STUDY DRUG: SEL-212 (a combination of SEL-037 and SEL-110.36)
STUDY NUMBER: SEL-212/301
VERSION: 6.1
EFFECTIVE DATE: 15 December 2022

A RANDOMIZED DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF SEL-212 IN PATIENTS WITH GOUT REFRACTORY TO CONVENTIONAL THERAPY

Sponsor Selecta Biosciences
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Approvers:	**Signature:**	**Date:**
[redacted]		December 16, 2022
[redacted]		December 16, 2022

SELECTA BIOSCIENCES CLINICAL STUDY PROTOCOL

A RANDOMIZED DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF SEL-212 IN PATIENTS WITH GOUT REFRACTORY TO CONVENTIONAL THERAPY

STUDY NUMBER: SEL-212/301

CONTACT INFORMATION

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INVESTIGATOR'S AGREEMENT

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with applicable regulatory requirements, this protocol, any future amendments, and with any other study conduct procedures provided by Selecta Biosciences. (Sponsor).
- Not to implement any changes to the protocol without agreement from the Sponsor and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the patients, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the study drug(s), as described in this protocol, and any other information provided by the Sponsor including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, any IB supplement as applicable, or any approved product label as applicable.
- That I am aware of, and will comply with, "good clinical practices" (GCP) and all applicable regulatory requirements.
- That I will provide full and unencumbered access to source documents and medical records needed for the Sponsor, representatives of the Sponsor and regulatory authorities to verify source data and related documentation with respect to this trial.
- To ensure that all persons assisting me with the study are adequately informed about the Sponsor study drug(s) and of their study-related duties and functions as described in the protocol.
- That I have been informed that certain regulatory authorities require the Sponsor to obtain and supply, as necessary, details about the Investigator's ownership interest in the Sponsor or the study drug, and more generally about his/her financial ties with the Sponsor. The Sponsor will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply Selecta Biosciences with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children);
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study; and
- Agree that Selecta Biosciences may disclose any information it has about such ownership interests and financial ties to regulatory authorities.

Printed Name of Investigator

Signature of Investigator

Date

2. SYNOPSIS

Name of Sponsor/Company:

Selecta Biosciences

65 Grove Street

Watertown, MA 02472, USA

Name of Investigational Product:

SEL-212 (a combination of SEL-037 and SEL-110.36)

Name of Active Ingredient:

SEL-037 (pegadricase, recombinant pegylated *C. utilis* urate oxidase)

SEL-110.36 (a nanoparticle composed of PLA [poly{D,L-lactide}] and PLA-PEG [poly{D,L—lactide}-block-poly {ethylene-glycol}] encapsulating rapamycin)

Title of Study:

A Randomized Double-Blind, Placebo-controlled Study of SEL-212 in Patients with Gout Refractory to Conventional Therapy

Study Center(s): approximately 40 study centers (North America)

Studied Period:	**Phase of Development:**
24 months	Phase 3

Objectives:

Primary:

- To assess the reduction in serum uric acid (sUA) in patients with gout refractory to conventional treatment treated with two different dose levels of SEL-212 compared to placebo

Secondary:

- To compare the pharmacodynamic (PD) effect on sUA in patients with gout refractory to conventional treatment treated with two different dose levels of SEL-212 compared to placebo
- To assess change(s) of the following in patients with gout refractory to conventional treatment treated with two different dose levels of SEL-212 compared to placebo:
  - Tophus burden
  - Patient Reported Outcomes (PROs) including assessments of: patients' quality of life (QoL) (SF-36), activity limitation (HAQ-DI), and Provider Global Assessment of Disease Activity
  - Gout flares
  - Joint tenderness and swelling
- To assess effects on the formation of anti-uricase and anti-pegadricase antibodies

- To assess the safety and tolerability of SEL-212 compared to placebo
- To assess the reduction in serum uric acid (sUA) in patients with gout refractory to conventional treatment treated with two different dose levels of SEL-212 compared to placebo, amongst those with tophi at baseline

Exploratory:

- To assess the levels of uricase activity in patients receiving SEL-212 compared to placebo
- To assess the effect on monosodium urate crystal deposits and/or total body monosodium urate crystal deposits in patients with gout refractory to conventional treatment treated with two different dose levels of SEL-212 compared to placebo (imaging patients only)
- To assess the status of biomarkers related to inflammation and tolerogenic immunologic responses in patients with gout refractory to conventional treatment treated with two different dose levels of SEL-212 compared to placebo
- To assess the relationship between multiomic markers of gout and treatment effect in patients with gout refractory to conventional treatment treated with two different dose levels of SEL-212 compared to placebo
- To assess the impact on patient's self-assessment of gout flares and burden of disease using a validated patient diary (weekly) in patients treated with two different dose levels of SEL-212 compared to placebo
- To assess the correlation between immune tolerance related multiomic markers and anti-pegadricase antibody formation in patients treated with two different dose levels of SEL-212

Methodology:

This is one of two replicate randomized, double-blind, placebo-controlled, parallel arm trials to determine the safety and efficacy of two different dose levels of SEL-212 compared to placebo. The study will randomize approximately 120 patients with chronic refractory gout. Approximately 60% of the randomized patients will have tophi at Baseline. Patients, stratified as to the presence or absence of tophi, will be randomized in a 1:1:1 allocation ratio prior to Baseline to receive treatment with one of two dose levels of SEL-212 or placebo every 28 days for approximately 6 months in each trial (SEL-212/301 and SEL-212/302). These two trials will have identical designs with respect to being double-blinded, placebo-controlled as well as identical sample sizes, inclusion/exclusion criteria, efficacy/safety assessments and timing thereof, but will be distinguished by the blinded 6-month extension in SEL-212/301 and that SEL-212/302 will include sites outside of the United States. [redacted] Efficacy assessments will be conducted at intervals that are appropriate to determine treatment effect with samples for the primary endpoint drawn during Treatment Period 6. Samples will be collected at intervals that are appropriate to determine the uricase activity of SEL-212. Safety will be monitored throughout the study with an independent data safety monitoring board (DSMB). After successful completion of the double-blind treatment phase, patients successfully completing six months in SEL-212/301 will continue, in a blinded fashion, to be treated with the identical investigational treatment, (either one of two dose levels of SEL-212 or placebo) for 6 additional doses, every 28

days, lasting approximately 6 months. This will provide up to 12 months of continuous treatment with SEL-212 in a placebo-controlled fashion.

Screening Phase

After providing written informed consent, the patient is considered enrolled in the study. Patients will be evaluated for inclusion during the Screening Phase. For all patients, the standard Screening Phase will be up to 45 days prior to Baseline. The Screening Phase may be initiated by a preliminary screening with an abbreviated informed consent focused on COVID-19 testing and serum uric acid levels followed by providing study-wide informed consent and the remainder of screening assessments if determined to proceed. **Of note**, if the sUA level obtained during preliminary screening meets eligibility requirements (i.e., ≥ 7 mg/dL), the sUA should **not** be repeated during the subsequent complete screening assessment. Concurrently with the Screening Phase, a premedication period for potential gout flare with colchicine (or a non-steroidal anti-inflammatory drug [NSAID], if colchicine is contraindicated) of at least 7 days prior to Baseline will be required for all patients, and a washout period of at least 7 days will be required prior to Baseline for patients on any urate-lowering therapy (ULT). Both the ULT washout period and the gout flare prophylaxis period may be started earlier than 7 days prior to Baseline. At the discretion of the PI, chronic refractory gout patients whose sUA is lower than the eligibility level of ≥ 7 mg/dL on prescreening or initial screen, may undergo ULT washout prior to retesting the sUA. Initiation of gout flare prophylaxis with colchicine (or non-steroidal anti-inflammatory drug [NSAID], if colchicine is contraindicated) can also be considered coincidentally with the ULT washout to prevent a potential gout flare.

Double-Blind Treatment Phase

The total duration of the double-blind Treatment Phase will be approximately 6 months (i.e., 168 days, consisting of six 28-day treatment cycles).

Eligible patients, stratified according to the presence or absence of tophi, will be randomized in a 1:1:1 allocation ratio prior to Baseline to receive one of two dose levels of SEL-212 or placebo. The SEL-212 doses will differ as to the SEL-110.36 component. Participants will receive SEL-037 administered at a dose of 0.2 mg/kg via intravenous (IV) infusion immediately after receiving SEL-110.36 at a dose of either 0.1 mg/kg (SEL-212A) or 0.15 mg/kg (SEL-212B) via IV infusion. The placebo will consist of normal saline that will be administered in the same way that the SEL-212 components are administered to maintain the integrity of the study blind.

Patients will complete 6 treatment periods each having a duration of 28 days. Patients will receive treatment with study drug or placebo on Day 0 of each treatment period for a total of 6 doses. For each treatment cycle, patients will receive premedication to minimize the potential for infusion reactions during study drug administration. After completing the study drug infusions, patients will remain at the investigational site for 1 hour for safety assessments.

With each dose, a blood sample will be drawn for assessment of sUA level and uricase activity immediately prior to infusion (i.e., Time 0 h) with SEL-212 or placebo and 1 hour after the infusion of the second component of SEL-212 or of placebo is completed. Serum uric acid levels will be assessed through additional post-infusion blood samples at pre-determined time points by an independent, central, unblinded medical monitor.

Gout flares will be assessed at each study visit during the Treatment Phase using a validated definition of flares in patients with established gout (*Gaffo 2018*). In addition, in an exploratory manner, gout flares will be self-assessed by the patient weekly after randomization and in each Treatment Period using a weekly flare diary (*Poiley 2016*). Health Questionnaires, tophus burden, and joint swelling and tenderness will be assessed on Day 0 of Treatment Periods 1 and 4, and at the end of Treatment Period 6 or early termination (ET) if a patient discontinues the study prior to the end of 6 monthly infusions. Samples for anti-uricase, anti-PEG, and anti-pegadricase antibody levels will be taken (i) prior to administration of study drug dosing and at Day 21 for each of the six treatment periods throughout the trial, and (ii) at the end of Treatment Period 6, or at early termination (ET). Exploratory assessments of inflammatory/immunologic biomarkers and multiomic analysis will also be assessed.

Safety laboratory samples, consisting of, but not limited to, complete blood count (CBC) including white blood cell count (WBC) and absolute neutrophil count; liver function tests (LFTs) including aspartate aminotransferase (AST) and alanine transaminase (ALT),; serum lipids (including triglycerides and low density lipoprotein (LDL)); analyses of renal function including creatinine, urine-albumin-creatinine ratio (UACR), and estimated glomerular filtration rate (eGFR) will be collected on Day 0 and Day 21 of Treatment Period 1, on Day 21 only of each of Treatment Periods 2-5, and on Day 21 and Day 28 / ET of Treatment Period 6. On Treatment Period 1 Day 0, safety laboratory samples will be collected pre-infusion in both the SEL-212 arms and the placebo arm. Concomitant medications and procedures and adverse events (AEs) will be monitored continuously during the study. Post-Baseline chest X-rays (CXR) will be taken at six months and at one year / early termination to assess for presence of or changes in interstitial lung disease (ILD) compared to baseline CXR.

Follow-Up Phase

Patients will be followed for safety monitoring for 30 (+ 4) days after their final study drug infusion and will have an End of Study visit by telephone at the following times: either (1) at completion of the Extension Phase or (2) at early termination if the patient voluntarily withdraws consent. Patients who terminate the study prematurely will have all ET assessments performed. Patients who terminate the study prematurely who are unable to be on-site for the ET visit will be contacted by telephone for safety follow-up.

If withdrawn from study drug, the patient will continue study visits to the end of Treatment Period 12.

Double-Blind Extension Phase

Patients will enroll in a double-blind extension to begin after the conclusion of Treatment Period 6. Patients in any cohort who have met the stopping rule during the blinded treatment phase will continue study visits in the extension phase without study drug administration. All SEL-212 patients in the extension phase will receive up to an additional 6 monthly doses of SEL-212 at the same dose level as during the Treatment Phase for those that maintain Day 21 sUA <6 mg/dL. Patients who meet the stopping rule during the extension phase will be withdrawn from study drug and will continue study visits to the end of the extension phase.

Data and Safety Monitoring Committee (DSMB)

An independent Data and Safety Monitoring Board (DSMB) will be formed by charter to assist in reviewing safety data and may provide recommendations to the Sponsor regarding study drug dose adjustment or study termination.

Stopping Rules

A patient will be withdrawn from study drug for meeting the following stopping rule:

- sUA level < 2.0 mg/dL, measured 1 hour after the infusion of the second component of study drug is completed during Treatment Period 1

  AND

- sUA level > 1.0 mg/dL measured at the Day 21 visit of Treatment Period 1 or sUA level > 6.0 mg/dL at the Day 21 visit of any of Treatment Periods 2-11

Stopping rules will be assessed by an independent, central, unblinded medical monitor.

If withdrawn from study drug during the double-blind treatment period (Treatment Period 1 to 6) or the double-blind extension period (Treatment Period 7 to 12), regardless of reason, the patient will continue study visits to the end of Treatment Period 12. The window for all Day 21 visits is +2/-1 days.

If a Day 21 visit sUA value drawn within the protocol window is not available, but if a sUA value drawn at an unscheduled visit after the Day 21 window is available prior to dosing that is ≤ 1.0 mg/dL during Treatment Period 1 or ≤ 6.0 mg/dL during any of Treatment Periods 2-11, the patient will not be required to be withdrawn from study drug and will be eligible to receive their subsequent dose.

If 1) a Day 21 visit sUA value drawn within the protocol window is not available and no subsequent sUA results are available or 2) a Day 21 visit sUA value drawn within the protocol window is not available and a subsequent sUA drawn at an unscheduled visit after the Day 21 window is > 1.0 mg/dL during Treatment Period 1 or > 6.0 mg/dL during any of Treatment Periods 2-11, then the patient will be withdrawn from study drug based on the protocol deviation. If a protocol deviation occurs where a patient is not able to be dosed within the dosing day window (for example in the case of COVID-19 restrictions temporarily preventing dosing) the current treatment period will be extended up to a maximum of 90 days without skipping doses for patients with a Day 21 visit sUA value ≤ 1.0 mg/dL during Treatment Period 1 or ≤ 6.0 mg/dL during Treatment Periods 2-11 in the D21 visit window or subsequent up to the rescheduled dosing visit. If this protocol deviation occurs such that the patient was unable to be dosed within the dosing day window for the Treatment Period 7 Day 0 dose, then the Treatment Period 6 Day 28 visit should still occur 28 days (+3/-4 days) after the Treatment Period 6 dose or as close to the visit window as possible to collect the final primary endpoint SUA sample. In this specific instance, the dosing day Treatment Period 7 Day 0 should then occur as soon as possible afterward up to a maximum of 90 days from the preceding dose.

To maintain the blind, a central group of unblinded pre-specified medical personnel will adjudicate the implementation of the stopping rules.

If withdrawn from study drug, the patient will continue study visits to the end of Treatment Period 12. At the discretion of the Investigator, the patient will be permitted to return to ULT 60 days after

the patient's last study drug treatment. ULT shall not be SEL-212 or any experimental or marketed uricase (e.g., rasburicase (Elitek, Fasturtec), pegloticase (Krystexxa®)), for the remainder of the study.

Number of Patients (Planned):

- Planned Enrollment: Approximately 120 patients randomized (total):
  - SEL-212A: approximately 40 patients
  - SEL-212B: approximately 40 patients
  - Placebo: approximately 40 patients

Approximately 60% of the randomized patients will have tophi at Baseline

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

A patient must meet all the following criteria to be eligible for this study:

1. Has provided written informed consent prior to the conduct of any study specific procedures;
2. Understands and is willing and able to comply with study requirements, including the schedule of follow-up visits;
3. Has negative results of an FDA Emergency Use Authorized COVID-19 molecular assay for detection of SARS-CoV-2 RNA from a nasal or oropharyngeal specimen;
4. Has a history of symptomatic gout defined as:
   - ≥ 3 gout flares within 18 months of Screening or
   - Presence of ≥ 1 gout tophus or
   - Current diagnosis of gouty arthritis
5. At the Screening Visit male age 19 – 80 years, inclusive or female of non-childbearing potential age 19-80 years, inclusive, where non-childbearing potential is defined as:
   - > 6 weeks after hysterectomy with or without surgical bilateral salpingo-oophorectomy or
   - Post-menopausal (> 24 months of natural amenorrhea or in the absence of >24 months of amenorrhea, one documented confirmatory FSH measurement)
6. Has chronic refractory gout defined as having failed to normalize sUA and whose signs and symptoms are inadequately controlled with any of the xanthine oxidase inhibitors, either allopurinol and/or febuxostat at the medically appropriate dose, or for whom these drugs are contraindicated for the patient;
7. Has at Screening sUA ≥ 7 mg/dL
8. Has not participated in a clinical trial within 30 days of the Screening Visit and agrees to not participate in a clinical trial for the duration of the study;
9. Negative serology for HIV-1/-2 and negative antigen to hepatitis B and negative antibodies to hepatitis C.

Exclusion Criteria:

A patient who meets any of the following criteria will be excluded from this study:

1. Has a history of anaphylaxis, severe allergic reactions, or severe atopy;
2. Has a history of any allergy to pegylated products, including, but not limited to pegloticase (Krystexxa®), peginterferon alfa-2a (Pegasys®), peginterferon alfa-2b (PegIntron®), pegfilgrastim (Neulasta®), pegaptanib (Macugen®), pegaspargase (Oncaspar®), pegademase (Adagen®), peg-epoetin beta (Mircera®), pegvisomant (Somavert®) certolizumab pegol (Cimzia®), naloxegol (Movantik®), peginesatide (Omontys®), and doxorubicin liposome (Doxil®);
3. Is taking and cannot discontinue known major CYP3A4/P-gp inhibitors or major CYP3A4/P-gp inducers at least 14 days before dosing. Patients must remain off these medications for the duration of the study, including natural products such as St. John's Wort or grapefruit juice.
4. Is taking drugs known to interact with rapamycin (sirolimus - Rapamune®) such as cyclosporine, diltiazem, erythromycin, ketoconazole, posaconazole, voriconazole, itraconazole, rifampin, verapamil unless they are stopped 14 days prior to dosing and will not be used/prescribed during the trial.
5. Had major surgery within 3 months of initial screening.
6. Had a gout flare during Screening that was resolved for less than 1 week prior to first treatment with study drug (exclusive of chronic synovitis/arthritis) unless the patient has a history of inter-flare intervals of < 1 week.
7. Has uncontrolled diabetes at Screening with HbA1c ≥ 8.5%;
8. Has fasting Screening glucose > 240 mg/dL
9. Has fasting Screening triglyceride > 500 mg/dL;
10. Has fasting Screening low-density lipoprotein (LDL) > 200 mg/dL;
11. Has glucose-6-phosphate dehydrogenase (G6PD) deficiency;
12. Has uncontrolled hypertension defined as blood pressure > 170/100 mmHg at Screening and 1 week prior to dosing
13. Individual laboratory values which are exclusionary
    - White blood cell count (WBC) < 3.0 x10^9/L
    - Serum aspartate aminotransferase (AST) or alanine amino transferase (ALT) > 3x upper limit of normal (ULN) in the absence of known active liver disease
    - Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2
    - Urine-albumin-creatinine ratio (UACR) > 30 mg/g creatinine (conventional units) or > 3.39 mg/mmol creatinine (SI units)
    - Hemoglobin (Hgb) < 9 g/dL
    - Serum phosphate < 2.0 mg/dL
14. Is receiving ongoing treatment for arrhythmia, including placement of an implantable defibrillator, unless considered stable and on active treatment;
15. Has evidence of unstable cardiovascular disease or unstable cerebrovascular disease. This includes patients who have had a cardiac/vascular event(s) in the last 3 months including heart attack, stroke or vascular bypass surgery or patients who are deemed, by their

physician or PI, to have active cardiovascular, cerebrovascular or peripheral vascular symptoms/disease inadequately controlled by medication;

16. Has congestive heart failure, New York Heart Association Class III or IV;
17. Unless clinically stable and/or appropriately treated, electrocardiogram (ECG) with evidence of clinically significant arrhythmia or other abnormalities that, in the opinion of the investigator, are consistent with significant underlying cardiac disease;
18. History of significant hematological disorders within 5 years or autoimmune disorders, and/or patient is currently immunosuppressed or immunocompromised;
19. Prior exposure to any experimental or marketed uricase (e.g., rasburicase (Elitek, Fasturtec), pegloticase (Krystexxa®®), pegadricase (SEL-037))
20. Patient has received a live vaccine in the previous 6 months.
21. Patient is planning to receive any live vaccine during the study. Of note, inactivated vaccines are permitted but, study drug may affect response to vaccination; therefore, during study drug treatment, vaccination with inactivated vaccines may be less effective. Consider high-dose influenza vaccine to increase the likelihood of developing a protective immune response.
22. History of malignancy within the last 5 years other than basal skin cancer;
23. Any condition, that in the opinion of the investigator, would be negatively affected by rapamycin.
24. Patients with a documented history of moderate or severe alcohol or substance use disorder within the 12 months prior to randomization.
25. History of or evidence of clinically severe interstitial lung disease
26. Immunocompromised state, regardless of etiology
27. Patients who, in the opinion of the investigator, present with a condition that would compromise their safety or that would make study completion unlikely

Investigational Product and Placebo, Dosage and Mode of Administration:

Investigational Product

- SEL-212 is comprised of 2 components: SEL-110.36 and SEL-037
- SEL-110.36: nanoparticle composed of PLA and PLA-PEG encapsulating rapamycin.
- SEL-037: pegadricase, a recombinant pegylated *C. utilis* urate oxidase.

Dosage of Investigational Product

SEL-212A:

- SEL-110.36: 0.1 mg/kg based on patient's body weight
- SEL-037: 0.2 mg/kg based on patient's body weight

SEL-212B:

- SEL-110.36: 0.15 mg/kg based on patient's body weight
- SEL-037: 0.2 mg/kg based on patient's body weight

Mode of Administration

- Gout flare prophylaxis
  - Colchicine 0.6 mg oral (PO) every day starting at least 7 days prior to Day 0
    - Patients not already taking colchicine will receive colchicine 1.2 mg as a single loading dose followed by 0.6 mg daily as tolerated. If the patient cannot tolerate the loading dose level of 1.2 mg, then the patient will initiate and maintain colchicine at 0.6 mg per day. If the patient cannot tolerate the loading dose level of 0.6 mg, then the patient will initiate and maintain colchicine at 0.3 mg per day.
- Premedication (prior to study drug administration on Day 0 of each treatment period)
  - Prednisone (40 mg) oral (PO) approximately 24 (± 12) hours prior to dosing
  - Fexofenadine 180 mg oral (PO) approximately 12 (± 2) hours prior to dosing
  - Fexofenadine 180 mg oral (PO) approximately 2 (± 1) hours prior to dosing
  - Methylprednisolone 100 mg (or equivalent) up to 125 mg, depending on patient weight, IV approximately 1 (± 0.5) hours prior to dosing
- SEL-110.36
  - Blinded IV infusion with a syringe infusion pump at steady rate of 1.5 mL/hr for the first 30 minutes, then a rate adequate to deliver the remaining dose volume over a period of 60 minutes concurrently with normal saline. If an infusion reaction occurs during the administration of SEL-110.36, the infusion may be slowed, or stopped and then restarted at a slower rate at the discretion of the Investigator.
- SEL-037
  - Blinded administration up to 30 minutes after completion of the SEL-110.36 infusion.
  - Blinded administration via infusion pump over no less than 120 minutes. If an infusion reaction occurs during the administration of SEL-037, the infusion may be slowed, or stopped and then restarted at a slower rate at the discretion of the Investigator.

Placebo

Placebo will consist of normal saline. Normal saline will be administered sequentially in the same way that the SEL-212B components are administered to maintain the integrity of the study blind. All premedications will be given prior to placebo as well, to maintain the blind.

Duration of Treatment:

All patients are planned to receive study drug during a 168-day double-blind treatment phase consisting of six 28-day treatment cycles followed by a 168-day double-blind extension phase consisting of six 28-day treatment cycles. In total, patients are planned to receive approximately 12 months of treatment. Patients will receive study drug on Day 0 of each treatment period.

The total duration of participation in the study will range from approximately 50 to 55 weeks (352 to 383 days) as follows:

- Screening and/or washout and premedication period: up to 45 days (up to 6.5 weeks)
- Treatment Phase: 168 days (24 weeks)
- Extension Phase: 168 days (24 weeks)

- Safety Follow-Up: 30 days after last infusion

Criteria for Evaluation:

Efficacy:

The confirmatory analysis of efficacy will be performed at Day 28 of Treatment Period 6. Efficacy assessments performed in the extension phase of the study (Treatment Period 7 to Treatment Period 12) will be summarized using descriptive statistics by treatment group only.

Primary Efficacy Endpoint:

Each of the two active treatment groups, SEL-212A and SEL-212B, are compared to placebo with regards to the following primary efficacy endpoint:

- The percentage of patients who achieve and maintain reduction of sUA < 6 mg/dL for at least 80% of the time during Treatment Period 6 by Day 28

The main estimand for the primary efficacy endpoint considers, for the comparison between each SEL-212 treatment group versus placebo, the difference in the percentage of treatment responders whereby a responder is defined as a subject who has sUA < 6 mg/dL for at least 80% of the time during Treatment Period 6. For this primary estimand, intercurrent events which lead to a discontinuation of study treatment due to lack of efficacy (includes meeting the stopping criteria), treatment-related or non-treatment related AE, patients with a positive COVID-19 test result along with severe or critical symptoms of COVID-19, used a prohibited medication that significantly lowers sUA, or death will be considered as treatment failures following the composite strategy, for all other intercurrent events such as use of a prohibited medication that does not lower sUA, the treatment-policy strategy will be used.

