploratory parameters will be listed individually, displayed in appropriate graphics and summarized using descriptive statistics.

10.6 Exposure to Study Drug

A listing with information about the study drug administration will be provided.

10.7 Baseline Parameters and Concomitant Medications

Summary statistics (mean, median, standard deviation, min, max, number of available observations) will be provided for continuous demographic variables (e.g., age, height, weight). Individual subject/patient listings of demographic data will be provided.

Qualitative demographic characteristics (gender, race) will be summarized by counts and percentages. Other baseline subject/patient characteristics (medical history, physical examination clinical findings, previous medications, inclusion/exclusion checklist) will only be listed.

Distributions of these parameters will be compared between the treatment groups only descriptively. No statistical inference will be performed.

Previous and concomitant medications will be coded according to the World Health Organization (WHO) drug code and the anatomic therapeutic chemical (ATC) class code. Concomitant medications will be summarized by tabulating the number and percentages of subjects/patients treated.

10.8 Exploratory Analyses

A definition of the exploratory parameters is described in Section 8.11.4. Exploratory parameters will be listed individually, displayed in appropriate graphics and summarized using descriptive statistics. The PD (exploratory) set will be used. Also, the PP set and the “all-treated set” will be used.

Exploratory data-driven analyses can be performed with the caveat that any statistical inference will not have any confirmatory value.

10.9 Interim Safety Report

For Parts 1 and 2, the interim safety analysis will be conducted by the SRC on safety/tolerability and available PK data up to and including 14 days post-dose after completion of at least 6 evaluable subjects per treatment group (subject assessed as pharmacokinetically evaluable at Day 14). For Part 3, the interim safety analysis will be conducted by the SRC on safety/tolerability and available PK data up to and including 28 days post last dose after completion of at least 6 evaluable subjects per treatment group (subject assessed as pharmacokinetically evaluable at Day 28 post last dose.

Based on the results of the interim analysis (including but not limited to AEs, vital signs, ECGs, and clinical laboratory tests), a decision will be taken by the Principal Investigator(s) and Lipum AB whether the next cohort can start with the planned dose. This decision will only be made after discussion between the Principal Investigator(s) and the Sponsor and after mutual agreement and must be submitted to the IEC/IRB for approval before dosing can proceed.

10.10 Clinical Study Report

Safety and tolerability parameters as well as PK and exploratory parameters (BSSL, CRP, hsCRP, ESR and S-calprotectin) will be evaluated in a Clinical Study Report. Certain exploratory parameters may be reported separately.

11 REFERENCES

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3. Nagy G, Roodenrijs NMT, Welsing PMJ et al. EULAR definition of difficult-to-treat rheumatoid arthritis. Ann Rheum Dis 2021; 80:31–35.
4. Lindquist S, Hernell O. Lipid digestion and absorption in early life: an update. Curr Opin Clin Nutr Metab Care. 2010; 13:314-20.
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6. Investigators Brochure, edition 1.0, dated 08 August 2022.
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8. Aletaha D, Neogi T, Alan J Silman AJ. Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010 Sep;62(9):2569-81. doi: 10.1002/art.27584.

12 PROCEDURES AND GOOD CLINICAL PRACTICE

12.1 Procedures

12.1.1 Protocol Amendments

A change to a protocol has to be considered as an amendment as soon as these documents have been approved by IECs/IRBs or Health Authorities. The Sponsor is responsible to assess whether an amendment is substantial or non-substantial. Each amendment must be documented in writing by Lipum AB or its delegate. It should be reviewed by the Principal Investigator(s), Sponsor and other relevant team members, if appropriate.

Adaptations of the core Subject Information and Informed Consent requested by IECs/IRBs are not considered as amendments, as long as they do not significantly change the core document or affect the protocol.

12.1.1.1 Non-substantial Amendment

Administrative or logistical minor changes require a non-substantial amendment. Such changes include but are not limited to changes in study staff or contact details (e.g., Lipum AB instead of CRO monitors) or minor changes in the packaging or labeling of study drug.

The implementation of a non-substantial amendment could be done with or without (according to national regulations) notification to the appropriate IECs/IRBs and Health Authorities. It does not require their approval or to be signed by the investigators.

12.1.1.2 Substantial Amendment

Significant changes require a substantial amendment. Significant changes include but are not limited to: new data affecting the safety of subjects/patients, change of the objectives/ parameters of the study, eligibility criteria, dose regimen, study assessments/procedures, treatment or study duration, change of Principal Investigator or Sponsor's legal representative, with or without the need to modify the core Subject Information and Informed Consent.