Key Secondary Efficacy Endpoints:

Each of the two active treatment groups, SEL-212A and SEL-212B, are compared to placebo with regards to the following key secondary efficacy endpoints. Respective estimands of interest are defined.

- Reduction of mean sUA as computed by subtracting the Baseline sUA level from the mean sUA (area under the sUA time curve) during Treatment Period 6
- Percent reduction of mean sUA as computed by subtracting the Baseline sUA level from the mean sUA (area under the sUA time curve) during Treatment Period 6
- The change from Baseline to Day 28 of Treatment Period 6 in the physical summary score of the Short Form Health Survey (SF-36)
- In patients with tophi at Baseline, the percentage of patients with at least partial response (PR) (as best response) in overall tophus response evaluation until Day 28 of Treatment Period 6
- The percentage of patients who achieve and maintain reduction of sUA < 6 mg/dL for at least 80% of the time during Treatment Period 6 in subset of patients with tophi at baseline
- The change from Baseline to Day 28 of Treatment Period 6 in the number of tender joints

- The change from Baseline to Day 28 of Treatment Period 6 in the total score of the Health Assessment Questionnaire (HAQ-DI)
- Gout flare incidence during Treatment Periods 1-6
- Gout flare incidence during Treatment Periods 1-3

Additional Secondary Efficacy Endpoints:

Each of the two active treatment groups, SEL-212A and SEL-212B, are compared to placebo with regards to the following additional secondary efficacy endpoints:

- The percentage of patients who achieve and maintain reduction of sUA < 6 mg/dL for 100% of the time during Treatment Period 6
- Percentage of pre-dose sUA values < 6 mg/dL during Treatment Periods 2-6 for each patient
- Pre-treatment anti-pegadricase and anti-uricase antibody formation and levels in each treatment period in the SEL-212 active treatment arms during Treatment Periods 1-6
- The percentage of patients with development of new tophi in the subgroups of tophaceous patients and in non-tophaceous patients at Baseline during Treatment Periods 1-6
- In patients with tophi at Baseline, the percentage of patients with at least PR (as best response) in overall tophus response evaluation until Day 0 of Treatment Period 4
- Change from Baseline to Day 28 of Treatment Period 6 in subscales of Health Assessment Questionnaire (HAQ-DI), in Provider Global Assessment of Disease Activity, and in subscales of Short Form Health Survey (SF-36)
- The percentage of patients with at least 1 gout flare during Treatment Periods 1-3
- The percentage of patients with at least 1 gout flare during Treatment Periods 1-6
- Change from Baseline to Treatment Period 6 in number of swollen joints
- Length of time patients are anti-uricase antibody free or before induction of anti-uricase antibody levels above baseline in patients receiving SEL-212
- Length of time patients are anti-pegadricase antibody free or before induction of anti-pegadricase antibody levels above baseline in patients receiving SEL-212

Exploratory Endpoints for the Double-Blind Treatment Phase:

The exploratory endpoints of the double-blind Treatment Period of this study are:

- Levels of uricase activity in patients receiving SEL-212
- Levels of monosodium urate crystal deposits and/or total body monosodium urate crystal deposits (imaging patients only)
- Levels of inflammatory and tolerogenic biomarkers
- Changes in antibody production (anti-uricase and anti-pegadricase) in patients in the SEL-212 group
- Gout flare incidence during Treatment Periods 4-6

- Gout flare incidence during Treatment Periods 1-3 based on self-reported weekly gout flare diary
- Gout flare incidence during Treatment Periods 1-6 based on self-reported weekly gout flare diary
- Gout flare incidence during Treatment Periods 4-6 based on self-reported weekly gout flare diary
- Assessment of association between multiomic markers of gout and treatment effect in patients treated with SEL-212
- Comparison of immune tolerance related multiomic markers in patients on SEL-212 who developed anti-uricase and anti-pegadricase antibodies vs. those patients on SEL-212 that did not develop anti-uricase and anti-pegadricase antibodies

Exploratory Endpoints for the Double-Blind Extension Phase:

The exploratory endpoints of the double-blind Extension Period of this study are:

- The change from Baseline to each Treatment Period (7-12) in the extension phase of sUA level
- The change from Baseline to each Treatment Period (7-12) in the extension phase in number of tender joints and number of swollen joints
- In patients with tophi at Baseline, the percentage of patients with at least PR (as best response) in overall tophus response evaluation in each Treatment Period (7-12) in the extension phase
- The change from Baseline to each Treatment Period (7-12) in the extension phase in the total score and in subscales of the Health Assessment Questionnaire (HAQ-DI)
- The change from Baseline to each Treatment Period (7-12) in the extension phase in the summary scores and in subscales of the Short Form Health Survey (SF-36)
- Gout flare incidence in Treatment Periods 1-9 and in Treatment Periods 1-12 and percentage of patients with at least one gout flare in Treatment Periods 1-9 and in Treatment Periods 1-12 in the extension phase in the subgroup of patients continued into extension phase
- Number of pre-dose sUA values < 6 mg/dL for each patient stratified by cumulative number of Treatment Periods 7-12 for the subgroup of patients continued into extension phase
- Pre-treatment anti-pegadricase and anti-uricase antibody formation and levels for each treatment period during extension phase in the SEL-212 active treatment arms
- Percentage of patients with development of new tophi in each Treatment Period (7-12) in the extension phase in the subgroups of tophaceous patients and in non tophaceous patients at study baseline (Day 0 Treatment Period 1) and at baseline of extension phase (Day 0 Treatment Period 7)
- Change from baseline to each Treatment Period (7-12) in the extension phase in Provider Global Assessment of Disease Activity

- Length of time patients are anti-uricase antibody free or before induction of anti-uricase antibody levels above baseline in patients receiving SEL-212 in the subgroup of patients continued into extension phase
- Length of time patients are anti-pegadricase antibody free or before induction of anti-pegadricase antibody levels above baseline in patients receiving SEL-212 during extension phase
- Levels of uricase activity in patients receiving SEL-212 during extension phase
- Levels of monosodium urate crystal deposits and/or total body monosodium urate crystal deposits (imaging patients only) during extension phase
- Levels of inflammatory and tolerogenic biomarkers during extension phase
- Changes in antibody production (anti-uricase and anti-pegadricase) in patients in the SEL-212 groups during extension phase
- Assessment of association between multiomic markers of gout and treatment effect in patients treated with SEL-212 during extension phase
- Immune tolerance related multiomic markers in patients on SEL-212 who developed anti-uricase and anti-pegadricase antibodies vs. those patients on SEL-212 that did not develop anti-uricase and anti-pegadricase antibodies

Safety:

Safety Endpoints:

- Safety and tolerability of SEL-212 compared to placebo as assessed by AEs, adverse events of special interest (AESI), serious AEs (SAEs), deaths, and discontinuations due to AEs
- Additional safety assessments will include review and evaluation of laboratory testing including hematology, coagulation, chemistry, urinalysis; eGFR, UACR, vital signs; immunogenicity analyses; 12-lead ECGs; and physical examination findings.

Statistical Methods

Details of the statistical methods outlined in the protocol for this study will be documented in a Statistical Analysis Plan (SAP), which will be finalized prior to database lock. The SAP may add additional exploratory analyses; modifications to the planned analyses will be identified as such in the final SAP.

Analysis Populations

- Screened / Randomized Set: The Screened Set will include all patients who signed an informed consent. The Randomized Set will include all patients randomized and will be used for the presentation in all patient listings. Randomized but not treated patients will be replaced.
- Safety Set (SS): The Safety Set will include all patients who were administered any amount of study drug. Patients will be analyzed according to treatment received. The SS will be used for all analyses of safety endpoints.
- Intent-to-Treat (ITT) Set: The Intent-to-Treat (ITT) Set will include all randomized and treated patients. Patients will be analyzed according to randomized treatment group assignment. The ITT will be used as primary population for analyses of efficacy endpoints.

- Modified ITT: The modified ITT will include all randomized patients who were dosed, except those who discontinue treatment due to a COVID-19 infection as defined in section 12.1.8.7 or do not have at least two sUA measurements 7 days apart in TP6 due to a/multiple missed visits due to a COVID-19 infection or subsequent complications as defined in section 12.1.8.7. Patients will be analyzed according to randomized treatment.
- Per Protocol Set: The Per Protocol Set (PPS) will include all patients who were administered at least one complete dose of study drug, who have at least one post-baseline assessment of sUA, who have sufficient data to assess the primary efficacy endpoint, and who have no major Protocol deviations affecting the primary efficacy assessments. Patients will be analyzed according to randomized treatment. The PPS will be defined for the double-blind treatment phase of the study only. Criteria for exclusion from the PPS will be provided in the Statistical Analysis Plan.
- All Randomized Set: The all randomized set will include all patients who were randomized. Patients will be analyzed according to randomized treatment group assignment.
- The Extension Phase Evaluable Set (EPS) will include all subjects of the safety set who continue in the double-blind extension phase.

Efficacy Analyses

Only efficacy endpoints of the double-blind treatment phase will be tested in a confirmatory way. Estimands are defined for the confirmatory analysis of efficacy in the double-blind treatment period. Most of the efficacy endpoints continue to be assessed in the double-blind extension period, also. However, only descriptive summaries and comparisons will be provided for the extension period.

Primary Efficacy Analysis

The primary efficacy endpoint is the percentage of patients in each of the SEL-212 dose groups versus placebo who achieve and maintain reduction of sUA < 6 mg/dL for at least 80% of the time during Treatment Period 6.

The main estimand for the primary efficacy endpoint will consider a binary variable indicating the treatment response when having completed 6 cycles of study treatment, whereby a responder is defined as a subject who has sUA < 6 mg/dL for at least 80% of the time during Treatment Period 6. For this primary estimand, intercurrent events which lead to a discontinuation of study treatment due to lack of efficacy (includes meeting the stopping criteria), treatment-related or non-treatment related AE, patients with a positive COVID-19 test result along with severe or critical symptoms of COVID-19, used a prohibited medication that lowers sUA, or death will be considered as treatment failures following the composite strategy, for all other intercurrent events such as use of a prohibited medication that does not lower sUA, the treatment-policy strategy will be used. The population-level summary is defined as the difference in the percentage of treatment responders of each SEL-212 treatment group versus placebo. Missing response will be multiple imputed. The statistical testing of each SEL-212 treatment group versus placebo will be performed using the Mantel-Haenszel (MH) estimate and test for common risk difference considering the randomization stratum of tophus presence (yes/no) with a two-sided type 1 error rate $\alpha = 2.5\%$ to adjust for the two comparisons against placebo.

Further estimands will be defined in the SAP. However, only the test results of the main estimand will be considered as confirmatory. Sensitivity analysis will be performed using the tipping-point analysis.

The analysis of the estimands will be carried out based on the ITT population primarily. Supportive analyses will be performed on the mITT, all randomized and the PP populations.

The sUA time curve will be used to estimate the proportion of time that the sUA level is below 6 mg/dL. Based on the serum samples collected during Treatment Period 6, an estimate of the time with sUA < 6 mg/dL can be determined by connecting each two neighboring data points with a straight line. If the sUA time curve goes above 6 mg/dL the linear interpolation method will be used to estimate the point in time at which the sUA time curve intercepts the line between the last sUA value < 6 mg/dL and the first value ≥ 6 mg/dL. The proportion of time that the sUA level is < 6 mg/dL will be computed by taking the ratio between the time during which the sUA level remains < 6 mg/dL (if necessary, using the linear interpolation method) and the entire time interval within Treatment Period 6. For a patient to be considered a responder in Treatment Period 6, the proportion of time that the sUA level is < 6 mg/dL (i.e., percentage of nonhyperuricemic time) during Treatment Period 6 must be at least 80%. A frequency table of the percentage of responder will be provided by treatment group.

Additionally, a summary table with the total time a patient has sUA values ≤ 6 mg/dL in Treatment Period 6 will be provided by treatment group.

Summary table of the actual values and change from Baseline for sUA results will be provided for each scheduled sampling time point by treatment group. Additionally, mean sUA level, reduction in mean sUA and percent reduction in mean sUA from Baseline during Treatment Period 6 will be presented by treatment group.

- Mean sUA level is defined as the area under the sUA time curve (computed using the linear trapezoidal rule during Treatment Period 6) divided by the corresponding time interval.
- Reduction in mean sUA is computed by subtracting Baseline sUA level from mean sUA during Treatment Period 6.
- Percent reduction in the mean sUA from Baseline is computed as the mean sUA level during Treatment Period 6 minus Baseline sUA level divided by Baseline sUA level multiplied by 100%

Key Secondary Efficacy Analysis

If the superiority of both (one) SEL-212 treatment group(s) against placebo for the main estimand of the primary efficacy is shown with a p-value ≤ 0.025, the hierarchical testing approach will continue to the testing of the main estimands of the key secondary efficacy comparing pairwise both (one) SEL-212 treatments against placebo. Only the main estimands of the key secondary efficacy will be tested in the successive order. The test result of the nth key secondary efficacy estimand will be considered as confirmatory if the p-value of the two-sided test of the previous estimand resulted in a value less or equal 0.025.

Most main estimands with a continuous or numerical endpoint will be tested between each SEL-212 treatment group versus placebo using the mixed model for repeated measures (MMRM) with the change from baseline in the respective variable as dependent variable, and treatment, treatment-by-period interaction, randomization stratum and baseline value of the respective variable as fixed effect variables. The Least Square (LS) Mean difference between each SEL-212 and placebo treatments groups will be estimated on the treatment-by-period interaction with Treatment Period 6, along with its 97.5% confidence interval, and 2-sided p-values.

The main estimands defined for binary or response variables will be tested between each SEL-212 treatment group versus placebo using the Mantel-Haenszel (MH) estimate and test for common risk

difference considering the randomization stratum of tophus presence (yes/no) or Chi-square test with continuity correction (when comparing the subgroup of patients with tophus at Baseline), as appropriate. The difference of proportions between each SEL-212 and placebo treatments groups will be presented along with its 97.5% confidence interval, and 2-sided p-values.

Descriptive summaries will be provided for all endpoints by treatment group and period, if appropriate.

Further Secondary Efficacy Endpoints and Analyses (During the Double-Blind Treatment Period)

Additional secondary efficacy endpoints will be summarized by treatment group using descriptive statistics for the ITT population and will be compared between each SEL-212 treatment group and placebo using MH or Chi-square tests, as appropriate, in case of binary endpoints or using ANCOVA or MMRM, as appropriate, in case of continuous or numerical endpoints. Exploratory p-values of two-sided tests with 95% confidence intervals for treatment differences between each SEL-212 treatment group and placebo will be presented.

Safety Analyses

Safety summaries will be presented for the double-blind treatment phase considering all dosed patients (Safety Set) and for the subgroup of patients in the double-blind extension phase (Extension Phase Evaluable Set).

All AEs will be coded and grouped into Preferred Terms (PT) by System Organ Class (SOC), using the most recent MedDRA Version. All AEs will be summarized by SOC and PT. Summaries by each treatment group for the whole study as well as separately for the double-blind treatment phase and extension phase will be provided overall and by SOC and PT with the number and percentage of patients reporting TEAEs, serious TEAEs, AESIs, treatment-related TEAEs, TEAEs leading to withdrawal and TEAEs leading to death. TEAEs will also be summarized by maximum intensity and relationship to study drug. Event rates by treatment group and overall will be provided for patients with at least one related TEAE, at least one SAE, and at least one TEAE of special interest. Additionally, the rate difference with 95% confidence interval comparing each SEL-212 treatment group to placebo as well as comparing the integrated SEL-212 arms to placebo will be provided.

Laboratory data will be summarized by the type of laboratory test and will be presented for each scheduled visit stratified by treatment group and overall. Shift tables of the number of patients with low/normal/high (or abnormal/normal) values at each scheduled post-baseline visit compared to the low/normal/high (or abnormal/normal) categorization at Baseline will be provided by treatment group, and overall. Summary tables of actual values and changes from Baseline will be provided for each continuous laboratory parameter at each scheduled visit by treatment group and overall.

Summary tables of the actual values and changes from Baseline will be provided for each vital sign parameter at each scheduled visit by treatment group, and overall.

For each 12-lead ECG variable the actual value and the change from Baseline will be summarized for the scheduled visits by treatment group, and overall. A shift table of the number and percentage of subjects with normal and abnormal, and clinically significant abnormal values at each scheduled post-baseline visit compared to respective categorization at baseline will be provided by treatment group for the overall ECG interpretation.

Frequency tables of abnormal clinically significant evaluations as well as the number and percentage of patients with noteworthy QTcF/QTcB values (> 450, > 480 and > 500 ms) and of patients with noteworthy QTcF/QTcB changes from baseline (≥ 30 but <60; ≥ 60 ms) will be provided.

Sample Size Determination

The primary efficacy criterion in this study is defined as the rate of the patients who achieve and maintain reduction of sUA < 6 mg/dL for at least 80% of the time during Treatment Period 6. The responder rate for the primary estimand in all randomized and dosed patients is assumed to be 45% in SEL-212 and 5% in placebo. Considering a randomization ratio of 1:1:1 for SEL-212A and SEL-212B against placebo, a statistical power of 90%, a two-sided alpha-level of 2.5% in each pairwise test against placebo, and using the Chi-square test with continuity correction, 32:32:32 randomized and dosed patients will be required for the following groups: SEL-212A, SEL-212B, and placebo. Considering the potential that some randomized patients will terminate early (approx. 8%), the number of the patients required to be randomized (and not replaced) in total was 105 (i.e.,35:35:35) to demonstrate efficacy. The randomized but not dosed patients will be replaced.

An additional 15 patients have been added to the study sample size to account for potential treatment discontinuations that may occur due to the ongoing COVID-19 pandemic as a result of the emergence of COVID-19 variants which were not accounted for in the sample size calculations resulting in approximately 120 patients (i.e., 40:40:40) to be randomized and dosed to demonstrate efficacy.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Definition or Explanation
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
cm	centimeter
COVID-19	SARS-CoV-2 corona virus infection
CR	Complete Response
CRF	case report form
CRO	contract research organization
CT	computed tomography
CXR	chest x-ray
CYP3A4	Cytochrome P450, family 3, subfamily A
d	day
dL	deciliter
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EOS	End-of-Study
EPS	Extension Phase Evaluable Set
ET	Early Termination
FAAN	Food Allergy & Anaphylaxis Network
FAS	Full Analysis Set
FSH	Follicle Stimulating Hormone
G6PD	glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
GFR	glomerular filtration rate
h	hour
HAQ-DI	Health Assessment Questionnaire-Disability Index
HbA1c	hemoglobin A1c

Abbreviation or Specialist Term	Definition or Explanation
HBsAg	hepatitis-B surface antigen
hCG	human chorionic gonadotropin
Hct	hematocrit
HCVAb	hepatitis-C antibody
HDL	high density lipoprotein
Hgb	hemoglobin
HIV	human immunodeficiency virus
I	Improved
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
ITT	Intent to Treat
IUD	intrauterine device
IUS	intrauterine hormone releasing system
IV	intravenous
kg	kilogram
LDL	low-density lipoprotein
mg	milligram
MH	Mantel-Haenszel
mmHg	millimeters of mercury
MMRM	mixed model for repeated measures
MR	Marked Response
ms	millisecond
mTOR	mammalian target of rapamycin
NIAID	National Institute of Allergy and Infectious Diseases
NSAID	non-steroidal anti-inflammatory drug
PD	pharmacodynamics
PD	Progressive Disease
PEG	polyethylene glycol
PLA	poly [D,L-lactide]
Plt	platelet
PPS	Per Protocol Set
PR	Partial Response
PrGA	Provider Global Assessment of Disease Activity

Abbreviation or Specialist Term	Definition or Explanation
PT	Preferred Term
PT	prothrombin time
QD	once daily
RA	rheumatoid arthritis
RBC	red blood cell
RCTC	Rheumatology Common Toxicity Criteria
SAE	serious adverse event
SAP	statistical analysis plan
Scr	Screening Phase
SD	Stable Disease
SF-36	Short Form Health Survey
SOC	System Organ Class
SS	Safety Set
sUA	serum uric acid
TEAE	treatment-emergent adverse event
TID	three times daily
UACR	urine-albumin-creatinine ratio
UE	Unable to Evaluate
ULN	upper limit of normal
ULT	urate lowering therapy
US FDA	United States Food and Drug Administration
USP	United States Pharmacopeia
WBC	white blood cell

5. INTRODUCTION

5.1 Gout and Refractory Gout

Gout is a chronic inflammatory condition with intermittent episodes of acute inflammatory arthritis characterized by elevated uric acid levels and caused by the formation of urate crystals in joint fluid leading to intensely painful joint inflammation. Chronic hyperuricemia leads to further deposition of uric acid in soft tissues resulting in destructive arthritis and formation of tophi and renal calculi (*Choi 2005, So 2008, Wortmann 2008*). Gout is a common disease with increasing incidence, driven mainly by an aging population, with some contribution from the increasing prevalence of obesity and the use of diuretics (*Choi 2006, Luk 2005*).

The incidence of gout increases as circulating uric acid levels increase (*Campion 1987*) and lowering circulating urate levels is a primary means of managing gout. The American College of Rheumatology guidelines recommend lowering uric acid level to at least below 6 mg/dL and preferably below 5 mg/dL (*Khanna 2012a, Khanna 2012b*).

The progression of gout is believed to have 4 pathophysiological stages (*Dalbeth 2011*):

1. Hyperuricemia without monosodium urate crystal deposition or gout
2. Crystal deposition without symptomatic gout
3. Crystal deposition with acute gout flares
4. Advanced or severe gout, characterized by tophi, chronic gouty arthritis, and radiographic erosions

Refractory gout is a serious condition affecting approximately 160,000 patients in the United States and is characterized by uric acid levels that are not adequately controlled by conventional therapies.

5.2 Symptoms of Gout

The symptoms and clinical signs of gout have a broad spectrum of severity. Most symptoms present as intermittent attacks or flares while others present as more severe, refractory disease have monosodium urate crystal deposition with a constellation of severe manifestations including gout flares, multiple joints with chronic gouty arthritis and subcutaneous tophus (*Bursill 2019*). In tophaceous gout, tophi commonly develop in the fingers, hands, and feet around the olecranon, and under the skin on the ears, but may also develop in other tissues and organs such as the kidneys and heart valves (*Ryan 2016*). Pro-inflammatory cytokines and white cell debris are usually present in tophi, which suggest a state of chronic monosodium urate-crystal-stimulated inflammation (*Dalbeth 2010*). These tophi can erupt through the skin, become inflamed and painful, and discharge urate crystals and eventually may cause deformities and secondary osteoarthritis (*Ryan 2016*). They can infiltrate into the bone, causing bone erosion and joint damage (*Dalbeth 2008*). Additional complications include obstruction of the joint and infection as well as urolithiasis with uric acid stones or calcium oxalate stones (*Ryan 2016*). Tophaceous gout is associated with more frequent flares, which may be so painful and debilitating that they lead to joint replacement or surgical excision. Over time, flares become polyarticular, additive, and increase in severity (*Brook 2010*).

5.3 Gout and Hyperuricemia: Exacerbation of Existing Comorbidities

The effect of chronic, severe, refractory gout on quality of life is more pronounced in patients with medical comorbidities as these complicate the therapeutic management of their symptoms and increase their risk of cardiovascular events and all-cause mortality. It is also well-documented that the presence of these comorbidities has a significant impact on patients' physical functioning, healthcare utilization, and quality of life (*Khanna 2012a*).

Chronic, uncontrolled gout and hyperuricemia are associated with metabolic disorders, type 2 diabetes, hypertension, and renal and cardiovascular diseases (*Strand 2012*; *Becker 2009*; *Chandratre 2013*). There is strong evidence that shows hyperuricemia contributes to worse outcomes under these conditions, and there is increasing mechanistic, epidemiological, and clinical data to indicate that elevated serum uric acid (sUA) levels can exacerbate and contribute to the progression of comorbidities (*Rock 2013*; *Mallamaci 2015*).

Data from 5707 patients in the National Health and Nutrition Examination Survey (NHANES) were obtained from 2007-2008, and prevalence of major gout comorbidities were correlated with hyperuricemia levels (*Zhu 2012*). This analysis revealed the presence of hypertension, chronic kidney disease, obesity, diabetes, nephrolithiasis, myocardial infarction, heart failure, and stroke was substantially higher in individuals with gout compared to those without gout. Furthermore, the prevalence of these comorbidities increased proportionally to the level of hyperuricemia, with the incidence of comorbidities being highest among individuals with both gout and hyperuricemia.

5.4 Impact on Quality of Life

One longitudinal study in this patient population reports that approximately 70% of patients with chronic refractory gout have at least 1 tophus and an average of 7 flares per year. In a separate study of chronic refractory gout, patients self-reported more than 60% of these flares as crippling (*Brook 2010*). Symptoms of pain, limited mobility, and disability are debilitating and deeply affect physical function and emotional and social functioning, and disease severity correlates with a marked compromise in quality of life (*Strand 2012, Becker 2009*).

The relationship between self-reported quality of life and disability and disease severity have been evaluated in multiple clinical studies. Over 100 subjects with chronic refractory gout evaluated using the Medical Outcomes Study Short Form-36 assessment, and results revealed that patients with chronic refractory gout have significantly lower subscales analogous to those of 75-year old individuals (*Becker 2009*). Specifically, disease severity, as characterized by number of flares in the past year, number of tender or swollen joints, or presence of tophi, significantly correlates with worse quality of life scores in all areas, which include bodily pain, general health, mental health, physical functioning and vitality. Subjects with comorbidities experienced worse physical functioning (*Strand 2012*).

There is also evidence that gout affects workplace productivity, as studies in patients with chronic, refractory gout self-report work absences due to flares, losing 25.1 workdays on average per year.

Another study specifically found employees with gout missed 4.56 more days of work per year than those without gout (*Edwards 2011*).