Substantial amendments are to be approved by the appropriate IECs/IRBs and by the Health Authorities. The implementation of a substantial amendment can only occur after formal approval by the appropriate IECs/IRBs and/or Health Authorities and must be signed by the investigators.

12.1.1.3 Urgent Amendment

An urgent amendment might become necessary to preserve the safety of the subjects/patients included in the study. The requirements for approval should in no way prevent any immediate action being taken by the investigators or Lipum AB in the best interests of the subjects/patients. Therefore, if deemed necessary, an Investigator can implement an immediate change to the protocol for safety reasons. This means that, exceptionally, the implementation of urgent amendments will occur before submission to and approval by IECs/IRBs and Health Authorities.

In such cases, the Investigator must notify Lipum AB within 24 hours. A related substantial amendment will be written within 10 working days by QPS Netherlands B.V. and submitted to the appropriate IECs/IRBs and Health Authorities.

12.1.2 Site Monitoring

Clinical site monitoring is conducted by the CRA/monitor to ensure that the rights and well-being of human subjects are protected, that the reported study data are accurate, complete, and

verifiable, and that the conduct of the study is in compliance with the currently approved protocol/amendment(s), with ICH-GCP, SOPs and with applicable regulatory requirement(s).

Details of clinical site monitoring are documented in a study specific MP. The MP describes includes a detailed description of:

- the objectives and scope of monitoring,
- the responsibilities of the CRA/monitor,
- timelines of monitoring,
- procedures (site initiation, interim monitoring visits, close out and protocol deviations),
- at what level of detail monitoring will be performed,
- communication and the distribution of monitoring reports.

In general, an initiation visit will be performed before the first screening visit. Interim monitoring visits and contacts will occur at regular intervals thereafter, according to a frequency defined in the MP. A close-out visit will be performed after study closure. The Investigator is expected to be able to meet the CRA/monitor during these visits. The CRA/monitor will be available between visits if the Investigator or other staff needs information or advice. The CRA/monitor is to be informed by the Sponsor and/or Investigator about any relevant study updates as soon as possible.

The Investigator will supply the Sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

The Investigator may convert study site visits to remote monitoring visits (telemedicine, telehealth, video presence or via other systems), with the approval of the Sponsor.

12.1.3 Data Management

12.1.3.1 Data Collection

A Subject Screening and Enrollment Log will be completed for all eligible or non-eligible subjects/patients with the reasons for exclusion.

Data will be collected according to local SOP of the clinic.

For each randomized subject/patient, regardless of study drug initiation, an eCRF must be completed and signed by a Principal Investigator or sub-investigator. This also applies to randomized subjects/patients who fail to complete the study. If a subject/patient withdraws from the study, the reason must be noted on the eCRF. The eCRF is to be completed on an ongoing basis. Designated investigator staff will enter the data required by the protocol into the eCRF. Designated investigator site staff will not be given access to the electronic data capture system until they have been trained. The Investigator or sub-investigator must certify that the data entered into the eCRF are complete and accurate.

12.1.3.2 Database Management and Quality Control

After completion of the eCRF, each subject/patient will be electronically approved (signed) by the Investigator.

The CRA/monitor will perform source data verification according to the MP and the SOPs of QPS Netherlands B.V. The CRA will use eCRF systems to track the monitoring queries and their resolution by the site.

All eCRF data will be validated by Data Management of QPS Netherlands B.V., according to specifications described in the Data Management Plan and the applicable SOPs.

After the eCRF has been declared complete and accurate, the eCRF will be locked, after written approval of the Sponsor. Any changes to the eCRF after that time require a database unlock and can only be made after receipt of written approval of the Sponsor.

12.1.4 Recording of Data and Retention of Documents

The Investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents will be classified into two different categories: Investigator Site File (ISF), and subject/patient clinical source documents (electronic and/or paper).

The ISF will contain the protocol/amendments, FDA form 1572 for studies conducted under a US IND, financial disclosure form, eCRFs, IEC/IRB and Health Authority approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, screening and enrolment logs, and other appropriate documents/correspondence as per ICH/GCP and local regulations.

Subject/patient clinical source documents include, but are not limited to subject/patient hospital/clinic records, physician's and nurse's notes, original laboratory, ECG, X-ray, pathology and special assessment reports, consultant letters, etc.