Hospitalizations with a principal diagnosis of gout has steadily increased over the past 2 decades (*Lim 2016*). In contrast, hospitalizations due to rheumatoid arthritis (RA) has dramatically decreased over this same time period correlating with the development of effective biologic drugs to treat RA. In 2005, the number of hospitalizations due to gout exceeded the number of hospitalizations due to RA, and this gap has steadily increased. Hospitalization costs for gout and RA show a similar trend. Similarly, general population studies have shown a substantial reduction in premature death in RA patients but not in gout patients (*Rai 2016*). The findings likely reflect lack of effective therapies for severe gout.

Together, these data show that the burden of chronic, severe, refractory gout extends well beyond that of physical discomfort, affecting almost every domain of life thus stressing the seriousness of the disease and an unmet need for new therapies given its refractory nature. Lowering serum urate levels can prevent further deposition of urate crystals, thus leading to a reduction in flare incidence and resolution of existing tophi. The American College of Rheumatology guidelines recommend a target serum urate of less than 6 mg/dL for patients on urate lowering therapy, with a target of less than 5 mg/dL for patients with chronic, severe disease, because this level is associated with more rapid resolution of tophi (*Dalbeth 2011*).

5.5 Approved Therapies for Chronic Gout Refractory to Conventional Therapy

An estimated ~>200,000 gout patients fail to normalize their levels of sUA, have symptoms that are uncontrolled with the currently available treatments aimed at lowering urate levels, or suffer from comorbidities that preclude their use of conventional therapies (*Strand 2012*). Lack of treatment options leads to unabated disease progression.

Currently, conventional therapies for the treatment of gout involve the inhibition of uric acid production and the improvement of uric acid renal clearance. The administration of exogenous uricase, an enzyme not present in humans that converts uric acid into the water-soluble compound, allantoin, is used only in instances of gout that is refractory to first and second lines of therapy (*Richette 2016*).

There are 2 uricase products currently used to treat hyperuricemia, albeit under different circumstances: rasburicase (ELITEK®) used for treating hyperuricemia in patients receiving anticancer therapy expected to result in tumor lysis and pegloticase (Krystexxa®) indicated for the treatment of chronic gout refractory to conventional therapy.

Rasburicase is a recombinant, unpegylated urate-oxidase enzyme produced by genetically modified *S. cerevisiae*. It is indicated for tumor lysis syndrome, and its use in treating gout is off-label. Its clinical use in gout is limited because it is highly immunogenic and has a short plasma half-life at approximately 18 to 24 hours, making it an unsuitable treatment for chronic refractory gout (*Terkeltaub 2009*).

Pegloticase is a pegylated recombinant porcine- or baboon-derived uricase. It is currently the only FDA-approved product for the treatment of chronic gout refractory to conventional therapy (*Krystexxa®*

Prescribing Information 2014). While its use is associated with improvements in musculoskeletal function, quality of life, and pain, only approximately 42% of patients maintain a target serum urate level less than 6 mg/dL after 6 months of the approved dose regimen of 8 mg once every 2 weeks. The vast majority of patients (89%) develop anti-pegloticase antibodies (*Lipsky 2014*). High titer antibodies appear to adversely affect the pharmacokinetics and pharmacodynamics of the enzyme and are associated with a decrease in therapeutic response and increased risk of infusion reactions. Approximately 26% of patients taking Krystexxa® report infusion reactions, 6.5% experience anaphylaxis, and the incidence of infusion reactions correlate with high anti-pegloticase antibody titer (*Sundy 2011*). These adverse events are typically preceded by a loss of urate-lowering effects.

In addition to infusion reactions and gout flares, the most common adverse reactions with Krystexxa® are nausea, contusion, nasopharyngitis, constipation, chest pain, anaphylaxis, and vomiting. In the 2 pivotal trials, there were 4 reported cases of exacerbations of pre-existing congestive heart failure in subjects receiving Krystexxa® every 2 weeks.

The high rate of treatment failure and the potential for anaphylactic reactions are potential drawbacks of Krystexxa® since its approval.

5.6 Unmet Medical Need

Current, approved uricase products carry substantial safety risks associated with immunogenicity, including anaphylaxis, as well as reduced efficacy over time as antibodies develop against the exogenous enzyme.

Selecta Biosciences has developed SEL-212, the first drug product designed to reduce or prevent an immunologic response and improve efficacy, safety, and tolerability of a uricase enzyme (pegadricase) in patients who require long-term treatment to manage symptoms and progression of chronic refractory gout. Selecta uses its proprietary, antigen-specific ImmTOR technology to encapsulate the approved immunomodulatory drug, rapamycin, to mitigate formation of anti-drug antibodies by inducing antigen-specific regulatory T cells. Selecta is leveraging its nanoparticle technology encapsulating rapamycin (ImmTOR) with the goal of inducing durable antigen-specific immune tolerance to pegadricase, a pegylated uricase. Specifically, SEL-212, in its current formulation, is a combination intravenous drug product that consists of a pegylated recombinant uricase (pegadricase; SEL-037) and a biodegradable nanoparticle containing rapamycin (SEL-110.36), a small molecule inhibitor of the mammalian target of rapamycin (mTOR) pathway. Pegadricase is derived from *Candida utilis* and metabolizes poorly soluble uric acid to the more soluble metabolite, allantoin. Administration of SEL-110.36 just prior to pegadricase is intended to induce immune tolerance to prevent the formation of anti-uricase antibodies that may compromise efficacy or safety of pegadricase.

The development of SEL-212 remains focused on mitigating the formation of antidrug antibodies with the goal of providing a product with better efficacy and safety profiles in patients than the only approved available therapy.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objective

The primary objective of this study is to assess the reduction in sUA in patients with gout refractory to conventional treatment treated with two different dose levels of SEL-212 compared to placebo.

6.1.2 Secondary Objectives

The secondary objectives of this study are:

- To compare the pharmacodynamic (PD) effect on sUA in patients with gout refractory to conventional treatment treated with two different dose levels of SEL-212 compared to placebo
- To assess change of the following in patients with gout refractory to conventional treatment treated with two different dose levels of SEL-212 compared to placebo:
  - Tophus burden
  - Patient Reported Outcomes (PROs) including assessments of: patients' quality of life (QoL) (SF-36); activity limitation (HAQ-DI); and Provider Global Assessment of Disease Activity
  - Gout flares
  - Joint tenderness and swelling
- To assess effects on the formation of anti-uricase and anti-pegadricase antibodies
- To assess the safety and tolerability of SEL-212 compared to placebo
- To assess the reduction in serum uric acid (sUA) in patients with gout refractory to conventional treatment treated with two different dose levels of SEL-212 compared to placebo, amongst those with tophi at baseline

6.1.3 Exploratory Objectives

The exploratory objectives of this study are:

- To assess the levels of uricase activity in patients receiving SEL-212 compared to placebo
- To assess the effect on monosodium urate crystal deposits and/or total body monosodium urate crystal uric deposits in patients with gout refractory to conventional treatment treated with two different dose levels of SEL-212 compared to placebo (imaging patients only)
- To assess the status of biomarkers related to inflammation and tolerogenic immunologic responses in patients with gout refractory to conventional treatment treated with two different dose levels of SEL-212 compared to placebo
- To assess the relationship between multiomic markers of gout and treatment effect in patients with gout refractory to conventional treatment treated with SEL-212 compared to placebo
- To assess the impact on patient's self-assessment of gout flares and burden of disease using a validated patient diary (weekly) in patients treated with two different dose levels of SEL-212 compared to placebo

- To assess the correlation between immune tolerance related multiomic markers and anti-pegadricase antibody formation in patients treated with two different dose levels of SEL-212

6.2 Study Endpoints

The confirmatory analysis of efficacy will be performed at Day 28 of Treatment Period 6. Efficacy assessments performed in the extension phase of the study (Treatment Period 7 to Treatment Period 12) will be summarized using descriptive statistics by treatment group only.

6.2.1 Primary Efficacy Endpoint

Each of the two active treatment groups, SEL-212A and SEL-212B, are compared to placebo with regards to the following primary endpoint:

- The percentage of patients who achieve and maintain reduction of sUA < 6 mg/dL for at least 80% of the time during Treatment Period 6 by Day 28.

6.2.2 Secondary Efficacy Endpoints

6.2.2.1 Key Secondary Efficacy Endpoints

Each of the two active treatment groups, SEL-212A and SEL-212B, are compared to placebo with regards to the following key secondary efficacy endpoints:

- Reduction of mean sUA as computed by subtracting the Baseline sUA level from the mean sUA (area under the sUA time curve) during Treatment Period 6
- Percent reduction of mean sUA as computed by subtracting the Baseline sUA level from the mean sUA (area under the sUA time curve) during Treatment Period 6
- The change from Baseline to Day 28 of Treatment Period 6 in the physical summary score of the Short Form Health Survey (SF-36)
- In patients with tophi at Baseline, the percentage of patients with at least partial response (PR) (as best response) in overall tophus response evaluation until Day 28 of Treatment Period 6
- The percentage of patients who achieve and maintain reduction of sUA < 6 mg/dL for at least 80% of the time during Treatment Period 6 in the subset of patients with tophi at baseline
- The change from Baseline to Day 28 of Treatment Period 6 in number of tender joints
- The change from Baseline to Day 28 of Treatment Period 6 in the total score of the Health Assessment Questionnaire (HAQ-DI)
- Gout flare incidence during Treatment Periods 1-6
- Gout flare incidence during Treatment Periods 1-3

6.2.2.2 Additional Secondary Efficacy Endpoints for Double-Blind Treatment Phase

Each of the two active treatment groups, SEL-212A and SEL-212B, are compared to placebo with regards to the following additional secondary efficacy endpoints:

- The percentage of patients who achieve and maintain reduction of sUA < 6 mg/dL for 100% of the time during Treatment Period 6

- Percentage of pre-dose sUA values ≤ 6 mg/dL during Treatment Periods 2-6 for each patient
- Pre-treatment anti-pegadricase and anti-uricase antibody formation and levels in each treatment period in the SEL-212 active treatment arms during Treatment Periods 1-6
- The percentage of patients with development of new tophi in the subgroups of tophaceous patients and in non-tophaceous patients at Baseline during Treatment Periods 1-6
- In patients with tophi at Baseline, the percentage of patients with at least PR (as best response) in overall tophus response evaluation until Day 0 of Treatment Period 4
- Change from Baseline to Day 28 of Treatment Period 6 in the subscales of Health Assessment Questionnaire (HAQ-DI), in Provider Global Assessment of Disease Activity, and in subscales of Short Form Health Survey (SF-36)
- The percentage of patients with at least 1 gout flare during Treatment Periods 1-3
- The percentage of patients with at least 1 gout flare during Treatment Periods 1-6
- Change from baseline to Treatment Period 6 in number of swollen joints
- Length of time patients are anti-uricase antibody free or before induction of anti-uricase antibody levels above baseline in patients receiving SEL-212
- Length of time patients are anti-pegadricase antibody free or before induction of anti-pegadricase antibody levels above baseline in patients receiving SEL-212

6.2.3 Exploratory Endpoints for Double-Blind Treatment Phase

The exploratory endpoints of the double-blind Treatment Period of this study are:

- Levels of uricase activity in patients receiving SEL-212
- Levels of monosodium urate crystal deposits and/or total body monosodium urate crystal deposits (imaging patients only)
- Levels of inflammatory and tolerogenic biomarkers
- Changes in antibody production (anti-uricase and anti-pegadricase) in patients in the SEL-212 groups
- Gout flare incidence during Treatment Periods 4-6
- Gout flare incidence during Treatment Periods 1-3 based on self-reported weekly gout flare diary
- Gout flare incidence during Treatment Periods 1-6 based on self-reported weekly gout flare diary
- Gout flare incidence in the Treatment Periods 4-6 based on self-reported weekly gout flare diary
- Assessment of association between multiomic markers of gout and treatment effect in patients treated with SEL-212
- Comparison of immune tolerance related multiomic markers in patients on SEL-212 who developed anti-uricase and anti-pegadricase antibodies vs. those patients on SEL-212 that did not develop anti-uricase and anti-pegadricase antibodies

6.2.4 Exploratory Endpoints for Double-Blind Extension Phase

The exploratory endpoints of the double-blind Extension Period of this study are:

- The change from Baseline to each Treatment Period (7-12) in the extension phase of sUA level
- The change from Baseline to each Treatment Period (7-12) in the extension phase in number of tender joints and number of swollen joints
- In patients with tophi at Baseline, the percentage of patients with at least PR (as best response) in overall tophus response evaluation in each Treatment Period (7-12) in the extension phase
- The change from Baseline to each Treatment Period (7-12) in the extension phase in the total score and in subscales of the Health Assessment Questionnaire (HAQ-DI)
- The change from Baseline to each Treatment Period (7-12) in the extension phase in the summary score and in subscales of the Short Form Health Survey (SF-36)
- Gout flare incidence in Treatment Periods 1-9 and in Treatment Periods 1-12 and percentage of patients with at least one gout flare in Treatment Periods 1-9 and in Treatment Periods 1-12 in the extension phase in the subgroup of patients continued into extension phase
- Number of pre-dose sUA values < 6 mg/dL for each patient stratified by cumulative number of Treatment Periods 7-12 for the subgroup of patients continued into extension phase
- Pre-treatment anti-pegadricase and anti-uricase antibody formation and levels for each treatment period during extension phase in the SEL-212 active treatment arms
- Percentage of patients with development of new tophi in each Treatment Period (7-12) in the extension phase in the subgroups of tophaceous patients and in non tophaceous patients at study baseline (Day 0 Treatment Period 1) and at baseline of extension phase (Day 0 Treatment Period 7)
- Change from baseline to each Treatment Period (7-12) in the extension phase in Provider Global Assessment of Disease Activity
- Length of time patients are anti-uricase antibody free or before induction of anti-uricase antibody levels above baseline in patients receiving SEL-212 in the subgroup of patients continued into extension phase
- Length of time patients are anti-pegadricase antibody free or before induction of anti-pegadricase antibody levels above baseline in patients receiving SEL-212 during extension phase
- Levels of uricase activity in patients receiving SEL-212 during extension phase
- Levels of monosodium urate crystal deposits and/or total body monosodium urate crystal deposits (imaging patients only) during extension phase
- Levels of inflammatory and tolerogenic biomarkers during extension phase
- Changes in antibody production (anti-uricase and anti-pegadricase) in patients in the SEL-212 groups during extension phase
- Assessment of association between multiomic markers of gout and treatment effect in patients treated with SEL-212 during extension phase
- Immune tolerance related multiomic markers in patients on SEL-212 who developed anti-uricase and anti-pegadricase antibodies vs. those patients on SEL-212 that did not develop anti-uricase and anti-pegadricase antibodies

6.2.5 Safety Endpoints

The safety endpoints of this study are:

- Safety and tolerability of SEL-212 compared to placebo as assessed by AEs, AESI, serious AEs (SAEs), deaths, and discontinuations due to AEs
- Additional safety assessments will include review and evaluation of laboratory testing including hematology, coagulation, chemistry, eGFR, urinalysis; UACR, vital signs; immunogenicity analyses; 12-lead ECGs; and physical examination findings.

7. INVESTIGATIONAL PLAN

7.1 Overall Study Design

This is one of two replicate randomized, double-blind, placebo-controlled, parallel-arm trials to determine the safety and efficacy of two different dose levels of SEL-212 compared to placebo. The study will randomize approximately 120 patients with chronic refractory gout. Approximately 60% of the randomized patients will have tophi at Baseline. Patients, stratified as to the presence or absence of tophi, will be randomized in a 1:1:1 allocation ratio prior to Baseline to receive treatment with one of two dose levels of SEL-212 or placebo every 28 days for approximately 6 months in each trial (SEL-212/301 and SEL-212/302). These two trials will have identical designs with respect to being double-blinded, placebo-controlled as well as identical sample sizes, inclusion/exclusion criteria, efficacy/safety assessments and timing thereof, but will be distinguished by the blinded 6-month extension in SEL-212/301 and that SEL-212/302 will include sites outside of the United States. [redacted] Efficacy assessments will be conducted at intervals that are appropriate to determine treatment effect with samples for the primary endpoint drawn during Treatment Period 6. Samples will be collected at intervals that are appropriate to determine the uricase activity of SEL-212. Safety will be monitored throughout the study with an independent data safety monitoring board (DSMB). After successful completion of the double-blind treatment phase, patients successfully completing six months in SEL-212/301 will continue, in a blinded fashion, to be treated with the identical investigational treatment (one of two dose levels of SEL-212 or placebo) for 6 additional doses, every 28 days, lasting approximately 6 months. This will provide up to 12 months of continuous treatment with SEL-212 in a placebo-controlled fashion.

The study will be divided into 3 study phases: Screening, Treatment, and Follow-up, described below. The study is depicted schematically in Figure 1.

The total duration of participation in the study will range from approximately 50 to 55 weeks (352 to 383 days) as follows:

- Screening and/or washout and premedication Phase: up to 45 days (up to 6.5 weeks)
- Treatment Phase: 168 days (24 weeks)
- Extension Phase: 168 days (24 weeks)
- Safety Follow-Up: 30 days after last infusion

7.1.1 Screening Phase

After providing written informed consent, the patient is considered enrolled in the study. Patients will be evaluated for inclusion during the Screening Phase. For all patients, the standard Screening Phase will be up to 45 days prior to Baseline. The Screening Phase may be initiated by a preliminary screening with an abbreviated informed consent focused on COVID-19 testing and serum uric acid levels followed by providing study-wide informed consent and the remainder of screening assessments if determined to proceed. **Of note**, if the sUA level obtained during preliminary screening meets eligibility requirements

(i.e., ≥ 7 mg/dL), the sUA should **not** be repeated during the subsequent complete screening assessment. Concurrently with the Screening Phase, a premedication period for potential gout flare with colchicine (or non-steroidal anti-inflammatory drug [NSAID], if colchicine is contraindicated) of at least 7 days prior to Baseline will be required for all patients, and a washout period of at least 7 days will be required prior to Baseline for patients on any urate-lowering therapy (ULT). Both the ULT washout period and the gout flare prophylaxis period may be started earlier than 7 days prior to Baseline. At the discretion of the PI, chronic refractory gout patients whose sUA is lower than the eligibility level of ≥7 mg/dL on prescreening or initial screen, may undergo ULT washout prior to retesting the sUA. Initiation of gout flare prophylaxis with colchicine (or non-steroidal anti-inflammatory drug [NSAID], if colchicine is contraindicated) can also be considered coincidentally with the ULT washout to prevent a potential gout flare.

7.1.2 Double Blind Treatment Phase

The total duration of the double-blind Treatment Phase will be approximately 6 months (i.e., 168 days, consisting of six 28-day treatment cycles).

Eligible patients, stratified as to the presence or absence of tophi, will be randomized in a 1:1:1 allocation ratio prior to baseline to receive one of two dose levels of SEL-212 or placebo. The SEL-212 doses will differ as to the SEL-110.36 component. Participants will receive SEL-037 administered at a dose level of 0.2 mg/kg via intravenous (IV) infusion immediately after receiving SEL-110.36 at a dose level of either 0.1 mg/kg (SEL-212A) or 0.15 mg/kg (SEL-212B) via IV infusion. The placebo will consist of normal saline that will be administered in the same way that the SEL-212 components are administered to maintain the integrity of the study blind. Refer to Section 10 for details about study drug administration.

Patients will complete 6 treatment periods each having a duration of 28 days. Patients will receive treatment with study drug or placebo on Day 0 of each treatment period for a total of 6 doses. For each treatment cycle, participants will receive premedication to minimize the potential for infusion reactions during study drug administration. After completing the study drug infusions, participants will remain at the investigational site for 1 hour for safety assessments.

With each dose, a blood sample will be drawn for assessment of sUA level and uricase activity immediately prior to infusion (i.e., Time 0 h) with SEL-212 or placebo and 1 hour after the infusion of the second component of SEL-212 or of placebo is completed. Serum uric acid will be assessed through additional post-infusion blood samples at pre-determined time points by an independent, central, unblinded medical monitor.

Gout flares will be assessed at each study visit during the Treatment Phase using a validated definition of flares in patients with established gout (*Gaffo 2018*). In addition, in an exploratory manner, gout flares will be self-assessed by the patient weekly after randomization and in each Treatment Period using a weekly flare diary (*Poiley 2016*). Health Questionnaires, tophus burden and joint swelling and tenderness will be assessed on Day 0 of Treatment Periods 1 and 4, and at the end of Treatment Period

6 or early termination (ET) if a patient discontinues the study prior to the end of 6 monthly infusions. Samples for anti-uricase, anti-PEG, and anti-pegadricase antibody levels will be taken (i) prior to administration of study drug dosing and at Day 21 for each of the six treatment periods throughout the trial and (ii) at the end of Treatment Period 6 or at ET. Exploratory assessments of inflammatory/immunologic biomarkers and multiomic analysis will also be assessed.

Safety laboratory samples, consisting of, but not limited to, complete blood count (CBC) including white blood cell count (WBC) and absolute neutrophil count; liver function tests (LFTs) including aspartate aminotransferase (AST) and alanine transaminase (ALT); serum lipids (including triglycerides and low density lipoprotein (LDL)), analyses of renal function including creatinine, urine albumin creatinine ratio (UACR), and estimated glomerular filtration rate (eGFR) will be collected on Day 0 and Day 21 of Treatment Period 1, on Day 21 only of each of Treatment Periods 2-5, and on Day 21 and Day 28 / ET of Treatment Period 6. On Treatment Period 1 Day 0, safety laboratory samples will be collected pre-infusion in both the SEL-212 arm and the placebo arm. Concomitant medications and procedures and adverse events (AEs) will be monitored continuously during the study. Post-Baseline chest X-rays (CXR) will be taken at six months and one year / ET to assess for presence of or changes in interstitial lung disease (ILD) compared to baseline CXR.

7.1.3 Follow-Up Phase

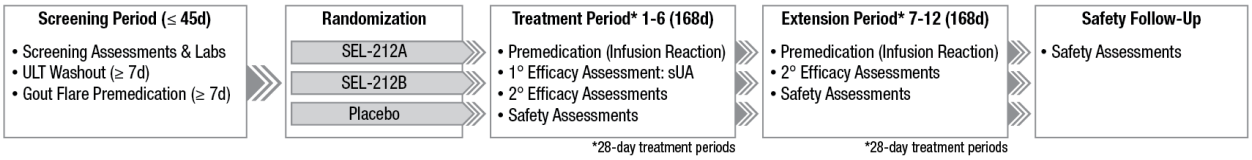
Patients will be followed for safety monitoring (30 + 4 days) after their final study drug infusion and will have an End of Study visit by telephone at the following times: either (1) at completion of the Extension Phase or (2) at early termination if the patient voluntarily withdraws consent. Patients who terminate the study prematurely will continue to be followed by having all Early Termination assessments performed. Patients who terminate the study prematurely who are unable to be on-site for the Early Termination visit will be contacted by telephone for safety follow-up.

If withdrawn from study drug, regardless of reason, the patient will continue study visits to the end of Treatment Period 12.

7.1.4 Double-Blind Extension Phase

Patients will enroll in a double-blind extension to begin after the conclusion of Treatment Period 6. Patients in any cohort who have met the stopping rule during the blinded treatment phase will continue study visits in the extension phase without study drug administration. All SEL-212 patients in the extension phase will receive up to an additional 6 monthly doses of SEL-212 at the same dose level as during the Treatment Phase for those that maintain Day 21 sUA <6 mg/dL. Patients who meet the stopping rule during the extension phase will be withdrawn from study drug and will continue study visits to the end of the extension phase.

Figure 1: Study Schematic



7.2 Number of Patients

The study will randomize approximately 120 patients with chronic refractory gout. Approximately 60% of the randomized patients will have tophi at Baseline

7.3 Treatment Assignment

Patients will be randomized in a double-blind way with an allocation ratio of 1:1:1 to receive treatment with two different dose levels of SEL-212 or placebo. Randomization will be stratified by presence/absence of tophi.

7.4 Dose Adjustment Criteria

Unless otherwise specified, study drug will be administered as described in Section 9 and Section 10.

7.4.1 Safety Criteria for Adjustment or Stopping Doses

7.4.1.1 SEL-212 or Placebo

A patient will be withdrawn from study drug for meeting the following stopping rule:

- sUA level < 2.0 mg/dL, measured 1 hour after the infusion of the second component of study drug is completed during Treatment Period 1

  AND

- sUA level > 1.0 mg/dL measured at the Day 21 visit of Treatment Period 1 or sUA level > 6.0 mg/dL at the Day 21 visit of any of Treatment Periods 2-11

  Stopping rules will be assessed by an independent, central, unblinded medical monitor.

If withdrawn from study drug during the double-blind treatment period (Treatment Period 1 to 6) or the double-blind extension period (Treatment Period 7 to 12), regardless of reason, the patient will continue study visits to the end of Treatment Period 12.

The window for all Day 21 visits is +2/-1 days. If a Day 21 visit sUA value drawn within the protocol window is not available, but if a sUA value drawn at an unscheduled visit after the Day 21 window is available prior to dosing that is ≤ 1.0 mg/dL during Treatment Period 1 or ≤ 6.0 mg/dL during Treatment Periods 2-11, the patient will not be required to be withdrawn from study drug and will be eligible to receive their subsequent dose.