These two categories of documents must be kept on file by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). No study document should be destroyed without prior written approval from Lipum AB. Should the Investigator wish to assign the study records to another party, or move them to another location, Lipum AB must be notified in advance.

When source documents are required for the continued care of the subject/patient, appropriate copies should be made for storing outside of the site.

The handling of personal data will comply with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation.

12.1.5 Audit

Lipum AB’s quality assurance (QA) Manager or delegate may conduct audits of clinical research activities in accordance with internal SOPs to evaluate compliance with the principles of GCP and ICH related guidelines.

Health Authorities may also wish to conduct an inspection (during the study or after its completion). Should an inspection be requested by Health Authorities, the Investigator must inform Lipum AB immediately that such request has been made.

The Investigator will permit such audits by Lipum AB or Health Authorities and facilitate them by providing access to the relevant source documents.

12.1.6 Handling of Study Drug(s)

Lipum AB will supply all study drug(s) to the site according to local regulations. Drug supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the drug labels. The site must maintain an accurate record of the shipment and dispensing of study drug(s) on an accountability form, which must be given to the monitor at the end of the study. An accurate record of the date and amount of study drug(s) dispensed to each subject/patient must be available for inspection at any time.

All drug supplies are to be used only for this protocol and not for any other purpose. The responsible person must not destroy any drug labels, or unused drug supply. Upon termination of the study, the monitor will collect used and unused drug subject/patient kits. They will be sent to the warehouse, where the Sponsor or its deputy will check drug accountability. In certain circumstances, used and unused drug containers can be destroyed at the site once drug accountability is final and checked by the Sponsor or its deputy and written permission for destruction has been obtained from Lipum AB.

12.1.7 Publication of Study Results

In accordance with standard editorial and ethical practice, Lipum AB will support publication of the data.

12.1.8 Disclosure and Confidentiality

By signing the protocol, the Investigator agrees to keep all information provided by Lipum AB in strict confidence and to request similar confidentiality from his/her staff and the IEC/IRB. Study documents provided by Lipum AB (e.g. investigators' brochures, protocols, eCRFs and other protocol-related documents) will be stored appropriately to ensure their confidentiality. The information provided by Lipum AB to the Investigator may not be disclosed to others without direct written authorization from Lipum AB, except to the extent necessary to obtain informed consent from subjects/patients who wish to participate in the study.

12.1.9 Stopping rules for Subject/Patient

Should a subject/patient experience an AE or SAE that meets the following criteria, the subject/patient may be immediately discontinued from the study:

- Any AE or SAE in the judgement of the Investigator or subject/patient justifies withdrawal due to its severity, nature, or requirement for treatment, regardless of the causal relationship to the study drug.
- Clinically relevant test procedure results which endanger the subject/patient.

The reason(s) will have to be recorded on the appropriate page of the eCRF for each prematurely discontinued subject/patient.

For discontinued subjects/patients, the assessments scheduled for the EOS examination will be performed as soon as possible after study drug administration.

If the Sponsor terminates or suspends the study, the Investigator should promptly inform the IEC/IRF (and/or regulatory authorities where required) of a temporary halt including the reason for such an action.

12.1.10 Premature Termination or Suspension of the Study

Both Lipum AB and the Investigator reserve the right to terminate the study at any time.

If a study is prematurely terminated or suspended, Lipum AB will promptly inform the investigators, the IECs/IRBs and Health Authorities, as appropriate, and provide the reason(s) for the termination or suspension.

If the study is prematurely terminated or suspended for any reason, the Investigator in agreement with Lipum AB should promptly inform the enrolled subjects/patients and ensure their appropriate treatment and follow-up.

In addition, if the Investigator terminates or suspends a study without prior agreement of the Sponsor, the Investigator should promptly inform Lipum AB and the IEC/IRB, and should provide the Sponsor and the IEC/IRB with a detailed written explanation of the termination or suspension.

If the IEC/IRB terminates or suspends its approval/favorable opinion of a study, the Investigator should promptly notify Lipum AB and provide Lipum AB with a detailed written explanation of the termination or suspension.

12.2 Good Clinical Practice

12.2.1 Ethics and Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, Somerset-West, Edinburgh, Washington DC, Seoul and Fortaleza) and with the laws and regulations of the country in which the clinical research is conducted.