If 1) a Day 21 visit sUA value drawn within the protocol window is not available and no subsequent sUA results are available or 2) a Day 21 visit sUA value drawn within the protocol window is not available and

a subsequent sUA drawn at an unscheduled visit after the Day 21 window is > 1.0 mg/dL during Treatment Period 1 or > 6.0 mg/dL during Treatment Periods 2-11, then the patient will be withdrawn from study drug based on the protocol deviation. If a protocol deviation occurs where a patient is not able to be dosed within the dosing day window (for example in the case of COVID-19 restrictions temporarily preventing dosing) the current treatment period will be extended up to a maximum of 90 days without skipping doses for patients with a Day 21 visit sUA value ≤ 1.0 mg/dL during Treatment Period 1 or ≤ 6.0 mg/dL during Treatment Periods 2-11 in the D21 visit window or subsequent up to the rescheduled dosing visit. If this protocol deviation occurs such that the patient was unable to be dosed within the dosing day window for the Treatment Period 7 Day 0 dose, then the Treatment Period 6 Day 28 visit should still occur 28 days (+3/-4 days) after the Treatment Period 6 dose or as close to the visit window as possible to collect the final primary endpoint sUA sample. In this specific instance, the dosing day Treatment Period 7 Day 0 should then occur as soon as possible afterward up to a maximum of 90 days from the preceding dose.

To maintain the blind, a central group of unblinded pre-specified medical personnel will adjudicate the implementation of the stopping rules.

If withdrawn from study drug, the patient will continue study visits to the end of Treatment Period 12. At the discretion of the Investigator, the patient will be permitted to return to ULT 60 days after the patient's last study drug treatment. ULT shall not be SEL-212 or any experimental or marketed uricase (e.g., rasburicase (Elitek, Fasturtec), pegloticase (Krystexxa®), for the remainder of the study.

7.4.2 Criteria for Adjustment or Stopping Doses

An independent Data and Safety Monitoring Board (DSMB) will be formed by charter to assist in reviewing safety data and may provide recommendations to the Sponsor regarding study drug dose adjustment or study termination.

7.5 Criteria for Study Termination

The study can be terminated at any time at the Sponsor's sole discretion. Otherwise, the study will be terminated when all patients have completed follow-up assessments (Appendix C) or the Sponsor or regulatory agency(ies) have determined there is an unacceptable risk to patients or additional dosing or procedures are not warranted or necessary.

The study may be terminated at a particular investigational site under the following conditions:

- The Investigator fails to enroll patients at an acceptable rate;
- The Investigator fails to comply with pertinent regulations;
- There is insufficient adherence (i.e., compliance) to the protocol;
- Knowingly false information is submitted to the IRB/IEC, Sponsor or designee, or regulatory authorities.

7.6 Study Rationale

7.6.1 Rationale for the Study Design

Refractory gout is a serious condition affecting approximately >200,000 patients in the United States and is characterized by uric acid levels that are not adequately controlled by xanthine oxidase inhibitors, such as allopurinol or febuxostat, or for whom such drugs are contraindicated. About 5% to 10% of gout patients are not treated effectively with allopurinol and thus continue to have acute flares and may experience destructive joint damage and tophus formation (Edwards 2008, Fels 2008). Additionally, approximately 2% of gout patients exposed develop hypersensitivity to allopurinol which can lead to very serious complications and even death (Markel 2005).

Pegloticase (Krystexxa®), a pegylated uricase, was approved by the United States Food and Drug Administration (FDA) in 2010 for the treatment of chronic gout in patients refractory to conventional therapy. Pegloticase is effective in lowering serum uric acid after a single dose. However, >58% of subjects treated with pegloticase experience loss of efficacy within 6 months with the vast majority experiencing loss of efficacy within 3 months due to the formation of anti-drug antibodies (ADAs) with the possibility of infusion reactions, sometimes severe.

SEL-212 is a combination drug product consisting of SEL-037 and SEL-110.36. SEL-037 (pegadricase, pegylated recombinant *Candida utilis* urate oxidase) is an investigational biological therapeutic product presented as a lyophilized pegylated recombinant uricase for intravenous injection. SEL-110.36 is designed to inhibit the formation of ADAs when concomitantly administered with a biologic, specifically, the uricase, pegadricase or SEL-037.

The overall development of SEL-212 remains focused on mitigating the formation of ADAs with the goal of providing a product with better efficacy and safety profiles in patients than the only approved available therapy.

Study SEL-212/301 is a randomized, double-blind, placebo-controlled, parallel-arm study to determine the safety and efficacy of multiple doses of SEL-212 compared to placebo.

A randomized, controlled study is the gold-standard for evaluation of efficacy in clinical research. Randomized, controlled studies are quantitative, comparative, controlled experiments in which treatment effect sizes may be determined with less bias than observational trials. Randomization is considered the most powerful experimental design in clinical trials: with other variables equal between groups, on average, any differences in outcome can be attributed to the intervention.

The blinding scheme in this study will be applied to all patients, Investigators, study personnel, and Sponsor personnel involved in the conduct of the study, except for a designated unblinded statistician who will generate and have access to the randomization codes, a designated unblinded site representative (e.g., pharmacist) who will prepare study drug on the day of treatment, an unblinded infusion nurse who will be responsible for dosing the patient, a designated unblinded medical monitor for assessing the treatment stopping rules, and unblinded drug supply personnel. Blinding and randomization will reduce the potential for treatment bias and will improve the veracity of detected

efficacy and safety signals, particularly in the use of patient-reported quality of life assessments. The parallel arms involving active treatment and placebo will permit adequate statistical comparison of the groups for efficacy and safety signal detection.

Placebo (normal saline) rather than an active control will be employed in this study for ethical and practical considerations. The approved therapeutic for patients with gout refractory to conventional therapy (pegloticase) and the uricase product currently used to treat hyperuricemia (rasburicase) include exogenous enzymes that are highly immunogenic (Section 5.5) and that would expose patients randomized to an active control group to unnecessary risk. The dosing regimens of the approved enzymes are substantially different from the dosing regimen of SEL-212 and would defeat the steps taken to blind the study. The use of multiple doses of SEL-212 will help determine optimal efficacy: safety profile in a heterogenous population of patients with significant co-morbidities.

7.6.2 Rationale for the Study Population

The selection of this study population (Section 8) is based primarily on the desired therapeutic indication that the Sponsor will seek. Other selection criteria were set in order to maximize the ability to detect efficacy signals while minimizing any undue risk to the enrolled patients. Therefore, the severity and refractoriness of the patient's disease and sUA level are key Inclusion Criteria (Section 8.1). In order to enhance the safety of patients on treatment, key Exclusion Criteria involve history of severe allergies or allergies to products that have similar features to the components of SEL-212, medical factors that might be exacerbated while on treatment, and prior exposure to experimental or marketed uricase therapies.

7.6.3 Rationale for the Selected Dose

Dose selection for this Phase 3 study was based on safety and efficacy analyses of the clinical development program for SEL-212, beginning with a completed Phase 1b study (Study SEL-212/101: "A Phase I Single Ascending Dose Safety, Pharmacokinetic and Pharmacodynamics Study of SEL-212 in Subjects with Elevated Blood Uric Acid," NCT02648269) and a Phase 2 study (Study SEL-212/201: "An Open Label Phase II Multiple Dose Safety, Pharmacokinetic and Pharmacodynamics Study of SEL-212 Followed by Open Label Administration of SEL-037 in Subjects with Symptomatic Gout and Elevated Blood Uric Acid" NCT02959918).

7.6.3.1 Phase 1b Study with SEL-212

This was a Phase 1b double-blind, sequential, single-ascending-dose study (SEL-110; Cohorts 1, 3, 5, and 7) combined with an open label, single-ascending-dose study (SEL-212; Cohorts 2, 4, 6, 10, 12 and 14) to assess the safety, tolerability, and PK of SEL-212 and SEL-110. Additionally, the study was to assess the PD (ability to reduce sUA) and immunogenicity (ability to prevent ADAs to uricase and pegadricase) of SEL-212. Generally, patients were dosed on a cohort basis in an ascending stepwise manner. A control group was dosed with SEL-037 only.

In the Phase 1b study (SEL-212/101), patients (N = 64) with a serum uric acid level ≥ 6 mg/dL, with or without a history of gout, were administered SEL-110 alone, SEL-037 (pegadricase) alone, or SEL-212 (SEL-037 + SEL-110) as an intravenous infusion. Mitigation of ADAs and a dose-dependent reduction in

sUA levels occurred from study Day 1 to Day 30 in patients administered SEL-212 (data on file). There was no effect of SEL-110 alone on sUA levels, and patients administered SEL-037 alone developed ADAs that resulted in loss of sUA control by Day 14. SEL-212 was generally well tolerated at all dose levels. The maximum tolerated dose of SEL-110 was determined to be 0.3 mg/kg. Data from this study were used to select additional dose levels of each component of SEL-212 for evaluation in the Phase 2 study SEL-212/201.

7.6.3.2 Phase 2 Studies with SEL-212

7.6.3.2.1 Phase 2 Study SEL-212/201

The Phase 2 study SEL-212/201 was designed as an open-label, ascending multiple-dose study of the combination drug, SEL-212, combined with an open-label, multiple-dose evaluation of SEL-037 (pegadricase) alone in patients with symptomatic gout and elevated blood uric acid. Part A of the study consisted of three 28-day treatment cycles of SEL-212, which was then followed by Part B, which consisted of two 28-day treatment cycles of SEL-037 alone, with a primary objective of assessing the safety, tolerability, PK, PD of SEL-212 (i.e., the combination of SEL-110 and SEL-037). Additional assessments include the ability of SEL-212 to reduce serum uric acid levels and prevent anti-drug antibodies to uricase and pegadricase. Part C of the study consisted of 5 monthly doses of SEL-212.

In Study SEL-212/201 with SEL-212, sUA levels remained consistently below 6 mg/dL in 70% to 89% of evaluable Part A patients administered SEL-212 once monthly for 3 months. The control of sUA occurred in the context of low incidences of infusion reactions, anaphylaxis, and gout flares as well as treatment-emergent adverse events (TEAEs) known to be potentially associated with rapamycin (sirolimus – Rapamune®). Data support a once monthly dosing regimen. For cohorts 7-12 with SEL-110 doses of 0.1 mg/kg or higher, 46% of evaluable patients had sUA <6 mg/dL at week 20.

In Part C cohorts receiving 5 monthly doses of SEL-212, 61%, 71%, and 67% of eligible patients in Cohorts 13, 15, and 17, respectively, maintained sUA control (sUA, <6 mg/dL) at week 12 without the development of ADAs. All 21 patients in cohorts 13, 15 and 17 who had sUA < 6 mg/dL at week 12, maintained sUA control through the end of treatment period 5 and had sUA < 6 mg/dL at week 20.

The efficacy signal of SEL-212 in SEL-212/201 persists across multiple treatment cycles in all cohorts and through all 5 treatment cycles when SEL-212 is given at each treatment, as demonstrated by dose-dependent reductions in sUA levels below 6 mg/dL and ADA suppression in conjunction with increasing SEL-110 dose levels up to 0.15 mg/kg.

Cohorts 7, 11, 13 and 17 represent the dose regimens that will be evaluated in the Phase 3 program (0.1 or 0.15 mg/kg SEL-110 and 0.2 mg/kg SEL-037). Part C cohorts 13, 15, and 17 received 5 once monthly doses of SEL-212, and patients in the proposed Phase 3 program will receive a total of 6 or 12 once monthly doses of SEL-212.

Across cohorts 1 to 17, 28 SAEs have been reported in 20 of 152 (13.2%) patients. They include 9 infusion reactions reported as related or possibly related to SEL-212. Of these 9 infusion reactions, only

3 occurred during repeat dosing of SEL-212 in cohorts 7, 13 and 17; 4 occurred in cohorts that received SEL-037 alone or SEL-037 with the lowest dose of SEL-110 (0.05 mg/mL); and 2 were due to dosing errors. All SAEs were successfully treated without complication. No study drug related SAEs or discontinuations involving gout flares, metabolic disorders, hypophosphatemia, or changes in lipid levels have been reported in the Phase 2 study SEL-212/201.

Leukopenia can be seen in patients taking high doses of rapamycin for extended periods of time. Leukopenia was reported by investigators in 11 (7.2%) and neutropenia in 6 (3.9%) of patients. One patient's neutropenia was reported as severe but not identified with a TEAE of infection. No SAEs or study drug discontinuations involving leukopenia or neutropenia have been reported.

Another TEAE seen in patients taking oral rapamycin is stomatitis (mTor Inhibitor associated stomatitis-mIAS) and was observed in the SEL-212 Phase 2 trial at a lesser rate than seen in previous clinical trials (*Peterson 2016*). Stomatitis or aphthous ulcers were reported in 19 (12.5%) of patients; all were mild or moderate in severity. The TEAEs categorized as stomatitis or oral lesions did not result in any SAEs, study drug discontinuations, or withdrawals. All resolved with minimal topical oral treatment of corticosteroids.

Additional TEAEs of particular interest for rapamycin are hyperglycemia, hypophosphatemia, and hypertriglyceridemia. These were reported in 5.9%, 3.9% and 17.8% of patients in the SEL-212 Phase 2 trial, respectively. These TEAEs resolved without any medical intervention, their duration was transient, and they did not result in any SAEs, study drug discontinuations, or withdrawals.

7.6.3.2.2 Phase 2 Study SEL-212/202

Study SEL-212/202 is a Phase 2 randomized, open-label, parallel-arm study to compare the safety and efficacy of IV infusions of SEL-212 compared to KRYSTEXXA for 6 months. The study has completed enrollment but is ongoing in the treatment phase. Data presented are based upon a data cutoff of 19 March 2020.

Subjects in the SEL-212 arm received study drug (SEL-110.36, 0.15 mg/kg + SEL-037, 0.2 mg/kg) every 28 days (Day 0 of each treatment period) for a total of 6 infusions. Subjects in the KRYSTEXXA arm received study drug (8 mg) every 14 days (per manufacturer's prescribing information, Day 0 and Day 14 of each treatment period) for a total of 12 infusions.

The planned enrollment was 150 subjects. Actual enrollment was 170 subjects and included 83 subjects in the SEL-212 arm and 87 subjects in the KRYSTEXXA arm.

Subjects ranged in age from 29 to 79 years with 163 males (95.9%) and 7 females (4.1%). Twenty-seven (27) subjects (15.8%) have completed the study and 22 subjects (12.9%) discontinued from the study. Primary reasons for early discontinuation from the study were withdrawal of consent in 13 (7.6%) subjects, adverse event in 3 (1.8%) subjects, lost to follow-up in 3 (1.8%) subjects; and "other" in 3 (1.8%) subjects.

Overall, 135 of the 169 (79.9%) subjects enrolled have experienced TEAEs: 71 of the 83 (85.5%) subjects who received SEL-212, and 64 of the 86 (74.4%) subjects who received KRYSTEXXA. Overall, 74 of the 169 (43.8%) subjects enrolled have experienced a TEAE that was considered by the investigator to be related or possibly related to study drug (i.e., drug-related): 41 of the 83 (49.4%) subjects who received SEL-212, and 33 of the 86 (38.4%) subjects who received KRYSTEXXA.

In the study, the following TEAEs were identified as Adverse Events of Special Interest (AESIs): infusion-related reactions, stomatitis and related terms, gout flares, infections, interstitial lung disease, malignancies, renal failure, and clinically significant laboratory tests demonstrating hyperlipidemia, worsening of renal function tests, proteinuria, and leukopenia. Subjects with at least 1 TEAE of special interest included 24 (27.9%) subjects who received KRYSTEXXA and 33 (39.8%) subjects who received SEL-212.

Overall, most TEAEs have been mild or moderate in severity. Eight (8) of the 83 (9.6%) subjects who received SEL-212 experienced a total of 14 severe TEAEs. Four (4) subjects experienced a single severe TEAE including anemia, gout, rotator cuff syndrome, and deep vein thrombosis (DVT); 2 subjects experienced 2 severe TEAEs including gastrointestinal haemorrhage and gout; and pulmonary embolism and DVT; and 2 subjects experienced 3 severe TEAEs including: arthralgia, joint swelling, and ligament pain; and presyncope and 2 gout attacks. In addition, 2 subjects who received SEL-212 each experienced a life-threatening TEAE, both anaphylactic reactions.

A total of 6 of the 86 (7.0%) subjects who received KRYSTEXXA experienced a total of 6 severe TEAEs. Subjects experienced a single severe TEAE including: 2 gout, an anaphylactic reaction, drug hypersensitivity, gastroenteritis, and an infusion-related reaction. In addition, 2 subjects who received KRYSTEXXA each experienced a life-threatening TEAE of cerebrovascular accident and hypertensive emergency, respectively. There have been no concerning trends in laboratory values, vital signs, or physical examination findings (data not shown).

Twelve (12) of the 169 (7.1%) subjects enrolled have experienced a total of 14 SAEs. Six (6) of the 83 (7.2%) subjects who received SEL-212 experienced a total of 7 SAEs and 6 of the 86 (7.0%) subjects who received KRYSTEXXA experienced a total of 7 SAEs. Two (2) of the SEL-212 SAEs were considered related or possibly related to SEL-212 and 3 of the KRYSTEXXA SAEs were considered related or possibly related to KRYSTEXXA by the investigator.

No deaths have been reported during the study.

In summary, the safety profile of SEL-212 in the ongoing Phase 2 clinical trial has not demonstrated any unexpected TEAEs. In the dose ranging Phase 2 Study SEL-212/201, in general, TEAEs were most frequently observed after the first treatment cycle and diminished with successive treatment cycles. Therefore, the potential risk of TEAEs did not appear to increase with repeated exposure to SEL-212.

Cohorts 7, 11, 13, and 17 from Phase 2 Study SEL-212/201 represent the dose regimens that will be evaluated in the Phase 3 program; and the dose administered in the Phase 2 study SEL-212/202 (SEL-

110.36, 0.15 mg/kg + SEL-037, 0.2 mg/kg) represents the high dose planned in the Phase 3 program. Data from these two Phase 2 studies support the doses to be administered in Phase 3 and efficacy data from Phase 2 Study SEL-212/201 support monthly dosing with SEL-212.

7.6.4 Rationale for the Primary Efficacy Endpoint

The incidence of gout increases as circulating uric acid levels increase (*Campion 1987*) and lowering circulating urate levels is a primary means of managing gout. The American College of Rheumatology recommends lowering urate levels to a target of less than 6 mg/dL at minimum (*Khanna 2012a*) to improve the signs and symptoms of gout.

Based on a proposed indication of treatment of chronic gout refractory to conventional therapy, the objectives of this study design are to assess the reduction in sUA in adult patients treated with SEL-212 compared to placebo. The proposed primary endpoint is comparison in the percentage of participants treated with two different dose levels of SEL-212 compared to placebo who achieve and maintain reduction of sUA <6 mg/dL for at least 80% of the time during Treatment Period 6.

7.6.5 Rationale for Secondary Efficacy Endpoints

Secondary endpoints were selected based on symptoms of chronic gout as well as quality of life as a consequence of chronic gout. Patients with severe, chronic gout are often refractory to oral therapies and often present with visible tophi that cause debilitating pain, corresponding to significantly reduced quality of life. Exacerbation of gout (flare) and joint tenderness and swelling impact a patients' ability to maintain physical activity and functioning and adversely affect quality of life. Several instruments will be used to assess quality of life and will include patient-reported outcomes, provider-reported assessments, and generalized assessments of overall quality of life.

7.6.6 Rationale for Other Assessments of Clinical Benefit

Exploratory assessments will be used to characterize the effect of SEL-212 on biomarkers of inflammation related to gout and multiomic markers of gout.

Genome wide association studies have identified multiple genetic markers in regulating uric acid metabolism. These markers may explain some of the variation observed in the control of serum uric acid levels in patients on SEL-212.

Recombinant uricases are highly immunogenic and formation of anti-drug antibodies can adversely affect durability of efficacy. Anti-uricase and anti-pegadricase antibodies will be assessed and correlated with response to SEL-212.

SEL-110 induces durable antigen-specific immune tolerance in preclinical models. Correlation of the mitigation of anti-drug antibodies with biomarkers related to immune tolerance would support the induction of antigen-specific immune tolerance against SEL-037.

Finally, visualization of the effect of SEL-212 on joint surfaces will use multiple imaging modalities, depending on the investigational site.

7.7 Benefits and Risks

Chronic gout refractory to conventional therapy is a rare and serious condition associated with increased mortality rate and significantly decreased quality of life and for which there are very limited treatment options. Data from the Phase 2 study SEL-212/201 provide preliminary clinical evidence demonstrating that SEL-212 is a substantial improvement over available therapy:

- Substantially increased percentage of patients that maintain control of sUA while on therapy
- Substantially reduced gout flare rate during therapy
- Substantially reduced risk of infusion reactions
- More convenient to and greater compliance by patients because of once monthly therapy
- Acceptable safety at the dose to be studied in this Phase 3 study
- Potential to re-treat patients after a gap in therapy (> 1 month) because of the mechanism of action of SEL-212

SEL-212 has the potential to be an unprecedented safe and effective treatment option for patients for which other treatment options are inadequate. The overall balance between benefits and risks appears acceptable for the Phase 3 study of SEL-212 in the intended population of patients with chronic gout refractory to conventional therapy.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1 Patient Inclusion Criteria

A patient must meet all the following criteria to be eligible for this study:

1. Has provided written informed consent prior to the conduct of any study specific procedures;
2. Understands and is willing and able to comply with study requirements, including the schedule of follow-up visits;
3. Has negative results of an FDA Emergency Use Authorized COVID-19 molecular assay for detection of SARS-CoV-2 RNA from a nasal or oropharyngeal specimen;
4. Has a history of symptomatic gout defined as:
   - ≥ 3 gout flares within 18 months of Screening or
   - Presence of ≥ 1 gout tophus or
   - Current diagnosis of gouty arthritis
5. At the Screening Visit male age 19 – 80 years, inclusive or female of non-childbearing potential age 19-80 years, inclusive, where non-childbearing potential is defined as:
   - > 6 weeks after hysterectomy with or without surgical bilateral salpingo-oophorectomy or
   - Post-menopausal (> 24 months of natural amenorrhea or in the absence of >24 months of amenorrhea, 1 documented confirmatory FSH measurement)
6. Has chronic refractory gout defined as having failed to normalize sUA and whose signs and symptoms are inadequately controlled with any of the xanthine oxidase inhibitors, either allopurinol and/or febuxostat, at the medically appropriate dose, or for whom these drugs are contraindicated for the patient
7. Has at Screening sUA ≥ 7 mg/dL
8. Has not participated in a clinical trial within 30 days of the Screening Visit and agrees to not participate in a clinical trial for the duration of the study;
9. Negative serology for HIV-1/-2 and negative antigen to hepatitis B and negative antibodies to hepatitis C.

8.2 Patient Exclusion Criteria

A patient who meets any of the following criteria will be excluded from this study:

1. Has a history of anaphylaxis, severe allergic reactions, or severe atopy;
2. Has a history of any allergy to pegylated products, including, but not limited to pegloticase (Krystexxa®), peginterferon alfa-2a (Pegasys®), peginterferon alfa-2b (PegIntron®), pegfilgrastim (Neulasta®), pegaptanib (Macugen®), pegaspargase (Oncaspar®), pegademase (Adagen®), peg-epoetin beta (Mircera®), pegvisomant (Somavert®) certolizumab pegol (Cimzia®), naloxegol (Movantik®), peginesatide (Omontys®), and doxorubicin liposome (Doxil®);
3. Is taking and cannot discontinue known major CYP3A4/P-gp inhibitors or major CYP3A4/P-gp inducers at least 14 days before dosing. Patients must remain off these medications for the duration of the study, including natural products such as St. John's Wort or grapefruit juice.

4. Is taking drugs known to interact with rapamycin (sirolimus – Rapamune®) such as cyclosporine, diltiazem, erythromycin, ketoconazole, posaconazole, voriconazole, itraconazole,, rifampin, verapamil unless they are stopped 14 days prior to dosing and will not be used/prescribed during the trial.
5. Had major surgery within 3 months of initial screening.
6. Had a gout flare during Screening that was resolved for less than 1 week prior to first treatment with study drug (exclusive of chronic synovitis/arthritis) unless the patient has a history of inter-flare intervals of < 1 week.
7. Has uncontrolled diabetes at Screening with HbA1c ≥ 8.5%;
8. Has fasting Screening glucose > 240 mg/dL
9. Has fasting Screening triglyceride > 500 mg/dL;
10. Has fasting Screening low-density lipoprotein (LDL) > 200 mg/dL;
11. Has glucose-6-phosphate dehydrogenase (G6PD) deficiency;
12. Has uncontrolled hypertension defined as blood pressure > 170/100 mmHg at Screening and 1 week prior to dosing
13. Individual laboratory values which are exclusionary
    - White blood cell count (WBC) < 3.0 x10^9/L
    - Serum aspartate aminotransferase (AST) or alanine amino transferase (ALT) > 3x upper limit of normal (ULN) in the absence of known active liver disease
    - Estimated Glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2
    - Urine-albumin-creatinine ratio (UACR) > 30 mg/g creatinine (conventional units) or > 3.39 mg/mmol creatinine (SI units)
    - Hemoglobin (Hgb) < 9 g/dL
    - Serum phosphate < 2.0 mg/dL
14. Is receiving ongoing treatment for arrhythmia, including placement of an implantable defibrillator, unless considered stable and on active treatment;
15. Has evidence of unstable cardiovascular disease or unstable cerebrovascular disease. This includes patients who have had a cardiac/vascular event(s) in the last 3 months including heart attack, stroke or vascular bypass surgery prior to dosing or patients who are deemed, by their physician or PI, to have active cardiovascular, cerebrovascular, or peripheral vascular symptoms/disease inadequately controlled by medication;
16. Has congestive heart failure, New York Heart Association Class III or IV;
17. Unless clinically stable and/or appropriately treated, electrocardiogram (ECG) with evidence of clinically significant arrhythmia, or other abnormalities that, in the opinion of the investigator, are consistent with significant underlying cardiac disease;
18. History of significant hematological disorders within 5 years or autoimmune disorders, and/or patient is currently immunosuppressed or immunocompromised;
19. Prior exposure to any experimental or marketed uricase (e.g., rasburicase (Elitek, Fasturtec), pegloticase (Krystexxa®), pegadricase (SEL-037))
20. Patient has received a live vaccine in the previous 6 months.

21. Patient is planning to receive any live vaccine during the study. Of note, inactivated vaccines are permitted but, study drug may affect response to vaccination; therefore, during study drug treatment vaccination with inactivated vaccines may be less effective. Consider high-dose influenza vaccine to increase the likelihood of developing a protective immune response.
22. History of malignancy within the last 5 years other than basal skin cancer;
23. Any condition, that in the opinion of the investigator, would be negatively affected by rapamycin.
24. Patients with a documented history of moderate or severe alcohol or substance use disorder within the 12 months prior to randomization.
25. History of or evidence of clinically severe interstitial lung disease
26. Immunocompromised state, regardless of etiology
27. Patients who, in the opinion of the investigator, present with a condition that would compromise their safety or that would make study completion unlikely

8.3 Patient Completion and Withdrawal Criteria

8.3.1 Screen Failures and Replaced Subjects

A patient is considered enrolled in the study at the time of ICF signature. Any patient that is screened but not dosed will be considered a screen failure and the reason for failure will be documented.

Any patient that is randomized but not dosed will be replaced and not included in the ITT population, and the reason for not being dosed will be documented.

Within the 45-day screening window, out-of-range laboratory tests may be repeated up to 2 times before declaring a screen failure (except for COVID-19 testing as described in Section 12.1.8.7). After the 45-day screening window, patients can be re-screened once.

8.3.2 Patient Completion

A patient will be considered to have completed the double-blind treatment phase of the study when the patient has completed Day 28 of Treatment Period 6. The patient will be considered to have completed the double-blind extension phase of the study when the patient has completed the Safety Follow-up visit that occurs 30 days (+ 4 day) after the Treatment Period 12 Day 0 visit. Enrolled patients who prematurely discontinue for any reason before completion of the study will be treated as outlined below in Section 8.3.3.1.

8.3.3 Enrolled Patient Withdrawal and Discontinuations

8.3.3.1 Withdrawal Procedures

Early termination from the study occurs when an enrolled patient withdraws consent or is lost to follow-up. The reason for withdrawal will be evaluated and recorded in the case report form (CRF) and source documents.

Patients may withdraw consent at any time. Reason(s) for withdrawal of consent, failure to return for the necessary visits, or termination from the study should be documented. All patients that withdraw

early upon termination should have the Early Termination visit assessments completed (i.e., End of Study assessments) (Appendix A or Appendix C), if the assessments pose no risk to the patient and the patient allows such assessments.

The Investigator should consult with the Sponsor/medical monitor prior to withdrawing study treatment from any patient in the study. Since this is a multiple-dose study, once dosed, patients generally should not be terminated by the Investigator. The patient should be followed through the end of Treatment Period 12, unless the patient withdraws consent or is lost to follow-up. In situations where continued participation in certain aspects of the study pose a risk to the patient, with consultation with the medical monitor, the Investigator should discontinue those procedures that pose a risk and should continue to collect data and conduct those assessments that do not put the patient at risk through the end of Treatment Period 12. Patients with compliance issues or major deviations that effect data quality will also continue to be followed through the end of Treatment Period 12 collecting as much data on the patient as possible, unless otherwise indicated by the Sponsor.

8.3.3.2 Patients Lost to Follow-Up

For patients to be considered as lost to follow-up, at least 3 contact attempts must be documented, of which the last must be a letter sent by a service that requires a delivery signature record (e.g., US Postal Service certified letter or Federal Express/UPS letter that requires signature of delivery). If the letter is undeliverable or no response is received within 7 days, the patient will be considered terminated due to lost to follow-up. Additional efforts, will be implemented to encourage overall continued trial participation including: 1) weekly phone calls to establish patients overall satisfaction with engagement in the trial and participation; 2) use of NSAIDs and/or colchicine as rescue medication for patients with breakthrough symptoms; and 3) access to disease related educational material for implementation of life-style/dietary changes related to amelioration of the disease process.

9. TREATMENT OF PATIENTS

9.1 Description of Study Drug

SEL-212 is comprised of 2 components: SEL-037 and SEL-110.36 (Table 1). Lyophilized SEL-037 supplied as 40 mg SEL-037, with phosphate buffer and mannitol as excipients, in a 20 mL borosilicate glass vial with a chlorobutyl rubber stopper and an aluminum-plastic combination blue cap. SEL-110.36, a lyophilized powder containing synthetic biodegradable polymeric nanoparticles encapsulating rapamycin, with sucrose and Tris buffer (tris(hydroxymethyl)aminoethane) as excipients in a 20 mL, Type 1 borosilicate glass vial with a chlorobutyl rubber stopper and an aluminum-plastic combination white cap. Vials are filled to provide 10 mg of SEL-110.36.

Table 1: Investigational Product

	Investigational Product	**Investigational Product**
Product Name:	SEL-037	SEL-110.36
Dosage Form:	Lyophilized powder for solution	Lyophilized powder for suspension
Unit Strength:	40 mg SEL-037 per vial	10 mg SEL-110.36 per vial
Route of Administration:	Intravenous infusion	Intravenous infusion via syringe pump
Physical Description:	20 mL borosilicate glass vial with rubber stopper and aluminum-plastic blue combination cap	20 mL borosilicate glass vial with rubber stopper and aluminum-plastic white combination cap
Manufacturer:	Manufactured for Selecta Biosciences by 3S and Emergent BioSolutions	Manufactured for Selecta Biosciences by LSNE Contract Manufacturing

9.2 Concomitant Medications and Therapies

Concomitant medications are permitted during this study unless otherwise restricted. Concomitant medications used in the 3 months prior to screening and during the study will be documented.

9.2.1 Uric Acid Lowering Therapy

Uric acid lowering therapy (ULT) including, but not limited to allopurinol, febuxostat (Uloric®), probenecid, lesinurad (Zurampic®, Duzallo®), losartan, pegloticase (Krystexxa®) and benzbromarone ULT, **are not permitted for use during the study**. Patients will undergo a ULT washout period prior to dosing with study drug according to the schedule described in Appendix A. Patients on a stable long term dose of losartan may be allowed to continue in the study without changing to another angiotensin II receptor blocker.

Patients cannot have any prior exposure to or be presently taking any experimental or marketed uricase therapy, as defined in Exclusion Criterion 19 (Section 8.2).

9.2.2 CYP3A4/P-gp Inducers and Inhibitors

The use of CYP3A4/P-gp major inducers or major inhibitors are prohibited 14 days prior to dosing and during the trial. Examples of major inducers include, but are not limited to carbamazepine-Tegretol®, phenobarbital, phenytoin-Dilantin®, rifampin/rifampicin-Rifadis®, St. John's Wort-Hypericum perforatum. Examples of major inhibitors include, but are not limited to nefazodone-Serazone®, itraconazole-Sporanox®, ketoconazole-Nizoral®, voricinazole-Vfend®, atraznavir-Reyataz®, indinavir-Crixvan®, nelfinavir-Viracept®, ritonavir-Norvir, saquinavir-Invirase®, clarithromycin-Biaxin®, telithomycin-Ketek®, and grapefruit juice.

9.2.3 Other Concomitant Medications

Patients on medications (e.g., antifungals and/or calcium channel blockers) that do not rely on a mechanism of action that is known to increase the level or effect of rapamycin (sirolimus – Rapamune®) are permitted to continue taking these medications prior to and during the study, and will not be noted as a protocol deviation.

9.3 Treatment Compliance

Study drug will be administered in the controlled environment of a clinical research center. Direct observation of the administration of the study drug by study staff will ensure compliance. The date and time of the start and stop of drug administration and volume infused will be recorded.

9.4 Randomization and Blinding

This is one of two replicate randomized, double-blind, placebo-controlled, parallel arm trials to determine the safety and efficacy of two different dose levels of SEL-212 compared to placebo. The study will randomize approximately 120 patients with chronic refractory gout. Approximately 60% of the randomized patients will have tophi at Baseline. Patients, stratified as to the presence or absence of tophi, will be randomized in a 1:1:1 allocation ratio prior to Baseline to receive one of two dose levels of SEL-212 or placebo every 28 days for approximately 6 months in trials SEL-212/301 and SEL-212/302. The SEL-212 doses will differ as to the SEL-110.36 component. Participants will receive SEL-037 administered at a dose of 0.2 mg/kg via intravenous (IV) infusion immediately after receiving SEL-110.36 at a dose of either 0.1 mg/kg (SEL-212A) or 0.15 mg/kg (SEL-212B) via IV infusion. The placebo will consist of normal saline that will be administered in the same way that the SEL-212 components are administered to maintain the integrity of the study blind. Prior to randomization, to ensure balance among the treatment groups with regard to the presence or absence of tophi, a stratified randomization algorithm will be incorporated into the IVR system, based on the presence or absence of prevalent tophi. All patients, Investigators, study personnel, and Sponsor personnel involved in the conduct of the study will be blinded to patient treatment assignment, except for a designated unblinded statistician who will generate and have access to the randomization codes, a designated unblinded site representative (e.g., pharmacist) who will prepare study drug on the day of treatment, an unblinded infusion nurse who will be responsible for dosing the patient, a designated unblinded medical monitor for assessing the treatment stopping rules, and unblinded drug supply personnel. Prior to study drug administration in Treatment Periods 2 through 12, the unblinded medical monitor will determine a

patient's eligibility for treatment with study drug by evaluating the patient's sUA level measured from the blood sample obtained from Day 21 of the most recently completed treatment period. The unblinded statistician and medical monitor will not otherwise participate in any study procedures or data analysis prior to unblinding of the data.

Central and site laboratory vendors will also be blinded to treatment assignment.

Certain post-dose laboratory results can be unblinding. Therefore, the results of such laboratory tests will be communicated only to unblinded personnel.

Study personnel will endeavor to safeguard the integrity of the study blind to minimize bias in the conduct of the study.

9.4.1 Procedures for Breaking the Blind Prior to Study Completion

Breaking the blind is expressly forbidden except in the event of a medical emergency where the identity of the treatment assignment must be known in order to properly treat the patient. If breaking the blind is required because of a medical emergency, the treatment identity for the unblinded patient only will be revealed by the qualified designee with approval from the Sponsor's medical monitor or designee.

In all cases where the code is broken, the Investigator must record the date and reason for code breaking. The unblinding should be noted in the participant's CRF.

9.4.2 Revealing Randomization

In the absence of a medical emergency, the blinded randomization for this study will not be revealed until all data are entered in the database, edits checks are performed, queries closed, CRFs are signed by the Investigator at each site, and the database is officially locked.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1 Study Drug

This is a randomized, double-blind study. The designated site representative (e.g., pharmacist) will be unblinded to enable preparation of study drug on the day of treatment. The site representative will take appropriate steps during study drug preparation to maintain the integrity of the study blind. Prior to study drug administration in Treatment Periods 2 through 12, the unblinded medical monitor will determine a patient's eligibility for treatment with study drug by evaluating the patient's sUA level measured from the blood sample obtained from Day 21 of the prior treatment period.

10.1.1 SEL-212

SEL-212 is comprised of 2 components: SEL-037 and SEL-110.36. Refer to Section 9.1 for complete descriptions of the components.

Two dose levels of SEL-212 will be investigated in this study:

SEL-212A:

- SEL-110.36: 0.1 mg/kg based on patient's body weight
- SEL-037: 0.2 mg/kg based on patient's body weight

SEL-212B:

- SEL-110.36: 0.15 mg/kg based on patient's body weight
- SEL-037: 0.2 mg/kg based on patient's body weight

10.1.2 Placebo

Placebo will consist of normal saline. Normal saline will be administered sequentially in the same way that the SEL-212 components are administered to maintain the integrity of the study blind.

10.2 Study Drug Packaging and Labeling

SEL-212 will be supplied in vials in individual cartons with cartons and vials unassigned to a patient.

10.3 Study Drug Storage

Upon receipt of the SEL-037 vials at the clinical site, the vials should be stored in a secured way at 2°C to 8°C within the primary or secondary box container in order to protect the SEL-037 from long-term light exposure.

Upon receipt of the SEL-110.36 vials at the clinical site, the vials should be stored in a secured way at 2°C to 8°C within the primary or secondary box container in order to protect the SEL-110.36 from long-term light exposure.

10.4 Study Drug Preparation

Doses of SEL-212 are calculated on a mg/kg basis according to a patient's weight. For Treatment Period 1, the patient's Screening weight will be used for dose preparation. For the remaining treatment

periods, the patient's weight at the Day 21 visit from the preceding treatment period will be used for dose calculation.

Detailed procedures and examples of dose calculations and study drug preparation are provided in the Study Operations Manual.

10.4.1 SEL-037 Preparation

Each vial of SEL-037 will be reconstituted with 6.9 mL of sterile water for injection United States Pharmacopeia (USP) or equivalent to a 6 mg/mL solution and then the appropriate volume of reconstituted solution will be diluted in 100 mL of room temperature 0.9% sodium chloride for injection, USP for administration. The detailed reconstitution procedure, including the time for vials to rest undisturbed and the number of gentle vial inversions to perform, is provided in the Study Operations Manual. The full resultant volume of the SEL-037-normal saline solution (100 mL saline + required volume of reconstituted SEL-037 + saline bag manufacturing overfill) will be administered in the allotted time. The SEL-037-normal saline solution infusion must be completed within 12 hours of the start of vial reconstitution. The infusion of SEL-037-normal saline solution must be completed within 6 hours of dilution. If not administered immediately, store refrigerated and use within the time specified above. SEL-037 should be administered on the same day and as soon as possible after reconstitution.

10.4.2 SEL-110.36 Preparation

Each vial of SEL-110.36 will be reconstituted with 4.9 mL of sterile water for injection United States Pharmacopeia (USP) or equivalent, to a 2 mg/mL suspension before being drawn into appropriately sized syringe/syringes for IV infusion with a syringe pump. The detailed reconstitution procedure, including the time for vials to rest undisturbed and the number of gentle vial inversions to perform, is provided in the Study Operations Manual. The SEL-110.36 dose must be completely administered within 12 hours of the start of vial reconstitution. SEL-110.36 should be administered on the same day and as soon as possible after reconstitution. If not administered immediately, store refrigerated and use within the time specified above.

10.4.3 Placebo Preparation

Placebo will consist of normal saline. An unblinded designated site representative (e.g., pharmacist) will prepare placebo infusions in a manner that maintains the integrity of the study blind.

10.5 Urate-Lowering Therapy Wash-out

Chronic refractory gout patients may elect to undergo wash-out of urate-lowering therapy at any point during Screening but must begin at least 7 days prior to the first dosing of study drug. Patients must continue to remain off ULT for as long as they participate in the clinical study.

10.6 Premedication

10.6.1 Gout Flares (Prophylaxis and Treatment)

All patients that are expected to be randomized will be premedicated for gout flare prevention. The regimen will begin at least 7 days prior to the first dosing of study drug and continue for as long as the patient is participating in the clinical study.

Patients not already taking colchicine will receive colchicine 1.2 mg as a single loading dose followed by 0.6 mg QD for the remainder of participation in the trial. If the patient cannot tolerate the loading dose level of 1.2 mg, then the patient will initiate and maintain colchicine at 0.6 mg per day. If the patient cannot tolerate the loading dose level of 0.6 mg, then the patient will initiate and maintain colchicine at 0.3 mg per day.

Patients with a documented medical reason that describes a contraindication to colchicine will receive ibuprofen 600 mg TID or an equivalent NSAID unless the patient has a contraindication to NSAID. At the discretion of the Investigator, a proton pump inhibitor may be prescribed with the NSAID as gastric prophylaxis. Patients with documented medical reasons that describe contraindications to both colchicine and NSAIDs will receive no premedication for gout flare.

Patients who began receiving a NSAID as gout flare prevention medication due to a contraindication to colchicine should continue to receive the NSAID during study participation.

As gout flares are expected to occur despite preventative premedication, incidents of gout flare are to be recorded as an AE and treated at the discretion of the Investigator to provide adequate patient care.

10.6.2 Premedication with Antihistamines and Steroids

All patients in the study will be pre-medicated with oral antihistamines and steroids as follows for prevention of infusion reactions:

- Prednisone (40 mg) oral (PO) approximately 24 (± 12) hours prior to dosing
- Fexofenadine (180 mg) oral (PO) approximately 12 (± 2) hours prior to dosing
- Fexofenadine (180 mg) oral (PO) approximately 2 (± 1) hours prior to dosing
- Methylprednisolone (100 mg) (or equivalent) up to 125 mg, depending on patient weight, IV approximately 1 (± 0.5) hours prior to dosing

Refer to Section 12.2.1.5 for guidance on reducing the risk of infusion reactions and for managing infusion reactions.

10.7 Administration

Before administration of study drug, patients will be premedicated with antihistamines and steroids as described in Section 10.6. The timing of premedication and study drug administration are presented graphically in Appendix E, Appendix F and Appendix G.

Patients will receive treatment with study drug on Day 0 of each treatment period for a total of 12 doses of study drug.

All study drugs should be administered through the same IV access. All blood samples should be drawn from an alternative venous access.

The reconstituted SEL-110.36 will be withdrawn from the vial and dosed via IV infusion with a syringe infusion pump utilizing an appropriately sized syringe. SEL-110.36 will be infused at a rate of 1.5 mL/hr for the first 30 minutes, then at a rate adequate to deliver the remaining dose volume over a period of 60 minutes concurrently with 125 mL normal saline. If an infusion reaction occurs during the administration of SEL-110.36, the infusion may be slowed, or stopped and then restarted at a slower rate at the discretion of the Investigator. Following the infusion of SEL-110.36, the main IV line must be flushed with normal saline prior to the start of the SEL-037 infusion. Refer to the Study Operations Manual for instructions regarding infusions for patients with medical history involving cardiovascular comorbidities.

SEL-037 infusion will start up to 30 minutes after completion of the SEL-110.36 infusion. SEL-037 will be infused via infusion pump over a time period of no less than 120 minutes. If an infusion reaction occurs during the administration of SEL-037, the infusion may be slowed, or stopped and then restarted at a slower rate at the discretion of the Investigator. Following the infusion of SEL-037, the main IV line must be flushed with normal saline.

The Investigator is permitted to modify the infusion parameters (decrease the rate of infusion or interrupt the infusion) if medically warranted in response to an AE. The Investigator will notify the unblinded medical monitor of any changes in infusion parameters. Detailed instructions for modifying the infusion parameters are included in the Study Operations Manual.

If an infusion reaction occurs, Investigators are permitted to use concomitant medications or treatments deemed necessary to provide adequate patient care. Investigators should also utilize the infusion reaction lab kit (samples for: chemistry, hematology, coagulation, histamine, serum tryptase, and anti-uricase) provided in the Study Operations Manual to collect additional blood specimens. In the case of a Grade 3 or 4 infusion reaction occurring during an infusion, the administration of study drug should be immediately discontinued, and the affected patient should be treated according to the clinical trial site's protocol for infusion reactions (e.g., monitoring, administration of antihistamines, corticosteroids, fluids and epinephrine, as clinically indicated). The patient should be withdrawn from subsequent study drug treatment.

10.8 Study Drug Accountability

Study drug will only be used as directed in the protocol. Study personnel will account for all vials of study drugs received, dispensed, and used for each patient, and vials returned. The date and time of reconstitution and dilution will be recorded. Used vials should be traceable back to the patient. The Investigator is responsible for the study drug accountability, reconciliation, and record maintenance.

10.9 Study Drug Handling and Disposal

Unused, partially used, and empty vials will be stored until the Sponsor or Sponsor's representative instructs the site to return or dispose of the vials. Unused supplies will be returned or disposed of using appropriate documentation according to International Conference on Harmonization-Good Clinical Practice (ICH-GCP), local requirements, applicable Occupational Safety and Health Administration and Environmental Protection Agency regulations, and applicable study-specific procedures.

11. ASSESSMENT OF EFFICACY

11.1 Activity Assessment

11.1.1 Serum Uric Acid Assessment

The primary endpoint of this study is the comparison in the percentage of patients treated with two different dose levels of SEL-212 compared to placebo who achieve and maintain reduction of sUA < 6 mg/dL for at least 80% of the time during Treatment Period 6.

Serum samples for measurement of sUA will be collected according to the schedule described in Appendix A and Appendix C. Methods used for processing samples and for measurement of sUA levels are described in the Study Operations Manual.

11.1.2 Uricase Activity

Serum samples for measurement of uricase activity will be collected according to the schedule described in Appendix A and Appendix C. Validated methods will be used for processing samples and for measurement of uricase activity as described in the Study Operations Manual.

11.2 Gout Assessment

11.2.1 Tophus Assessment

Assessment of tophi will be performed according to the schedule described in Appendix A and Appendix C.

Baseline photographs of the hands and feet of each patient will be obtained using a standardized method in all patients (whether or not a prevalent tophus was identified by the Investigator at Baseline), together with photographs of up to two other representative sites of tophaceous disease. The baseline photographs will be assessed by a Central Reader to prospectively identify sites of tophaceous disease present at the start of treatment. The Central Reader will be blinded to patient treatment assignment and to the Investigator's identification (or lack of identification) of a tophus to control for potential bias. Up to five tophi in the photographs will be chosen by the Central Reader for measurement over the course of therapy. The Central Reader will assess the photographs for size of each target tophus using the image analysis software. To be considered measurable, tophi are required to be ≥ 5 mm in the longest dimension at Baseline and to have borders distinguishable to the Central Reader. Up to two tophi (approximately > 10 mm in the longest dimension at Baseline) representative of the patient's tophus burden but unable to be accurately measured (e.g., due to location, shape, or other factors), may also be evaluated at the Central Reader's discretion. Once the Central Reader completes the assessment of photographs from a patient's study visit, the Central Reader will not be permitted to change the evaluation.

Individual response for measurable and unmeasured tophi will be assessed by the Central Reader by comparing the tophus area (approximated for unmeasured) to its baseline measurement using assessment categories described in Table 2.

Table 2: Individual Tophus Assessment Categories (by Central Reader)

Assessment	Measurable Tophus	Unmeasured Tophus
Complete Response (CR)	A 100% decrease in the area of the tophus	The disappearance of the tophus
Marked Response (MR)	At least a 75% decrease in the area of the tophus	
Improved (I)		An approximate 50% or more reduction from baseline in the size of the tophus
Partial Response (PR)	At least a 50% decrease in the area of the tophus	
Stable Disease (SD)	Neither a 50% decrease nor a 25% increase in the area of the tophus can be demonstrated	Neither improvement nor progression from baseline can be determined.
Progressive Disease (PD)	A 25% or more increase in the area of the tophus	An approximate 50% or more increase from baseline in the area of the tophus
Unable to Evaluate (UE)	The tophus cannot be accurately measured for any reason at any given post-baseline time point	The tophus cannot be assessed for any reason at any given post-baseline time point

The overall categorical tophus responses of CR, PR, SD, or PD will be based on the best response reported among all tophi (measurable and unmeasured) for an individual patient, as described in Table 3. For the principal analysis of tophus assessments, if any one tophus shows complete response (CR), the overall response will be reported as CR if there is no evidence of progressive disease (PD).

Table 3: Overall Tophus Response Categories

Overall Assessment	How to determine overall assessment:
Complete Response (CR)	If CR (no PD) for either measurable or unmeasured tophus
Partial Response (PR)	If MR or PR (no CR, PD) for measurable or Improved (I) for unmeasured tophus
Stable Disease (SD)	If SD (no CR, PR, PD) for either measurable or unmeasured tophus
Progressive Disease (PD)	If PD for any measurable or unmeasured tophus, or if any new tophus appears during the study
Unable to Evaluate (UE)	If UE for all measurable or unmeasured tophus

11.2.2 Gout Flare Assessment

Gout flare will be assessed as part of AE collection with severity determined as described in Section 12.2.2.3. Gout flares will be assessed at each study visit during the Treatment Phase using a validated definition of flares in patients with established gout (*Gaffo 2018*). In addition, in an exploratory manner, gout flares will be self-assessed weekly by the patient after randomization and in each Treatment Period using a weekly flare diary (*Poiley 2016*).

11.2.3 Joint Assessment

Tender and/or swollen joints will be counted. The following joints will be assessed: metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints of the hands; the metatarsophalangeal and interphalangeal joints of the feet; shoulder, elbow, wrist, knee, ankle, tarsus, sternoclavicular, and acromioclavicular joints.

11.3 Health Questionnaires: Patient Reported Outcomes and Quality of Life Assessment

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

The HAQ-DI will be administered according to the schedule described in Appendix A and Appendix C.

The HAQ-DI is an instrument that assesses fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both the upper and lower extremities. Standard scoring takes into account the use of aids and devices or assistance from another person. There are 20 items in 8 categories that represent a comprehensive set of functional activities: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. The stem of each item assesses a patient's functional ability using their usual equipment during the past week. Each category contains at least 2 specific sub-category questions. For example, under the category "walking," patients are asked about their ability to walk outdoors on flat ground and to climb up 5 steps. The HAQ-DI includes a patient global assessment of disease and a visual analog scale for pain assessment.

11.3.2 Provider Global Assessment of Disease Activity

The Provider Global Assessment of Disease Activity (PrGA) will be conducted according to the schedule described in Appendix A and Appendix C. The PrGA will be administered to assess the severity of the patient's disease on a scale from 0 (patients feels "very well") to 100 (patient feels "very poor"). Lower scores indicate less severe disease.

11.3.3 Short Form Health Survey 36 (SF-36)

The SF-36 will be administered according to the schedule described in Appendix A and Appendix C.

The SF-36 is a 36-item scale constructed to survey health status and quality of life (Ware 1992). The SF-36 assesses 8 health concepts: limitations in physical activities because of health problems; limitations in social activities because of physical or emotional problems; limitations in usual role activities because of physical health problems; bodily pain; general mental health (psychological distress and well-being); limitations in usual role activities because of emotional problems; vitality (energy and fatigue); and general health perceptions. The standard form of the instruments asks for patients to reply to questions according to how they have felt over the previous week.

11.4 Inflammation Biomarker and Multiomic Assessments

11.4.1 Inflammation Biomarkers of Gout

Blood samples will be drawn according to the schedule described in Appendix A and Appendix C for assessment of inflammation biomarkers. Validated methods will be used for processing

samples and for measurement of inflammation biomarkers as described in the Study Operations Manual.

11.4.2 Multiomic Markers of Gout

A blood sample will be drawn according to the schedule described in Appendix A and Appendix C for determination of correlations between multiomic markers of gout and observed treatment effect of study drug. Validated methods will be used for processing samples and for measurement of multiomic markers as described in the Study Operations Manual.

11.4.3 Biomarkers of Immune Tolerance

Blood samples will be drawn according to the schedule described in Appendix A and Appendix C for assessment of inflammation biomarkers. Validated methods will be used for processing samples and for measurement of inflammation biomarkers as described in the Study Operations Manual.

11.4.4 Multiomic Markers Related to Immune Tolerance

A blood sample will be drawn according to the schedule described in Appendix A and Appendix C for determination of correlations between multiomic markers of gout and observed treatment effect of study drug. Validated methods will be used for processing samples and for measurement of multiomic markers as described in the Study Operations Manual.

11.4.5 Human Leukocyte Antigen (HLA) Typing

A blood sample will be drawn according to the schedule described in Appendix A for determination of human leukocyte antigen (HLA). If the sampling timepoint has passed, then the sample for HLA typing should be drawn at the next scheduled study visit. Validated methods will be used for processing samples and for measurement of human leukocyte antigen as described in the Study Operations Manual.

11.4.6 Imaging Assessments

Multi-energy computed tomography (CT) scans will be performed at selected investigational sites as an exploratory measure to visualize uric acid deposits and/or total body uric acid deposits. Imaging will be conducted according to the schedule described in Appendix A and Appendix C. The Screening assessment should be performed after a preliminary determination of eligibility (Section 8) and prior to the first study drug dose on Day 0 of Treatment Period 1. Procedures for the multi-energy CT scan and analysis can be found in the Study Operations Manual.

12. ASSESSMENT OF SAFETY

12.1 Safety Parameters

12.1.1 Demographic/Medical History

Demographic and significant medical history will be documented according to the schedule described in Appendix A. Medical history will be recorded up to the time of dosing.

12.1.2 Concomitant Medications and Procedures

Concomitant medications and procedures will be documented according to the schedule described in Appendix A and Appendix C.

12.1.3 Vital Signs

Vital signs will be documented according to the schedule described in Appendix A and Appendix C.

Vital signs will include systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse (beats per minute, bpm), respiratory rate (breaths per minute), and temperature (°C). Blood pressure and heart rate will be recorded after at least 5 minutes of rest in a sitting position. The blood pressure measurement should be repeated after at least 30 seconds and the average of the 2 readings calculated and recorded.

12.1.4 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed according to the schedule described in Appendix A and Appendix C.

12.1.5 Weight and Height

Weight (kg) and height (cm) will be performed according to the schedule described in Appendix A and Appendix C. Height will be measured at Screening only. Weight will be used to calculate study drug dosage as described in Section 10.4.

12.1.6 Physical Examination

Physical examinations will be conducted according to the schedule described in Appendix A and Appendix C. Breast, rectal, and urogenital exams are not required unless warranted based on the clinical judgment of the patient's medical history or current medical condition. The physical exam should be done by a physician or physician's assistant or similarly qualified individual. At some visits a Directed Physical Examination will be performed. These exams will be focused on assessment of any patient complaints and concerns.

12.1.7 Chest X-ray

Chest X-rays (CXR) will be performed according to the schedule described in Appendix A and Appendix C. Post-baseline CXRs will be taken to assess for presence of or changes in interstitial lung disease (ILD) compared to baseline CXR.

12.1.8 Laboratory Assessments

All laboratory assessment will be conducted according to the schedule described in Appendix A and Appendix C. Procedures for processing samples are included in the Study Operations Manual.

12.1.8.1 Hematology

Hematology assessments will include white blood cells (WBC) count with differential, red blood cell (RBC) count, hematocrit (Hct), hemoglobin (Hgb), and platelet (Plt) count.

12.1.8.2 Blood Chemistry

Clinical chemistry assessments will include alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, blood urea nitrogen (BUN), creatinine, fibrinogen, glucose (fasting), and electrolytes (sodium, potassium, chloride, bicarbonate, phosphate, and magnesium), and urine for urine-albumin-creatinine ratio (UACR). If the UACR cannot be calculated due to the microalbumin analysis being below the limit of quantification for the analytical method (eg. <12 mg/dL), the low microalbumin can be used as a surrogate for an acceptable UACR.

12.1.8.3 Glomerular Filtration Rate (GFR)

Estimated glomerular filtration rate (eGFR) will be calculated according to the Study Operations Manual.

12.1.8.4 Lipids

Fasting lipid assessments will include total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides.

12.1.8.5 Coagulation

Coagulation assessments will include prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR).

12.1.8.6 Antibody Assessments

Blood samples will be collected for assessment of antibody development to pegadricase and uricase, and for neutralizing antibodies and anti-pegadricase point of service validation. All blood samples for assessment of antibody development are required to be collected prior to study drug dosing. Antibody samples collected after the screening period will be assessed only in patients in active treatment arms.

12.1.8.7 COVID-19 Testing

Patients with COVID-19 infection can experience a range of clinical manifestations, from no symptoms to critical illness.

Screening Visit:

During Screening, all patients should be tested for COVID-19 by an FDA Emergency Use Authorized COVID-19 molecular assay for detection of SARS-CoV-2 RNA. A patient with a positive test result is permitted to request re-testing. A patient who requests re-testing should wait at least 10 days after the date of the first positive COVID-19 diagnostic test, as long as no symptoms have developed. If the

second test is positive for COVID-19, then the patient will be excluded from enrollment. If the second test is negative for COVID-19, then the patient must be tested a third time at least 24 hours after the second test to confirm the negative result.

On Study:

Once a patient is enrolled in the study, the investigational site will manage the patient according to its institutional standards and procedures established for COVID-19. During the study, a patient presenting with both symptoms (only severe and critical illness as per definitions below) of COVID-19 and positive COVID-19 test results will be discontinued from study treatment. The patient will be permitted to resume study visits for continued assessments (but not treatment with SEL-212 or placebo) according to the institutional standards and/or procedures of the investigational site.

Patients with mild-moderate COVID-19 illness (as per definitions below) will be allowed to resume study visits (on treatment with SEL-212 or placebo) after resolution of acute symptoms of clinical disease (except for loss of smell and taste) and meeting quarantine requirements so long as their subsequent dose occurs ≤90 days from their prior dosing day as per section 7.4.1.1. Patients with mild-moderate COVID-19 illness can continue **non-dosing study visits** as per protocol mandated visit window prior to resolution of acute symptoms according to the institutional standards and/or procedures of the investigational site.

Enrolled patients in the study with mild-moderate COVID-19 illness can be treated with anti-SARS-CoV-2 monoclonal antibodies. These patients will be allowed to resume study visits (on treatment with SEL-212 or placebo) after 2 weeks of receiving monoclonal antibodies, and confirmation of resolution of acute symptoms of clinical disease (except for loss of smell and taste), and meeting quarantine requirements so long as their subsequent dose occurs ≤90 days from their prior dosing day as per section 7.4.1.1.

Regardless of COVID-19 disease severity, enrolled patients in the study who are treated for COVID-19 with anti-viral therapy (including Remdesivir), anti-cytokine therapies (including anti-IL-6 or anti-IL-1 therapy), or JAK-inhibitors will be discontinued from study treatment. These patients will be permitted to resume study visits for continued assessments (but not treatment with SEL-212 nor placebo) according to the institutional standards and/or procedures of the investigational site.

The categories of severity of illness (description and criteria) for COVID-19 are noted below as a reference:

Asymptomatic or Pre-symptomatic Infection: Individuals who test positive for COVID-19 but who have no symptoms that are consistent with COVID-19.

Mild Illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.

Moderate Illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO2) ≥94% on room air at sea level.

Severe Illness: Individuals who have SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50%.

Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

The Investigator will report a patient's positive test results for COVID-19 according to institutional standards and/or procedures.

12.1.8.8 Serology

Serology screening will include human immunodeficiency virus (HIV) antibodies 1 and 2, hepatitis-B surface antigen (HBsAg), and hepatitis-C antibody (HCVAb).

12.1.8.9 Drug Screen

Urine drug screen will include amphetamines, barbiturates, benzodiazepines, cocaine, and opiates.

12.1.8.10 Pregnancy Screen

Samples for urine pregnancy testing (hCG) will be obtained.

Male patients of reproductive potential who are having intercourse with female partners of childbearing potential must agree to use 2 forms of contraception, 1 of which must be a barrier method, during the study and for 4 months after the last study drug administration. Acceptable barrier methods include a condom and diaphragm. Acceptable forms of birth control for female partners of childbearing potential are non-hormonal and hormonal intrauterine devices, hormonal birth control pills, hormonal birth control patches, hormonal birth control injections, hormonal birth control implants. Spermicide used alone is not an acceptable method and must be used with another acceptable form birth control method. Abstinence is acceptable if consistent with the patient's normal lifestyle.

Female patients are required to have negative hCG test results throughout the study. If a female patient becomes pregnant after she begins taking study drug, the procedures in Section 12.2.2.7 should be followed.

In addition, for any reported case of delayed menstrual period (over 1 month between menstruations) and for those women with infrequent or irregular menstrual cycles, confirmation of absence of pregnancy should occur.

12.1.8.11 Definition of Childbearing Potential and Acceptable Contraceptive Methods

A woman is considered of childbearing potential (i.e., fertile), following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for > 24 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of > 24 months of amenorrhea, one confirmatory FSH measurement must be obtained or documented.

For female partners of childbearing potential, the following methods of contraception, when used consistently and correctly, are considered reliable for participation of male patients in the study:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, or implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal; occlusion
- Vasectomized partner (provided that partner is the sole sexual partner and that vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (refraining from heterosexual intercourse during the entire study period; the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient)

12.1.9 Premedication Regimen

Refer to Section 10.6 for procedures about premedication regimens to prevent infusion associated reactions and gout flare.

12.2 Adverse and Serious Adverse Events

12.2.1 Definition of Adverse Events

Definitions in this section are in accordance with 21 CFR 312.32.

12.2.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence associated with the use of a drug (i.e., study drug) in humans, whether or not considered drug related. 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 drug and does not imply any judgment about causality. An AE can arise with use of any drug or medicinal product. A treatment-emergent AE (TEAE) is an AE that starts or worsens at any time after initiation of study drug on Day 0 of Treatment Period 1 until the End of Study Visit (30 days after completion of the last dose of study drug).

Patients will be considered enrolled in the study upon signing the ICF. During the Screening Phase (from time informed consent is signed to immediately before dosing) any clinically significant changes in the patient's health will be recorded in the patient's medical history and will not be considered as AEs. AEs

(and thus SAEs) will be collected from the time the patient is dosed (infusion is started) until the end of the End of Study Visit.

12.2.1.2 Serious Adverse Event (SAE)

An SAE is any AE that occurs irrespective of study treatment assignment, if it satisfies any of these criteria:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization ≥ 24 hours or prolongs existing hospitalization;
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions;
- Is a congenital anomaly or birth defect;
- Is an important medical event that, based upon appropriate medical judgment, may jeopardize the patient or patient may require medical or surgical intervention to prevent one of the outcomes listed above.

12.2.1.3 Suspected Adverse Reaction

A suspected adverse reaction is an AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

12.2.1.4 Unexpected Adverse Events and Unexpected Suspected Drug Reaction

An AE or suspected adverse reaction (an AE where there is a reasonable possibility that the drug caused the event; suspected drug related) is considered "unexpected" if it is not listed in the SEL-212 Investigator's Brochure or is not listed at the specificity or severity that has been observed.

12.2.1.5 Infusion Reactions / Adverse Events of Special Interest

A study drug-related AE that occurs within 24 hours after initiation of study drug infusion will be assessed as an infusion reaction. An infusion reaction suspected to be anaphylaxis will be assessed according to the clinical criteria for the diagnosis of anaphylaxis based on the National Institute of Allergy and Infectious Diseases (NIAID) / Food Allergy & Anaphylaxis Network (FAAN) Symposium criteria. (*Sampson 2006*).

Infusion reactions will be managed and treated as described below. In addition to premedication with antihistamines and steroids (Section 10.6.2), the following steps will be implemented in this protocol to either reduce the risk of infusion reactions or manage infusion reactions.

- Patients with prior exposure to uricase therapy will be ineligible
- Patients with a history of anaphylaxis or severe allergic reactions, history of severe atopy, angioedema, or previous infusion reactions will be excluded from the trial.

- Study drug will be administered at controlled rates only in a healthcare setting and by healthcare providers sufficiently equipped and prepared to manage infusion reactions including anaphylaxis.
- In case of infusion reaction, sites will perform specific assessments as specified in the Study Operations Manual.
- Each patient will be observed for infusion reactions after dosing of study drug in the clinic for approximately 4.5 hours from the start of study drug infusion. Patients will be informed about the signs or symptoms of infusion reactions and will be instructed to notify the Investigator immediately if they believe they are experiencing a reaction.
- Each patient shall remain for a minimum of 1 hour after the completion of infusion of study drug for a period of safety observation.
- All patients will be contacted approximately 24 hours after infusion to determine whether any infusion reaction AEs occurred.
- Patients who experience an infusion reaction will be contacted approximately 24 hours after the event as follow-up.
- Only sites with immediate capability to appropriately respond to a reaction of this severity will be allowed to participate in the trial to reduce the risk to any patient.
- Infusion Reactions (an AESI) will be reported to Parexel Safety in the same manner as SAEs using the same form but ticking the AESI box rather than the SAE box.

Adverse events of special interest (AESI) will be recorded specifically for occurrences of: gout flares, infections, malignancies, viral infections, interstitial lung disease, stomatitis, infusion-related reactions including anaphylaxis, thrombosis (e.g., deep venous thrombosis, pulmonary embolism), and the following laboratory tests, if deemed clinically significant by the PI: hyperlipidemia, worsening of renal function tests, proteinuria, and leukopenia.

12.2.2 Recording Adverse Events

Patients will be encouraged to spontaneously report any changes in health from the time of signing the ICF through completion of the study. Study staff will also inquire about any changes in the patient's health.

All AEs will be recorded in the source document and the CRF. It is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) for the presence of AEs and for a complete evaluation of known AEs.

At minimum for each AE, the Investigator will evaluate and report the event name/term/description, onset (date and time), resolution (date and time), event severity/intensity, relationship to study drug, action taken in regards to study drug, whether the event is an SAE, and whether or not it caused the patient to discontinue the study. The event time is only required while the patient is in the clinic.

During the Screening Phase (from time informed consent is signed to immediately before dosing) any clinically significant changes in the patient's health will be recorded in the patient's medical history and will not be considered as AEs.

12.2.2.1 Adverse Event Term/Name/Description

The Investigator will attempt to establish a diagnosis of each AE based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be the AE term used to document the AE/SAE and not the individual signs/symptoms.

12.2.2.2 Relationship to Study Drug

The Investigator is obligated to assess the relationship between study drug and the occurrence of each AE. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug will be considered and investigated. The Investigator will also consult the SEL-212 Investigator's Brochure and/or Product Information for marketed products in the determination of his/her assessment.

The Investigator will assess causality as to whether the event is related or not related to study drug based on the following definitions:

- Not Related: If no valid reason exists for suggesting a relationship to study drug or the AE was more likely explained by causes other than study drug.
- Unlikely to be Related: Onset of the event has a reasonable temporal relationship to study drug administration and although a causal relationship is unlikely, it is biologically plausible.
- Possibly Related: Onset of the event has a strong temporal relationship to administration of the study drug and a causal relationship is biologically plausible
- Related: The study drug dosing and AE were closely related in time and the AE may be explained by exposure to study product: e.g., known pharmacological effect or recurrence on re-challenge.

There may be situations, particularly when an SAE has occurred, where the Investigator has minimal information to make an assessment in an initial SAE report. However, it is very important that the Investigator always makes an assessment of causality for every SAE prior to transmission of the SAE report. The Investigator may change his/her opinion of causality in light of follow-up information, amending the SAE report accordingly. Any assessment of causality made by the Investigator should also be documented in the patient's source medical record.

12.2.2.3 Adverse Event Intensity/Severity Grading

AEs will be classified according to the Rheumatology Common Toxicity Criteria, version 2.0 (*Woodworth 2007*).

- Grade 1 (mild): AE that is usually transient of short duration; or involves mild or minor symptoms which are of marginal clinical relevance; or is asymptomatic consisting of clinical or diagnostic observations alone; no intervention or only minimal treatment with non-prescription intervention was required. The event does not generally interfere with usual activities of daily living.
- Grade 2 (moderate): AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living (e.g., shopping, laundry,

transportation, or ability to conduct finances), causing discomfort but poses no significant or permanent risk or harm to the patient.

- Grade 3 (severe): AE that is medically significant/important but not life-threatening; may require brief hospitalization to prevent the event from worsening; interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
- Grade 4 (life-threatening): An AE, and/or its immediate sequelae, which is associated with an imminent risk of death or which is associated with physical or mental disabilities that affect or limit the ability of a person to perform activities of daily living (eating, ambulation, toileting, etc.); disability may be persistent or result in significant disability, incapacity or limitation of self-care activities.

For an assessment of anaphylaxis, the clinical criteria for the diagnosis of anaphylaxis will be based on the NIAID/FAAN Symposium criteria (*Sampson 2006*).

12.2.2.4 Assessment of Outcome

The result or conclusion of the AE will be assessed and recorded by the Investigator as:

- Fatal
- Not recovered/not resolved (the AE has not improved, or patient has not recuperated).
- Recovered/resolved (the AE has improved, or patient has recuperated)
- Recovered/resolved with sequelae (recuperated but retained pathological conditions resulting from the AE)
- Recovering/resolving (the patient is improving but the AE has not yet resolved)
- Unknown (not known, not observed, not recorded, or refused)

12.2.2.5 Action Taken with Study Drug

The action taken regarding study drug will be assessed by the investigator as:

- Dose not changed (dose completed)
- Dose interrupted (IV infusion was temporally modified by temporarily stopping the infusion; slowing of the rate of infusion should also be classified as interrupted)
- Drug withdrawn (IV infusion was modified through termination of the infusion)

A response option for increasing or decreasing the dose is not an available course of action in this study.

12.2.2.6 Laboratory and Diagnostic Abnormalities as Adverse Events

Clinically significant abnormal laboratory findings or other abnormal diagnostic assessments (e.g., ECGs, vital signs) that are detected in dosed patients or that significantly worsen relative to baseline in dosed patients will be reported as AEs. Clinical significance is based on the Investigator's judgment but will typically include findings that results in study withdrawal, result in active management of the patient, or are associated with clinical signs and symptoms. Since the study requires patients with elevated or abnormal sUA levels, abnormal sUA levels will typically not be an AE unless judged by the Investigator as being more severe than expected for the patient.

12.2.2.7 Pregnancy

While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE and followed. The outcome of all pregnancies must be followed up and documented even if the patient is no longer a study patient.

The Investigator, or his/her designee, will collect pregnancy information on every female who becomes pregnant while enrolled in this study and on every female partner of a male patient who becomes pregnant while the male partner is enrolled in this study. The Investigator will report to the Sponsor or Sponsor's designee within 24 hours of learning of a patient's or female partner of a patient's pregnancy. In the case of a female partner of a male participant enrolled in the study becoming pregnant while the male patient is enrolled in this study, a separate pregnancy partner informed consent form will be completed by the patient's partner. The patient or female partner of a patient must also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor or Sponsor Designee, as appropriate. Follow-up on the child will be to the first well-child visit. Any premature termination of the pregnancy will be reported.

A spontaneous abortion or congenital abnormalities/birth defects will be considered SAEs and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and is considered reasonably related to the study drug by the Investigator, will be reported to the Sponsor.

12.2.3 Reporting Adverse Events

12.2.3.1 Adverse Event Reporting Period

The study period during which AEs must be reported is from the time the patient is dosed until the 30 (± 1) days after the last infusion of study drug. During the Screening Phase (from time informed consent is signed up to the time of dosing) any clinically significant changes in the patient's health will be recorded in the patient's medical history and will not be considered as AEs.

Investigators are not obligated to actively seek AEs or SAEs in former study patients. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably related to the study drug, the Investigator should promptly notify the Sponsor.

12.2.3.2 SAE Reporting Procedures

On discovery, all SAEs should be immediately reported (latest within 24 hours of knowledge of the event) to PAREXEL Safety Services by:

Completing the SAE report form and faxing the documents to PAREXEL Safety Services, using the appropriate regional PAREXEL SAE fax numbers below:

NA (Billerica): +1 781 434 5957

or

Completing the SAE report form and submitting it to PAREXEL Safety Services via email utilizing the address (es) below:

NA: NorthAmerica_Medical@parexel.com

In the event that the site is unable to complete the SAE form to report the event within 24 hours of their knowledge of the event, the investigators may report the SAE over the telephone via the SAE answering service, and then provide the completed SAE form via fax or email. If questions arise regarding the reporting procedures or the specifics of the reporting of an event, sites may call utilizing the following numbers:

NA (Billerica): +1 781 434 5010

The Investigator will complete the SAE form and provide all case information available at the time of the initial report. The investigator must include the following mandatory case information:

1. The patient identification number
2. The event description
3. The seriousness criteria
4. The Investigator's causality assessment

The reporting Investigator must send the written and signed SAE report by facsimile or email, within 24 hours of observing, notification of, or learning of the SAE to PAREXEL Safety Services as described above. Follow-up information regarding an SAE and the supporting data, including laboratory findings and discharge summaries, should be sent by facsimile or email to PAREXEL Safety Services within 24 hours of receipt of the information.

If the Investigator does not have all information regarding an SAE, the Investigator will not wait to receive additional information before completing as much of the form as possible and notifying the safety group. The form will be updated when additional information is received. The Investigator will always provide at minimum: 1) AE term or event name/description, 2) patient identifier, 3) an assessment of causality (Section 12.2.2.2).

12.2.3.3 Regulatory Reporting Requirements for SAEs

The Sponsor or Sponsor representative will report fatal or life-threatening SAEs that are unexpected suspected adverse reactions to the relevant regulatory authorities within 7 calendar days, and non-fatal or life-threatening SAEs that are unexpected suspected adverse reactions within 15 calendar days as Investigational New Drug (IND) Safety Reports, in accordance with 21 CFR 312.32. Prompt notification of SAEs by the Investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other patients are met.

12.2.3.4 Reporting Safety Information to the IRB/IEC

The Investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

All Investigators involved in studies with this drug will receive a copy of each IND Safety Report. When an Investigator receives an IND Safety Report or other safety information (e.g., revised Clinical Investigator's Brochure/Investigator's Brochure), the responsible person according to local requirements is required to promptly notify his or her IRB/IEC.

12.2.4 Follow-up of Adverse Events

The Investigator is required to proactively follow each patient and provide further information regarding AEs and SAEs. All AEs and SAEs will be followed until 30 (+4) days after the last dose of study drug, resolution of the event, until the condition stabilizes, until the event is otherwise explained, or until the patient is lost to follow-up, whichever occurs earlier. Once resolved, the appropriate CRF entries and event reporting forms will be updated, as appropriate.

All AEs and SAEs documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts. The Investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The Sponsor or the Sponsor's designee may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The Investigator is obligated to assist. If a patient dies during participation in the study or during a recognized follow-up period, the Sponsor will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE forms, with all changes signed and dated by the Investigator. This information will also be entered into the CRF.

13. STATISTICS

Details of the statistical methods outlined in the protocol for this study, including the hierarchical ordering of the secondary endpoints, will be documented in a Statistical Analysis Plan (SAP), which will be finalized prior to database lock. The SAP may add additional exploratory analyses; modifications to the planned analyses will be identified as such in the final SAP.

13.1 Sample Size Determination

The primary efficacy criterion in this study is defined as the percentage of the patients who achieve and maintain reduction of sUA < 6 mg/dL for at least 80% of the time during Treatment Period 6 by Day 28.

The sample size estimation is based on the main estimand for the primary efficacy criterion from version 5.0 of the protocol. This estimand considered all patients who discontinue study treatment due to lack of efficacy (e.g., meeting stopping rule), due to treatment-related or non-treatment related AE as treatment failures, as well as initiating prohibited medication that lowers sUA, withdrawal of consent or lost to follow up for reasons other than COVID-19.

Based on the results in the Phase 2 study (SEL-212/201) with SEL-212, the responder rate in all randomized and dosed patients is assumed to be 45% in SEL-212. For placebo, a responder rate of 5% is assumed. Considering a randomization ratio of 1:1:1 for SEL-212A and SEL-212B against placebo, a statistical power of 90%, a two-sided alpha-level of 2.5% and using the Chi-square test with continuity correction for the 2 pairwise comparisons of each SEL-212 dose group against placebo, 32:32:32 randomized and dosed patients will be required for each treatment group. Considering the potential that some randomized patients will terminate the study early (approx. 8%), the number of the patients required to be randomized and dosed in total is 105 (i.e., 35:35:35) to demonstrate efficacy. Randomized but not treated subjects will be replaced. For the sample size estimation, the Chi-square test is used instead of the Mantel-Haenszel test, although the randomization will be stratified for tophus presence (yes/no), as there is no valid assumption of the distribution of this stratification variable within the eligible patient population.

From an amendment in version 6.0 of the protocol, the main estimand for the primary efficacy criterion was updated to include patients who present a positive COVID-19 test along with severe or critical symptoms of COVID-19, and patients who missed all assessments of sUA during Treatment Period 6, as treatment failures. As these are expected to be unrelated to the treatment then assuming that the number of additional treatment failures to each arm would be roughly equal, the difference in response rates can still be assumed to be 40%, unless the treatment failure rate due to positive COVID-19 tests along with severe of critical symptoms of COVID-19 is sufficiently high that a difference of 40% cannot be observed (I.e. the treatment failure rate in the active arms is >60%, so even if the responder rate for the placebo group is 0%, a difference of 40% cannot be observed).

To mitigate this risk, an additional 15 patients have been added to the study sample size to account for potential treatment discontinuations that may occur due to the ongoing COVID-19 pandemic as a result of the emergence of COVID-19 variants which were not accounted for in the sample size calculations

resulting in approximately 120 patients (i.e., 40:40:40) to be randomized and dosed to demonstrate efficacy.

Sample size calculations were performed with the software package nQuery 8, Version 8.5.0.0.

13.2 Analysis Populations

13.2.1 Screened / Randomized Set

The Screened Set will include all patients who signed an informed consent. The Randomized Set will include all patients randomized and will be used for the presentation of patients in all patient listings. Randomized but not treated subjects will be replaced.

13.2.2 Safety Set (SS)

The Safety Set will include all patients who were administered any amount of study drug. Patients will be analyzed according to treatment received. The SS will be used for all analyses of safety endpoints.

13.2.3 Intent-to-Treat (ITT) Set

The Intent-to-Treat (ITT) Set will include all randomized and dosed patients. Replaced subjects will not be included in the ITT. Patients will be analyzed according to randomized treatment. The ITT will be used as primary population for analyses of efficacy endpoints.

13.2.4 Modified ITT

The modified ITT will include all randomized patients who were dosed, except those who discontinue treatment due to a COVID-19 infection as defined in section 12.1.8.7 or do not have at least 2 sUA measurements 7 days apart in TP6 due to a/multiple missed visits due to a COVID-19 infection or subsequent complications as defined in section 12.1.8.7. Patients will be analyzed according to randomized treatment.

13.2.5 Per Protocol Set

The Per Protocol Set (PPS) will include all patients who were administered at least one complete dose of study drug, who have at least one post-baseline assessment of sUA, who have sufficient data to assess the primary efficacy endpoint, and who have no major Protocol deviations affecting the primary efficacy assessments. Patients will be analyzed according to randomized treatment. The PPS will be defined for the double-blind treatment phase of the study only. Criteria for exclusion from the PPS will be provided in the Statistical Analysis Plan.

13.2.6 All randomized Set

The all randomized set will include all patients who were randomized. Patients will be analyzed according to randomized treatment group assignment.

13.2.7 Extension Phase Evaluable Set

The Extension Phase Evaluable Set (EPS) will include all subjects of the safety set who continue in the double-blind extension phase.

13.3 Protocol Deviations

All protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management, dosing, and sampling procedures or patient assessment will be listed. The list of protocol deviations will be reviewed by the Sponsor, the principal investigator and the study statistician and finalized before database lock.

13.4 Efficacy Analyses

Only efficacy endpoints of the double-blind treatment phase will be tested in a confirmatory way. Estimands are defined for the confirmatory analysis of efficacy in the double-blind treatment period.

Most of the efficacy endpoints from the double-blind treatment period will be assessed during the double-blind extension period, also. However, only descriptive summaries and comparisons will be provided for the extension period.

13.4.1 Primary Efficacy

The primary efficacy endpoint is defined as:

- Percentage of patients on SEL-212 versus placebo who achieve and maintain reduction of sUA < 6 mg/dL for at least 80% of the time during Treatment Period 6 by Day 28

The main estimand for the primary efficacy endpoint is defined as follows:

- Targeted population: Of all patients with gout refractory to conventional treatment defined by the study inclusion / exclusion criteria, the analysis population will include patients who were randomized to study treatment and who were dosed(ITT population).
- Variable: Binary variable indicating the treatment response status, whereby a responder is defined as a patient who has sUA < 6 mg/dL for at least 80% of the time during Treatment Period 6.
- Population-level summary: Difference in the percentage of treatment responders of each SEL-212 treatment group versus placebo.
- Intercurrent events:
    - Intercurrent events which lead to a discontinuation of study treatment due to lack of efficacy (includes meeting the stopping criteria) will be defined as treatment failures according to the composite strategy.
    - Premature stopping of study treatment due to treatment-related or non-treatment-related AE, with the exception of a positive COVID-19 test result along with severe or critical symptoms of COVID-19 will be defined as treatment failures according to the composite strategy.
    - Premature stopping of study treatment due to a positive COVID-19 test result along with severe or critical symptoms of COVID-19 will be defined as treatment failures according to the composite strategy.
    - Death will be considered as treatment failures according to the composite strategy.

- Use of prohibited medication that lower sUA levels will be considered as treatment failures according to the composite strategy.

- All other intercurrent events (e.g. use of prohibited medication that do not lower sUA levels but are classified as a major protocol deviation) will be treated using the treatment policy strategy i.e. the assessment of the sUA in TP6 up to Day 28 will be used.

Further estimands of interest for the primary efficacy will be provided in the SAP.

Frequency table of the treatment responders for the main primary efficacy estimand and further estimands of interest will be provided by treatment group, and the difference between each SEL-212 treatment group and placebo will be presented together with 97.5% confidence intervals.

The statistical testing of each SEL-212 treatment group versus placebo in all estimands of primary efficacy will be performed using the Mantel-Haenszel (MH) estimate and test for common risk difference considering the randomization stratum of tophus presence (yes/no) with a two-sided type 1 error rate $\alpha = 2.5\%$ to adjust for the two comparisons against placebo. Only the test results of the main estimand will be considered as confirmatory.

All above described analyses will be repeated on the mITT, all randomised and on the PP population as a supportive analysis.

The sUA time curve with assessments at Day 0 pre-treatment (0 h), Day 0 post-treatment (4.5 h), Day 7, Day 14, Day 21, and Day 28 will be used to estimate the proportion of time that the sUA level is below 6 mg/dL. Based on the serum samples collected during Treatment Period 6, an estimate of the time with sUA < 6 mg/dL by Day 28 can be determined by connecting each two neighboring data points with a straight line. If the sUA time curve goes above 6 mg/dL the linear interpolation method will be used to estimate the point in time at which the sUA time curve intercepts the line between the last sUA value < 6 mg/dL and the first value ≥ 6 mg/dL. The proportion of time that the sUA level is < 6 mg/dL will be computed by taking the ratio between the time during which the sUA level remains < 6 mg/dL (if necessary, using the linear interpolation method) and the entire time interval within Treatment Period 6 by Day 28, or the last available assessment before Day 28. Actual times will be plotted on the time curve, but only the interpolation of actual times up to Day 28 will be used. If a point at Day 28 is not available on the curve (possibly due to an extension of TP6 for reasons such as presenting mild-moderate COVID-19 symptoms), then the next available assessment between Day 28 and up to, and including Day 0, pre-treatment (0 h) in Treatment Period 7 will be used to interpolate the curve up to Day 28. This can include the use of unscheduled sUA assessments. If there are no such assessments available, but the use of unscheduled assessments allows the extension of the time curve from the last scheduled assessment prior to Day 28 then these can also be used. If only 2 or fewer assessments are available (allowing for the use of assessments after Day 28 up to, and including Day 0, pre-treatment (0 h) of Treatment Period 7, and further unscheduled assessments prior to Day 28), and the first and last

attended assessments are less than 7 actual days apart, then the response evaluation of Treatment Period 6 will be missing. Otherwise, the response evaluation will be derived from the available data points.

The proportion of time that the sUA level is < 6 mg/dL, i.e., percentage of non-hyperuricemic time, will be computed by taking the ratio between the time during which the sUA level remains < 6 mg/dL (if necessary, using the linear interpolation method) and the entire time interval within Treatment Period 6 by Day 28 (or last available assessment prior to Day 28 if no assessments are available from Day 28 up to, and including Day 0, pre-treatment (0 h) in Treatment Period 7).

For a patient who has completed Treatment Period 6 to be considered a responder, the proportion of time that the sUA level is < 6 mg/dL (i.e., percentage of nonhyperuricemic time) during Treatment Period 6 by Day 28 must be at least 80%.

Frequency table of the percentage of responder in Treatment Period 6 (patients who achieve and maintain reduction of sUA < 6 mg/dL for at least 80% of the time in Treatment Period 6) will be provided by treatment group. Additionally, a summary table with the total time a patient has sUA values < 6 mg/dL in Treatment Period 6 will be provided by treatment group.

Summary table of the actual values and change from baseline for sUA results will be provided for each scheduled sampling time point by treatment group.

Additionally, mean sUA level, reduction in mean sUA and percent reduction in mean sUA from baseline during Treatment Period 6 will be presented by treatment group.

- Mean sUA level is defined as the area under the sUA time curve (computed using the linear trapezoidal rule during Treatment Period 6) divided by the corresponding time interval.
- Reduction in mean sUA is computed by subtracting baseline sUA level from mean sUA during Treatment Period 6.
- Percent reduction in the mean sUA from baseline is computed as the mean sUA level during Treatment Period 6 minus baseline sUA level divided by baseline sUA level multiplied by 100%.

13.4.2 Key Secondary Efficacy

Hierarchical testing of key efficacy:

If the superiority of both (one) SEL-212 treatment group(s) against placebo for the main estimand of the primary efficacy is shown with a p-value ≤ 0.025, the hierarchical testing approach will continue to the testing of the main estimands of the key secondary efficacy comparing pairwise both (one) SEL-212 treatments against placebo. Only the main estimands of the key secondary efficacy will be tested in the successive order of the key secondary efficacy endpoints listed below. The test result of the nth key secondary efficacy estimand will be considered as confirmatory if the p-value of the two-sided test of the previous estimand resulted in a value less or equal 0.025.

Key secondary efficacy endpoints:

1. Reduction of mean sUA as computed by subtracting the Baseline sUA level from the mean sUA (area under the sUA time curve) during Treatment Period 6
2. Percent reduction of mean sUA as computed by subtracting the Baseline sUA level from the mean sUA (area under the sUA time curve) during Treatment Period 6
3. The change from Baseline to Treatment Period 6 in the physical summary score of the Short Form Health Survey (SF-36)
4. In patients with tophi at Baseline, the percentage of patients with at least PR (as best response) in overall tophus response evaluation until Day 28 of Treatment Period 6
5. The percentage of patients who achieve and maintain reduction of sUA < 6 mg/dL for at least 80% of the time during Treatment Period TP6 by Day 28 in the subset of patients with tophi at baseline
6. The change from Baseline to Treatment Period 6 in number of tender joints
7. The change from Baseline to Treatment Period 6 in the total score of Health Assessment Questionnaire (HAQ-DI)
8. Gout flare incidence during Treatment Periods 1-6
9. Gout flare incidence during Treatment Periods 1-3

The targeted population for all estimands of the key secondary efficacy endpoints numbered as 1, 2, 3, 6, 7, 8 and 9 is the same population as for the primary efficacy. In case of the key secondary efficacy endpoints numbered 4 and 5, the targeted population is additionally restricted to patients with tophi at baseline.

The main estimand for the key secondary efficacy endpoint 'Reduction of mean sUA as computed by subtracting the Baseline sUA level from the mean sUA (area under the sUA time curve) during Treatment Period 6' considers as variables of interest 'absolute difference between mean sUA value recorded in TP6 and the baseline sUA value', whereby the handling of all intercurrent events except death will be according to the treatment policy strategy. For deaths, the last available value will be used (while-on-treatment strategy). The population-level summary is the difference in mean between each SEL-212 treatment group vs. placebo.

The main estimand for the key secondary efficacy endpoint 'Percent reduction of mean sUA as computed by subtracting the Baseline sUA level from the mean sUA (area under the sUA time curve) during Treatment Period 6' considers as variables of interest 'mean TP6 sUA value – baseline sUA value) ÷ baseline sUA value ×100', whereby the handling of all intercurrent events except death will be according to the treatment policy strategy. For deaths, the last available value will be used (while-on-treatment strategy). The population-level summary is the difference in mean between each SEL-212 treatment group vs. placebo.

The main estimand for the key secondary efficacy endpoint 'Change from Baseline to Day 28 of Treatment Period 6 of the Physical Summary Score of SF-36' consider as variable of interest 'Change from Baseline to 6 months after start of study treatment (Day 28 of treatment period 6)', whereby the handling of all intercurrent events except death will be according to the treatment-policy strategy. For

deaths, the last available value will be used (while-on-treatment strategy). The population-level summary is the difference between each SEL-212 treatment group versus placebo in the change from baseline in Physical Summary score of SF-36.

The main estimand for the key secondary efficacy endpoint 'percentage of patients with at least PR (as best response) in overall tophus response evaluation until Day 28 of Treatment Period 6' in patients with tophi at baseline considers as variable of interest the 'binary variable indicating whether the patient had experienced at least a PR or not in overall tophus response evaluation until Day 28 of Treatment Period 6', whereby the handling of all intercurrent events except death will be according to the treatment-policy strategy. For deaths, best response until the last available response evaluation will be used (while-on-treatment strategy). The population-level summary is the difference in the percentage of patients with at least PR in overall tophus response (best response) between each SEL-212 treatment group versus placebo.

The main estimand for the key secondary efficacy endpoint 'percentage of patients who achieve and maintain a reduction of sUA < 6 mg/dL for at least 80% of the time during Treatment Period 6 in a subset of patients with tophi at baseline' considers as variable of interest the 'Binary variable indicating response status, whereby a responder is defined as a patient who has sUA < 6 mg/dL for at least 80% of the time during Treatment Period 6'. All intercurrent events which lead to a discontinuation of study treatment due to lack of efficacy (includes meeting the stopping criteria) treatment-related or non-treatment-related AE, present a positive COVID-19 test result along with severe or critical symptoms of COVID-19, used a prohibited medication that significantly lowers sUA, or death, will be considered as treatment failures following the composite strategy. All other intercurrent events (e.g., use of a prohibited medication that does not lower sUA) will be treated using the treatment-policy strategy. The population-level summary is the difference in the percentage of treatment responders of each SEL-212 treatment group versus placebo.

The main estimand for the key secondary efficacy endpoint 'change from Baseline to Day 28 of Treatment Period 6 in number of tender joints' considers as variable of interest the 'absolute change in number of tender joints from Baseline to 6 months after start of study treatment (Day 28 of Month 6)', whereby the handling of all intercurrent events except death will be according to the treatment-policy strategy. For deaths, the last available value will be used (while-on-treatment strategy). The population-level summary is the difference in the change from baseline in number of tender joints between each SEL-212 treatment group versus placebo.

The main estimand for the key secondary efficacy endpoint 'Change from Baseline to Day 28 of Treatment Period 6 of the Total Score of HAQ-DI' consider as variable of interest 'Change from Baseline to 6 months after start of study treatment (Day 28 of Month 6)', whereby the handling of all intercurrent events except death will be according to the treatment-policy strategy. For deaths, the last available value will be used (while-on-treatment strategy). The population-level summary is the difference between each SEL-212 treatment group versus placebo in the change from baseline in the Total Score of HAQ-DI.

The main estimand for the key secondary efficacy endpoint 'gout flare incidence in Treatment Period 1 to Treatment Period 6' and 'gout flare incidence in Treatment Period 1 to Treatment Period 3' considers as variable of interest 'Incidence of gout flare during the whole treatment period from start of treatment until end of month 6'. and 'incidence of gout flare during the first 3 months of treatment'. Gout flare incidence is defined as the total number of gout flares a patient experiences in respective time period divided by the length of observation of the patient in this time period. The handling of all intercurrent events except death will be according to the treatment-policy strategy. For deaths, the while-on-treatment strategy will be used. The population-level summary is the difference in the gout flare incidences between each SEL-212 treatment group versus placebo for the whole treatment period (start of treatment until end of month 6) and for the first 3 months of treatment. The analysis will be performed separately for the whole treatment (Treatment Period 1 to Treatment Period 6) and for the first 3 months (Treatment Period 1 to Treatment Period 3). whereby the confirmatory statistical comparison will be performed first for the whole treatment, then for the first 3 months.

Further estimands for the key secondary efficacy during the double-blind treatment phase will be defined in the SAP.

For the above defined estimands, the key secondary efficacy endpoints which are numbered 1, 2, 8 and 9 will be tested between each SEL-212 treatment group versus placebo using an ANCOVA, adjusting for treatment, randomization stratum and baseline value of the respective variable. The Least Square (LS) Mean difference between each SEL-212 and placebo treatments groups will be estimated along with its 97.5% confidence interval, and 2-sided p-values.

For the above defined estimands, the key secondary efficacy endpoints which are numbered as 3, 6 and 7 above - will be tested between each SEL-212 treatment group versus placebo using the mixed model for repeated measures (MMRM) with the change to baseline in the respective variable as dependent variable, and treatment, treatment-by-period interaction, randomization stratum and baseline value of the respective variable as fixed effect variables. The Least Square (LS) Mean difference between each SEL-212 and placebo treatments groups will be estimated on the treatment-by-period interaction at Treatment Period 6, along with its 97.5% confidence interval, and 2-sided p-values.

For the above defined estimands, the key secondary endpoints numbered as 4 and 5 will be tested between each SEL-212 treatment group versus placebo using the Chi-square test with continuity correction.

The analysis of the estimands will be carried out based on the ITT population with multiple imputation of missing values.

The number of tender joints at scheduled visits and the change from baseline will be summarized by treatment group on the ITT, mITT, all randomised and PP populations.

Frequency table of tophaceous patients at baseline with / without tophus reduction will be provided by visit and treatment group on the ITT, mITT, all randomised and PP populations. Additionally, the time until the first tophus reduction (i.e., the first time CR or PR is assessed in overall tophus response) will be summarized using descriptive statistics by treatment group on the ITT, mITT, all randomised and PP populations.

The HAQ-DI total score and the SF-36 summary score at scheduled visits and the change from baseline will be summarized by treatment group on the ITT, mITT, all randomised and PP populations.

Frequency table of the number and percentage of patients reporting gout flares per 3-months period, will be summarized by period and treatment group on the ITT, mITT, all randomised and PP populations. Additionally, a frequency table of the number and percentage of patients reporting gout flares per 3-month period by severity (life-threatening / severe / moderate /mild) and treatment group will be provided. The number and percentage of patients with at least one life-threatening or severe versus the number and percentage of patients with only mild or moderate gout flares per 3 month period will be presented for each treatment group.

Further supportive analyses for key secondary efficacy variables will be defined in the SAP.

13.4.3 Further Secondary Efficacy Endpoints and Analyses in the Double-Blind Treatment Phase

Additional secondary efficacy endpoints will be summarized by treatment group using descriptive statistics on the ITT population and will be compared between each SEL-212 treatment group and placebo using MH considering the randomization stratum tophus presence (yes/no) in case of binary endpoints or using, or using continuity corrected Chi-square test in case of binary endpoints within subgroups with/without tophi at baseline. In case of continuous or numerical endpoints treatment groups will be compared by ANCOVA, or MMRM as appropriate. All tests – except the tests within subgroups of tophus yes/no at Baseline - will adjust for the randomization stratum and will present exploratory p-values of two-sided tests. In addition, 95% confidence intervals for treatment differences between each SEL-212 treatment group and placebo will be computed. Details will be provided in the SAP.

13.4.4 Exploratory Endpoints and Analyses in the Double-Blind Treatment and Extension Phase

The summary of exploratory endpoints for the double-blind treatment and the double-blind extension phase will be performed using descriptive summary statistics.

Association between multiomic markers of gout and the treatment effect in patients with SEL-212 will be investigated.

13.5 Safety Analyses

Safety summaries will be presented for the double-blind treatment phase considering all dosed patients (Safety set), and for the subgroup of patients in the double-blind extension phase (Extension Phase Evaluable Set).

13.5.1 Extent of Exposure

Frequency tables of number and percentage of patients who received all doses and descriptive statistics of doses and total cumulative doses by treatment group will be presented.

13.5.2 Adverse Events / Adverse Drug Reactions

All AEs will be coded and grouped into Preferred Terms (PT) by System Organ Class (SOC), using the most recent MedDRA Version. All AEs will be summarized by SOC and PT.

Summaries by each treatment group for the whole study (i.e., double-blind treatment phase and double-blind extension phase) and for the double-blind treatment phase will be provided on the Safety Set overall and by SOC and PT with the number and percentage of patients reporting TEAEs, serious TEAEs, treatment-related TEAEs, AEs of special interest (AESIs), infusion reactions (this is a study drug-related AE that occurs within 24 hours after initiation of study drug infusion), TEAEs leading to withdrawal and TEAEs leading to death. Additional analysis will be performed on a subset of infusion reactions (this is a study drug-related AE that occurs within 1 hour after completion of study drug infusion) that fulfil the criteria of an Allergic Reaction/Hypersensitivity according to the Rheumatology Common Toxicity Criteria, version 2.0. In the overall summary, additionally, the number and percentage of patients with at least one severe TEAE, with at least one moderate TEAE but no severe TEAE and with only mild TEAEs will be provided. Similar summaries will be produced for the subset of patients continued into the double-blind extension phase (i.e., on the EPS) considering the whole study but also separately for each treatment phase.

The number and percentage of patients with TEAEs / serious TEAEs / treatment-related TEAEs / TEAEs of special interest and TEAEs leading to withdrawal will be summarized by SOC and PT for each treatment group and overall for the whole study and for the double-blind treatment phase on the Safety Set. Similar summaries will be produced for the subset of patients continued into the double-blind extension phase (i.e., on the EPS) considering the whole study but, also separately for each treatment phase.

Event rates by treatment group and overall will be provided for patients with at least one related TEAE, at least one SAE, and at least one TEAE of special interest. Additionally, the rate difference with 95% confidence interval comparing each SEL-212 treatment group to placebo as well as comparing the integrated SEL-212 arms to placebo will be provided.

TEAEs will also be summarized by maximum intensity and relationship to study drug.

13.5.3 Laboratory Assessments

Laboratory data will be summarized by the type of laboratory test and will be presented for each scheduled visit stratified by treatment group and overall. Shift tables of the number of patients with

low/normal/high (or normal/abnormal, as appropriate) values at each scheduled post-baseline visit compared to the low/normal/high (or normal/abnormal, as appropriate) categorization at baseline will be provided by treatment group and overall. For the visits of the extension phase, additionally the shifts from baseline of the extension (Day 0 Treatment Period 7) will be provided. Summary tables of actual values and changes from baseline will be provided for each continuous laboratory parameter at each scheduled visit by treatment group and overall. For the visits of the extension phase, additionally the change from baseline of the extension will be provided.

13.5.4 Vital Signs

Summary tables of the actual values and changes from baseline will be provided for each vital sign parameter at each scheduled visit by treatment group and overall. For the visits of the extension phase, additionally the change from baseline of the extension will be provided.

13.5.5 ECG

For each 12-lead ECG variable the actual value and the change from baseline will be summarized for the scheduled visits by treatment group and overall. For the visits of the extension phase, additionally the change from baseline of the extension will be provided. A shift table of the number and percentage of patients with normal and abnormal, and clinically significant abnormal values at each scheduled post-baseline visit compared to the normal / abnormal /clinically significant abnormal categorization at baseline will be provided by treatment group for the overall interpretation. For the visits of the extension phase, additionally the shifts from baseline of the extension (Day 0 Treatment Period 7) will be provided.

Frequency tables of abnormal clinically significant evaluations as well as the number and percentage of patients with noteworthy QTcF/QTcB values (> 450, > 480 and > 500 ms) and of patients with noteworthy QTcF/QTcB changes from baseline (≥ 30 but <60; ≥ 60 ms) will be provided. For the extension phase additionally the number and percentage of patients with noteworthy QTcF/QTcB changes from baseline of the extension (Day 0 Treatment Period 7) will be provided

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Upon the patient's permission, medical information may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of this study must be made available for inspection upon request by representatives of the US FDA, national and local health authorities, the Sponsor or its representatives, and by the IRB/IEC (or equivalent).

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Study Monitoring

In accordance with applicable regulations, ICH-GCP and procedures covering the study, a monitor will contact the site prior to the patient enrollment to review the protocol and data collection procedures with site staff. In addition, the monitor will periodically contact the site, including conducting on-site visits at an appropriate frequency to ensure data quality and to ensure the safety and rights of patients are being protected.

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

15.2 Audits and Inspections

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, quality assurance audits may occur during the study or after the study is complete. Authorized representatives of the Sponsor, the CRO conducting the study, a regulatory authority, an IRB/IEC may visit the site to perform audits or inspections to examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH-GCP, and any applicable regulatory requirements.

If an audit or inspection occurs, the Investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

15.3 Protocol Modifications

The initial protocol as well as all protocol amendments must be signed and dated by the Investigator and approved by the IRB/IEC prior to implementation of the original protocol and any amendment. The Principal Investigator must submit all protocol modifications to the IRB/IEC, as applicable for specific Investigators, or applicable local regulatory authority. The Sponsor or designee will submit protocol modifications to the FDA as needed.

Departures from the protocol will be determined as allowable on a case-by-case basis or in event of an emergency involving patient safety. The Investigator or other physician in attendance must contact the Medical Monitor as soon as possible to discuss the circumstances of the emergency. The Medical Monitor, in concurrence with the Investigator, will decide whether the patient should continue to participate in the study. All protocol deviations and the reason for such deviations must be noted on the source document and in the CRF, and reported to the IRB/IEC as appropriate.

16. ETHICS AND GOOD CLINICAL PRACTICE COMPLIANCE

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki (*World Medical Association 2013*), and that the clinical trial data are credible.

The study will be conducted under a US IND and all applicable US FDA and local laws and regulations and Good Clinical Practice Guidelines. The Investigator agrees to conduct the study in compliance with the current version of US Food Drug & Cosmetic Act, Section 21 CFR, Part 312, Subpart D (Responsibilities of Sponsor and Investigators), part 50 (Protection of Human Subjects), part 56 (Institutional Review Boards), the principles of the Declaration of Helsinki, and with the laws and regulations of the country in which the research is conducted in order to afford the greatest protection to the individual. The Investigator must fully adhere to the principles outlined in the "Guideline for Good Clinical Practice" International Conference on Harmonisation (ICH) Tripartite Guideline and, for studies conducted in the EU/European Economic Area (EEA) countries, the Investigator will ensure compliance with the EU Clinical Trial Directive [2001/20/EC].

This study will be conducted in full compliance with the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) regulations in 21 CFR 56 and applicable local regulatory guidance, in accordance with ICH-GCP. IRB/IEC approval for the investigation must be obtained before the study is initiated. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

17. DATA HANDLING AND RECORDKEEPING

17.1 Data Management

17.1.1 Case Report Forms

Data for this study will be recorded via an EDC system using eCRFs. It will be transcribed by the site from the paper source documents onto the eCRF.

The information collected on eCRFs must be identical to the corresponding information appearing in original source documents. There are no exceptions to this rule. In general, source documentation will be found in a chart maintained by qualified medical personnel in a hospital, clinic, or physician's office. (The eCRF is not considered as source data for this trial).

Accurate and reliable data collection will be assured by verification and cross check of the eCRFs against the Investigator's records by the study monitor (source document verification), and the maintenance of a drug dispensing log by the Investigator.

As a matter of regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto eCRFs. Prior to submission, each completed eCRF must be reviewed for accuracy by the Investigator, corrected as necessary, and then approved and e-signed. The Investigator's e-signature serves to attest that the information contained on the eCRFs has been reviewed by the Investigator and is true and accurate.

The eCRFs should be completed by the Investigator or a qualified designee from the site as soon as the data are available. Instructions for the completion of eCRFs will be provided.

The eCRFs will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

17.1.2 Retention of Records

An Investigator must maintain adequate records to include the disposition of the study drug(s) and adequate and accurate source documentation that record all observations and other data pertinent to the investigation on each patient in the study. These records are to include the case report forms (CRFs), source documentation, and supporting data, including, for example, signed and dated informed consent forms and medical records (including progress notes by the physician and/or other qualified medical personnel, the patient's hospital and clinic chart[s], and the nurses' notes).

The FDA (21 CFR §312.62[c]) states that the Investigator shall retain the required records:

a. For a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or
b. If no application is to be filed or if the marketing application is not approved for such indication, until 2 years after the investigation is discontinued and the FDA is notified.

If neither a) nor b) applies, then the Investigator shall retain the required records for a minimum of 15 years after the completion or discontinuation of the study.

For sites outside the US, the Investigator must comply with US FDA regulations and with the record retention policies of the relevant national and local health authorities. The Investigator must obtain the Sponsor's written permission before disposing of any records.

If the Investigator retires, relocates, or for any reason withdraws from the study, then the study records may be transferred to an acceptable person or institution with the written approval of the Sponsor.

18. REPORTING STUDY RESULTS AND PUBLICATION POLICY

Following analysis of the data and upon request by the Investigator, the Sponsor will supply a listing of site-specific treatment assignments, tabulated data, and statistical analysis, as appropriate. A summary of the study results will be provided to each Investigator following its release by the Sponsor. The Investigator will acknowledge receipt of any data listings or study results.

Guidelines concerning publication of the results of this clinical study are contained within the formal Clinical Study Agreement associated with this protocol.

19. LIST OF REFERENCES

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20. APPENDICES

APPENDIX A SCHEDULE OF ASSESSMENTS: DOUBLE-BLIND TREATMENT PHASE

Assessment	Scr. - 45 d to D0 (Pre-dose)[3]	Double-Blind Treatment Phase															EOS[1]	ET
		TP1[2]		TP2[2]		TP3[2]		TP4[2]		TP5[2]		TP6[2]						
Day		D0	D21[4]	D0[5]	D21[4]	D0[5]	D21[4]	D0[5]	D21[4]	D0[5]	D21[4]	D0[5]	D7[4]	D14[4]	D21[4]	D28[5,25]		
Informed Consent	X																	
Demographics	X																	
Inclusion/Exclusion	X																	
Medical History	X																	
Chest X-Ray	X															X		X
Multi-energy CT[6]	X							X								X		X
Physical Examinations	X[7]	X[8]		X[8]		X[8]		X[8]		X[8]		X[8]				X[7]		X[7]
Vital Signs	X	X[9]		X[9]		X[9]		X[9]		X[9]		X[9]			X	X		X
Weight and Height[10]	X		X		X		X		X		X				X	X		X
12-Lead ECG	X															X		X
Screening Labs[11]	X																	
COVID-19 Testing	X	As clinically indicated. Refer to Section 12.1.8.7																
Urine Pregnancy Test	X																	
Washout: ULTs	X[13]	Patients will abstain from ULT use after the ULT washout period																
Document ULTs Discontinued	X																	
Dispense Premedication: Gout Flare and Infusion Reaction[12]	X		X		X		X		X		X				X			
Premedication: Gout Flare	X[14]	Continuously																
Randomization	X[15] <-------> X[15]																	
Premedication: Infusion Reaction		X[16]		X[16]		X[16]		X[16]		X[16]		X[16]						
Safety Labs: Chemistry[17]	X	X	X		X		X		X		X				X	X		X
Safety Labs: Hematology[18]	X	X	X		X		X		X		X				X	X		X
Safety Labs: Coagulation[19]	X	X	X		X		X		X		X				X	X		X
Safety Labs: Lipids[20]	X	X	X		X		X		X		X				X	X		X
Safety Labs: eGFR[17]	X	X	X		X		X		X		X				X	X		X
Blood Sample for Anti-Pegadricase[21]		X	X	X	X	X	X	X	X	X	X	X			X	X		X
Blood Sample for nAbs[21]		X	X	X	X	X	X	X	X	X	X	X			X	X		X
Blood Sample for Anti-Pegadricase POC Validation[21]		X	X	X	X	X	X	X	X	X	X	X			X	X		X
Blood Sample for Anti-Uricase[21]		X	X	X	X	X	X	X	X	X	X	X			X	X		X
Blood Sample for Biomarkers[6]		X		X		X						X	X			X		X

Blood Sample for Multiomic Markers		X		X		X		X		X		X	X			X		X
Blood Sample for HLA Typing			X															
Blood Sample for T Cell Analysis		X										X	X			X		X

Appendix A Schedule of Assessments, continued

Assessment	Scr. - 45 d to D0 (Pre-dose)[3]	Double-Blind Treatment Phase															EOS[1]	ET
		TP1[2]		TP2[2]		TP3[2]		TP4[2]		TP5[2]		TP6[2]						
Day		D0	D21[4]	D0[5]	D21[4]	D0[5]	D21[4]	D0[5]	D21[4]	D0[5]	D21[4]	D0[5]	D7[4]	D14[4]	D21[4]	D28[5,25]		
Tophus Assessment/Photography	X							X								X		X
Gout Flare Assessment[22]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Gout Flare Weekly Diary		Continuously on Weekly Basis[24]																X
Joint Assessment (tenderness, swelling)		X						X								X		X
Health Questionnaires[23]		X						X								X		X
Collect Sample for sUA	X	Refer to Schedule of Assessments (Appendix B) for sUA Sample Collection during Treatment Phase																X
PD/Uricase Activity Assessment		Refer to Schedule of Assessments (Appendix B) for PD/Uricase Activity Assessments during Treatment Phase																X
Study Drug Administration		Refer to Schedule of Assessments in Appendix B for Study Drug Administration during the Treatment Phase																
Infusion Reaction Follow-up		Refer to Section 12.2.1.5																
Concomitant Medications / Procedures		Continuously															X	X
AE Collection		Continuously															X	X
SAE Collection	Continuously																X	X

1. Phone call at 30 (+4) days after the last study drug infusion for assessment of concomitant medications/procedures, AEs, and SAEs.
2. Visit window at Day 21 of each Treatment Period is +2/-1 days; visit window at Day 7 and Day 14 of Treatment Period 6 is +2/-1 days; visit window at Day 28 of Treatment Period 6 is +3/-4 days.
3. Visit window is -2 days.
4. Assessments at this visit are permitted to be performed remotely (inclusive of collecting applicable lab draws and assessments per protocol visit windows).
5. Study drug dosing to occur 28 days from the previous dose with a window of -4 days to +3 day of the intended dosing day. If a protocol deviation occurs where a patient is not able to be dosed within the dosing day window, for example in the case of COVID-19 restrictions temporarily preventing dosing, the current treatment period will be extended up to a maximum of 90 days without skipping doses for patients with a Day 21 visit sUA value ≤ 1.0 mg/dL during Treatment Period 1 or ≤ 6.0 mg/dL during Treatment Periods 2-11 in the D21 visit window or subsequent up to the rescheduled dosing visit. If this protocol deviation occurs such that the patient was unable to be dosed within the dosing day window for the Treatment Period 7 Day 0 dose, then the Treatment Period 6 Day 28 visit should still occur 28 days (+3/-4 days) after the Treatment Period 6 dose or as close to the visit window as possible to collect the final primary endpoint SUA sample. In this specific instance, the dosing day Treatment Period 7 Day 0 should then occur as soon as possible afterward up to a maximum of 90 days from the preceding dose.
6. Assessment performed at select sites only
7. Full physical exam
8. Directed physical exam

9. Assess vital signs on Day 0 at Time 0 (pre-dose), within + 5 minutes after completion of infusion of the first component of study drug, and 1 hour (+ 5 minutes) after completion of infusion of the second component of study drug.
10. Height measured once during Screening only.
11. Screening labs to include: calcium, total complement, hemoglobin-A1c (HbA1c), hepatitis C antibody, hepatitis B surface antigen, human immunodeficiency virus 1/2 (HIV1/2), urinalysis, glucose-6-phosphate dehydrogenase (G6PD)
12. Dispense gout flare medication at Screening and as needed during the study. Dispense infusion reaction medication at Screening and at Day 21 of Treatment Periods 1-11.
13. Begin at least 7 days prior to Day 0 of Treatment Period 1.
14. Begin at least 7 days prior to Day 0 of Treatment Period 1.
15. Randomization is permitted at any time between Day -7 to Day 0 (prior to SEL-212 administration).
16. Premedication to minimize potential infusion reactions: oral antihistamines at 12 (± 2) hours and 2 (± 1) hours and IV steroids at 1 (± 0.5) hours prior to study drug.
17. Chemistry labs to include: Alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), Total Bilirubin, blood urea nitrogen (BUN), Creatinine, UACR, eGFR, Fibrinogen, Glucose (fasting), Electrolytes (sodium, potassium, chloride, bi-carbonate, phosphate and magnesium).
18. Hematology labs to include: white blood cells (WBC) count with differential, Red blood cell (RBC) count, Hematocrit (Hct), Hemoglobin (Hgb), Platelet (Plt) count, and absolute neutrophil count (Abneu)
19. Coagulation labs to include: prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR)
20. Fasting lipid labs to include: total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides
21. Collect sample prior to study drug dosing
22. Gout flares assessed based on validated gout flare definition (Gaffo 2018)
23. Refer to Section 11.3 for Health Questionnaires.
24. Start gout flare diary at Day 0 of Treatment Period 1.
25. Treatment Period 6 Day 28 assessments will be used for Treatment Period 7 Day 0 assessments. Do not repeat sample collection on Treatment Period 7 Day 0.

Abbreviations: CT: computed tomography; D (d): day; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; EOS: end of study; ET: early termination; h: hour; nAbs: neutralizing antibodies; PD: pharmacodynamic; RCTC: Rheumatology Common Toxicity Criteria; Scr: Screening Phase; sUA: serum uric acid; TP: treatment period; UACR: urine-albumin-creatinine ratio; ULT: urate lowering therapy

APPENDIX B SCHEDULE OF ASSESSMENTS: DOSING, SUA, AND URICASE ACTIVITY DURING THE DOUBLE-BLIND TREATMENT PHASE

Assessments	**Treatment Periods: 1, 2, 3, 4, and 5**					**Treatment Period 6**							
Day	**D0[1]**				**D21[2]**	**D0[1]**				**D7[2]**	**D14[2]**	**D21[2]**	**D28[3]**
Timepoint	**0h**	**~1.5h**	**~3.5h**	**~4.5h**		**0h**	**~1.5h**	**~3.5**	**~4.5h**				
Premedicate: Infusion Reaction	X[4]					X							
Blood Sample Uricase Activity	X[5]			X[6]	X	X[5]			X[6]	X	X	X	X
Blood Sample: sUA	X[5]			X[6]	X	X[5]			X[6]	X	X	X	X
Study Drug Infusion (Component 1)[7]	X----------X[8]					X----------X[8]							
Study Drug Infusion (Component 2)[9]		X[8]---------X					X[8]---------X						

1. Study drug dosing to occur 28 days from the previous dose with a window of -4 days to +3 day of the intended dosing day.
2. Assessments at this visit are permitted to be performed remotely (inclusive of collecting applicable lab draws and assessments per protocol visit windows).
3. Treatment Period 6 only. Treatment Period 6 Day 28 assessment will be used for Treatment Period 7 Day 0 pre-dose assessment. Do not repeat sample collection on Treatment Period 7 Day 0.
4. Premedication to minimize potential infusion reactions: oral antihistamines at 12 (± 2) hours and 2 (± 1) hours and IV steroids at 1 (± 0.5) hours prior to study drug.
5. Obtain sample prior to study drug infusion.
6. Obtain sample 1 hour (+15/-0 min) after completion of infusion of Component 2. If a patient is withdrawn from study drug, the post-dose uricase activity and post-dose sUA samples do not need to be collected.
7. Component 1 will be SEL-110.36 at 0.1 mg/kg for patients randomized to treatment with SEL-212A and SEL-110.36 at 0.15 mg/kg for patients randomized to SEL-212B or will be placebo for patients randomized to placebo.
8. Before starting infusion with Component 2, a period of up to approximately 30 minutes is permitted after completion of infusion of Component 1.
9. Component 2 will be SEL-037 for patients randomized to treatment with either SEL-212A or to SEL-212B or will be placebo for patients randomized to placebo.

APPENDIX C SCHEDULE OF ASSESSMENTS: DOUBLE-BLIND EXTENSION PHASE

Assessment	Double-Blind Extension Phase													EOS[1]	ET
	TP7[2]		TP8[2]		TP9[2]		TP10[2]		TP11[2]		TP12[2]				
Day	D0[4,18]	D21[3]	D0[4]	D21[3]	D0[4]	D21[3]	D0[4]	D21[3]	D0[4]	D21[3]	D0[4]	D21[3]	D28[4]		
Chest X-Ray	X												X		X
Multi-energy CT[5]	X												X		X
Physical Examinations	X[6]		X[7]		X[7]		X[7]		X[7]		X[7]		X[6]		X[6]
Vital Signs	X[8]		X[8]		X[8]		X[8]		X[8]		X[8]	X	X		X
Weight		X		X		X		X		X		X	X		X
12-Lead ECG	X												X		X
COVID-19 Testing	As clinically indicated. Refer to Section 12.1.8.7														
Dispense Premedication: Gout Flare and Infusion Reaction[9]		X		X		X		X		X					
Premedication: Gout Flare	Continuously														
Premedication: Infusion Reaction	X[10]		X[10]		X[10]		X[10]		X[10]		X[10]				
Safety Labs: Chemistry[11]	X	X		X		X		X		X		X	X		X
Safety Labs: Hematology[12]	X	X		X		X		X		X		X	X		X
Safety Labs: Coagulation[13]	X	X		X		X		X		X		X	X		X
Safety Labs: Lipids[14]	X	X		X		X		X		X		X	X		X
Safety Labs: eGFR[11]	X	X		X		X		X		X		X	X		X
Blood Sample for Anti-Pegadricase[15]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Blood Sample for nAbs[15]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Blood Sample for Anti-Pegadricase POC Validation[15]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Blood Sample for Anti-Uricase[15]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Blood Sample for Biomarkers[5]	X										X				X
Blood Sample for Multiomic Markers	X				X						X		X		X
Blood Sample for T Cell Analysis	X										X		X		X
Tophus Assessment/Photography	X						X						X		X
Gout Flare Assessment[16]	X		X		X		X		X		X		X		X
Gout Flare Weekly Diary	Continuously on Weekly Basis														
Joint Assessment (tenderness, swelling)	X						X						X		X
Health Questionnaires[17]	X						X						X		X
Collect Sample for sUA	Refer to Schedule of Assessments (Appendix D) for sUA Sample Collection during Treatment Phase														X
PD/Uricase Activity Assessment	Refer to Schedule of Assessments (Appendix D) for PD/Uricase Activity Assessments during Treatment Phase														X
Study Drug Administration	Refer to Schedule of Assessments in Appendix D for Study Drug Administration during the Treatment Phase														
Infusion Reaction Follow-up	Refer to Section 12.2.1.5														

Concomitant Medications / Procedures	Continuously	X	X
AE Collection	Continuously	X	X
SAE Collection	Continuously	X	X

1. Phone call at 30 (+4) days after the last study drug infusion for assessment of concomitant medications/procedures, AEs, and SAEs.
2. Visit window at Day 21 of each Treatment Period is +2/-1 days.
3. Assessments at this visit are permitted to be performed remotely (inclusive of collecting applicable lab draws and assessments per protocol visit windows).
4. Study drug dosing to occur 28 days from the previous dose with a window of -4 days to +3 day of the intended dosing day. If a protocol deviation occurs where a patient is not able to be dosed within the dosing day window, for example in the case of COVID-19 restrictions temporarily preventing dosing, the current treatment period will be extended up to a maximum of 90 days without skipping doses for patients with a Day 21 visit sUA value ≤ 1.0 mg/dL during Treatment Period 1 or ≤ 6.0 mg/dL during Treatment Periods 2-11 in the D21 visit window or subsequent up to the rescheduled dosing visit. Visit window for TP12D28 is -4 to +3 days.
5. Assessment performed at select sites only
6. Full physical exam
7. Directed physical exam
8. Assess vital signs on Day 0 at Time 0 (pre-dose), within + 5 minutes after completion of infusion of the first component of study drug, and 1 hour (+ 5 minutes) after completion of infusion of the second component of study drug.
9. Dispense gout flare medication as needed during the study. Dispense infusion reaction medication at Day 21 of Treatment Periods 1-11.
10. Pretreatment to minimize potential infusion reactions: oral antihistamines at 12 (± 2) hours and 2 (± 1) hours and IV steroids at 1 (± 0.5) hours prior to study drug.
11. Chemistry labs to include: Alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), Total Bilirubin, blood urea nitrogen (BUN), Creatinine, UACR, eGFR, Fibrinogen, Glucose (fasting), Electrolytes (sodium, potassium, chloride, bicarbonate, phosphate and magnesium)
12. Hematology labs to include: white blood cells (WBC) count with differential, Red blood cell (RBC) count, Hematocrit (Hct), Hemoglobin (Hgb), Platelet (Plt) count, and absolute neutrophil count (Abneu)
13. Coagulation labs to include: prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR)
14. Fasting lipid labs to include: total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides
15. Collect sample prior to study drug dosing
16. Gout flares assessed based on validated gout flare definition (Gaffo 2018)
17. Refer to Section 11.3 for Health Questionnaires.
18. Treatment Period 6 Day 28 assessments will be used for Treatment Period 7 Day 0 assessments. Do not repeat sample collection on Treatment Period 7 Day 0.

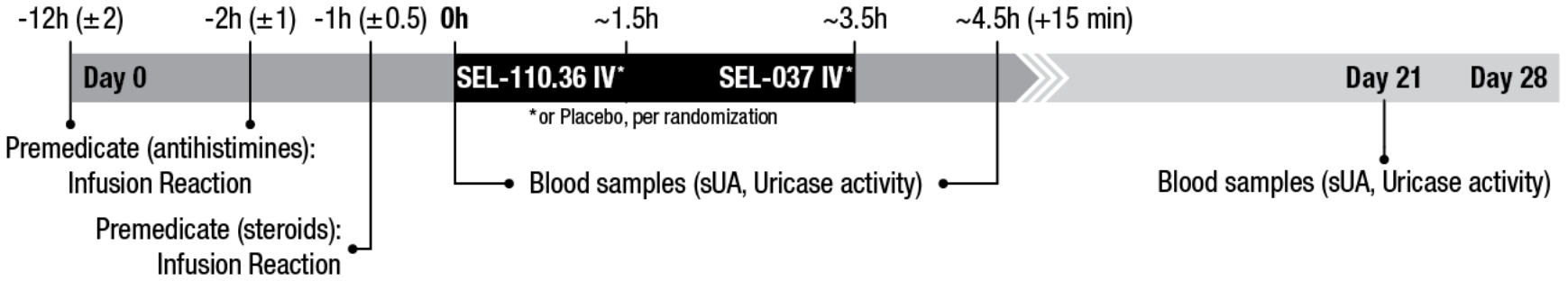
Abbreviations: CT: computed tomography; D (d): day; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; EOS: end of study; ET: early termination; h: hour; nAbs: neutralizing antibodies; PD: pharmacodynamic; RCTC: Rheumatology Common Toxicity Criteria; Scr: Screening Phase; sUA: serum uric acid; TP: treatment period; UACR: urine-albumin-creatinine ratio; ULT: urate lowering therapy

APPENDIX D SCHEDULE OF ASSESSMENTS: DOSING, SUA, AND URICASE ACTIVITY DURING THE DOUBLE-BLIND EXTENSION PHASE

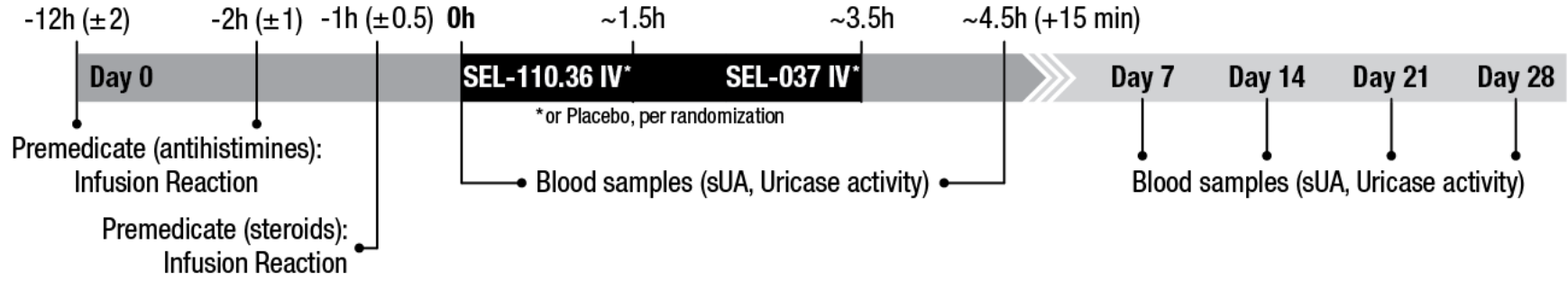
Assessments	**Treatment Periods: 7, 8, 9, 10, and 11**					**Treatment Period 12**					
Day	**D0[1,2]**				**D21[3]**	**D0[1]**				**D21[3]**	**D28[4]**
Timepoint	**0h**	**~1.5h**	**~3.5h**	**~4.5h**		**0h**	**~1.5h**	**~3.5**	**~4.5h**		
Premedicate: Infusion Reaction	X[5]					X					
Blood Sample Uricase Activity	X[6]			X[7]	X	X[6]			X[6]	X	X
Blood Sample: sUA	X[6]			X[7]	X	X[6]			X[6]	X	X
Study Drug Infusion (Component 1)[8]	X----------X[9]					X----------X[9]					
Study Drug Infusion (Component 2)[10]		X[9]---------X					X[9]---------X				

1. Study drug dosing to occur 28 days from the previous dose with a window of -4 days to +3 day of the intended dosing day.
2. Only on Treatment Period 7 Day 0: Treatment Period 6 Day 28 assessment will be used for Treatment Period 7 Day 0 pre-dose assessment. Do not repeat sample collection on Treatment Period 7 Day 0.
3. Assessments at this visit are permitted to be performed remotely (inclusive of collecting applicable lab draws and assessments per protocol visit windows).
4. Treatment Period 12 only.
5. Premedication to minimize potential infusion reactions: oral antihistamines at 12 (± 2) hours and 2 (± 1) hours and IV steroids at 1 (± 0.5) hours prior to study drug.
6. Obtain sample prior to study drug infusion.
7. Obtain sample 1 hour (+15/-0 min) after completion of infusion of Component 2.
8. Component 1 will be SEL-110.36 at 0.1 mg/kg for patients randomized to treatment with SEL-212A and SEL-110.36 at 0.15 mg/kg for patients randomized to SEL-212B or will be placebo for patients randomized to placebo.
9. Before starting infusion with Component 2, a period of up to approximately 30 minutes is permitted after completion of infusion of Component 1.
10. Component 2 will be SEL-037 for patients randomized to treatment with either SEL-212A or to SEL-212B or will be placebo for patients randomized to placebo.

APPENDIX E DOSING, SERUM URIC ACID, AND URICASE ACTIVITY ASSESSMENT SCHEDULE (TREATMENT PERIODS 1, 2, 3, 4, 5, AND 7, 8, 9, 10, 11)



APPENDIX F DOSING, SERUM URIC ACID, AND URICASE ACTIVITY ASSESSMENT SCHEDULE (TREATMENT PERIOD 6)



APPENDIX G DOSING, SERUM URIC ACID, AND URICASE ACTIVITY ASSESSMENT SCHEDULE (TREATMENT PERIOD 12)