All studies must follow the ICH/GCP Guidelines and, if applicable, the Code of Federal Regulations.

12.2.2 Quality Control and Quality Assurance

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

The Sponsor can decide to conduct an audit at the clinical study center. The audit will be conducted with the aim to ensure that the clinical study is performed and data are generated, documented (recorded) and reported in compliance with GCP and applicable regulatory requirements. An external party may be contracted for this purpose.

On request of the Sponsor, the QA department may perform a study audit including the data management process.

12.2.3 Independent Ethics Committee / Institutional Review Board

The Investigator will submit this protocol and any related document provided to the subject/patient (such as subject/patient information used to obtain informed consent) to an IEC or IRB. Approval from the committee must be obtained before starting the study, and should be documented in a dated letter to the Investigator, clearly identifying the study, the documents reviewed and the date of approval. A list of members participating in the meeting must be provided, including the functions of these members. If study staff were present, it must be clear that none of these persons voted.

Modifications made to the protocol after receipt of the IEC/IRB approval must also be submitted as amendments by the Investigator to the IEC/IRB in accordance with local procedures and regulations (see Section 12.1.1).

12.2.4 Informed Consent and Recruitment

It is the responsibility of the Investigator to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, and objectives of the study and potential hazards of the study drug. The Investigator must also explain to the subjects/patients that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason. Appropriate forms for documenting written informed consent will be provided to the site prior to the study.

The Informed Consent and Subject Information will be provided in English and/or the local language, as applicable.

Healthy subjects will be recruited via social media channels.

Patients will be recruited by referral from their treating rheumatologist.

12.2.5 Compensation to Subjects/Patients and Investigators

Lipum AB is providing insurance in order to indemnify (legal and financial coverage) the Investigator/center against claims arising from the study, except for claims that arise from malpractice and/or negligence.

The compensation of the subject/patient in the event of study-related injuries will comply with the applicable regulations.

13 STRUCTURED RISK ANALYSIS

13.1 Potential Issues of Concern

13.1.1 Level of Knowledge About Mechanism of Action

[redacted]

13.1.2 Previous Exposure of Human Beings with the Test Product(s) and/or Products with a Similar Biological Mechanism

First-in-human study, first-in-class drug, not applicable.

13.1.3 Can the Primary or Secondary Mechanism be Induced in Animals and/or in Ex-vivo Human Cell Material?

[redacted]

[redacted]

13.1.4 Selectivity of the Mechanism to Target Tissue in Animals and/or Human Beings

[redacted]

13.1.5 Analysis of Potential Effect

[redacted]

13.1.6 Pharmacokinetic Considerations

[redacted]

13.1.7 Study Population

Up to 48 healthy male and female volunteers, and 1 cohort of 8 RA patients will be enrolled, aged between 18-65 years. Females of childbearing potential may be enrolled if they agree to use appropriate contraception.

13.1.8 Interaction with Other Products

Metabolism and potential metabolic interactions have not been investigated. Based on the fact that both SOL-116 and its target BSSL being proteins, and since SOL-116 is not directly binding proinflammatory cytokines, there are no expected drug-drug interactions with small molecule drugs.

In the RA cohort, all patients will receive concomitant treatment with methotrexate (MTX). No pharmacodynamic interactions are expected as MTX affect the folic acid synthesis and SOL-116 affects cells in the immune system.

13.1.9 Predictability of Effect

The PK behavior of SOL-116 in the preclinical studies appears predictable and in line with what is expected after s.c. injections of a monoclonal antibody.

[redacted]

13.1.10 Can Effects be Managed?

No antidote is available. Treatment of adverse effect will be symptomatic, tailored to the nature of the events. Subjects with a history or known hypersensitivity or allergy are excluded from participation in the study. There is also immediate access to equipment, qualified staff and an intensive care unit in case of an acute emergency.

13.2 Synthesis

This is a First-in-Human trial with a First-in-Class novel investigational medicinal product. Given the available nonclinical safety data, the selected starting dose and the oversight of dose escalation steps by a Safety Review Committee and ethics committee, the overall risk assessments are acceptable in these populations of healthy volunteers and RA patients, given the dose and the close supervision during the study.

13.3 Category study

Conclusions	☑	Based on the risk analysis the study can be performed without additional conditions.
	☐	Based on the risk analysis the study can be performed with the following additional conditions:
	☐	Based on the risk analysis the study cannot be performed. The main issue is: