Statistical Analysis Plan

Sponsor Name: Selecta Biosciences

Protocol Number: SEL-212/302

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

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Author: [redacted]

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1.0	20-Dec-2022	[redacted]	Original
1.1	22-Feb-2022	[redacted]	Clarifications of baseline definition; clarification of covariates for % change of mean sUA; clarification of classification of gout flares occurring after study drug administration; correction of gout flare table description; clarification of multiple imputation model to use for responder analysis amongst tophi positive patients. Added deviations from protocol.

I confirm that I have reviewed this document and agree with the content.

Approvals

Parexel Approval

[redacted]

Name, Title	Signature	Date (DD-Mmm-YYYY)

Selecta Biosciences Approval

Name, Title	Signature	Date (DD-Mmm-YYYY)
[redacted]		
[redacted]		
[redacted]		

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1. Glossary of Abbreviations

Abbreviation	Description
Ab	Antibody
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Classification
eCRF	Electronic Case report form
CYP3A4	Cytochrome P450, family 3, subfamily A
d	Day, Study day
dL	Deciliter
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EOS	End of Study
ET	Early Termination
g	gram
h	Hour
HAQ-DI	Health Assessment Questionnaire-Disability Index
ICF	Informed consent form
ITT	Intent-to-Treat
IV	intravenous
kg	kilograms
LS	Least square
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MH	Mantel-Haenszel
mITT	Modified Intent-to-Treat
ml	Milliliters
MMRM	Mixed Model Repeated Measures
NSAIDs	Non-steroidal anti-inflammatory drug
PGA	The Provider Global Assessment of Disease Activity
PP	Per Protocol
PT	Preferred Term
RPMM	Regression and predictive mean matching
QD	Once Daily
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical Analysis Plan
Scr	Screening Period
SF-36	Short Form Health Survey 36
sUA	Serum Uric Acid
SOC	System Organ Class
SS	Safety Set

Abbreviation	Description
TEAE	Treatment-emergent adverse events
TLFs	Tables, Listings and Figures
TP	Treatment Period
ULN	Upper limit of normal
ULT	Uric acid lowering therapy
WHO-DD	World Health Organization Drug Dictionary

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

Parexel will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings.

2.2. Timings of Analyses

The primary analysis of safety and efficacy is planned after all patients complete the final study visit or terminate early from the study and the unblinding has happened.

3. Study Objectives

3.1. Primary Objective

The primary objective is 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.

3.2. Secondary and Exploratory Objectives

3.2.1 Secondary Objectives

- 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 suppression 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

3.2.2 Exploratory Objectives

- To assess the levels of uricase activity in patients receiving SEL-212 compared to placebo
- To assess the effect 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

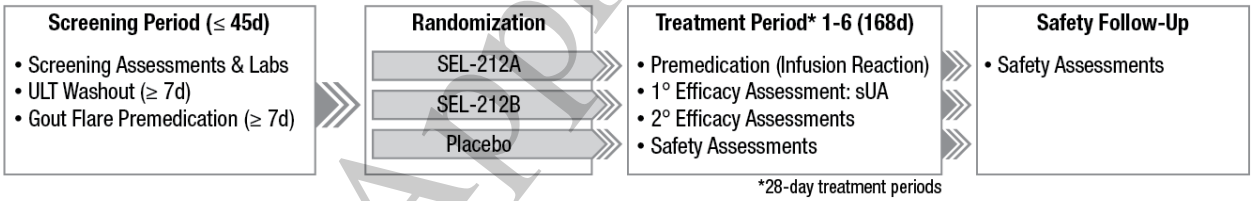
- To assess the correlation between immune tolerance related multiomic markers and anti-pegadricase antibody formation in patients treated with two different dose levels of SEL-212

3.3. Overall Study Design

This is one of the 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 control. The study will randomize approximately 141 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 a blinded 6-month extension in SEL-212/301. Efficacy assessments will be conducted at intervals that are appropriate to determine treatment effect with samples for the primary endpoint drawn during Treatment Period (TP) 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).

The study will be divided into 3 study periods: Screening phase, double-blind Treatment phase, and Follow-up phase as described below (Figure 1).

Figure 1: Study Schematic



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). Patients will receive study drug on Day 0 of each of the 6 treatment periods.

The total duration of participation in the study will be range from approximately 26 to 31 weeks (184 to 215 days) as follows:

- Screening and/or washout and premedication period: up to 45 days (up to 6.5 weeks): Concurrently with the Screening Phase, a premedication period with colchicine (or a non-steroidal anti-inflammatory drug [NSAID], if colchicine is contraindicated) of at least 7 days prior to Baseline for potential gout flare 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).
- Treatment Phase: 168 days (24 weeks)
- Safety Follow-Up: 30 (+4) days after last infusion: 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 the completion of the 6 month Treatment Phase or (2) at early termination if the patient either voluntarily withdraws or is deemed by the PI not to be eligible to continue in either of the treatment or placebo arms of the trial.

Patients who terminate the study prematurely will continue to be followed by having all ET assessments performed.

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 control 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.

For each treatment cycle, patients in both active treatments and placebo groups 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 (ie, 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. Uricase activity levels and sUA will be assessed through additional post-infusion blood samples at pre-determined time points by unblinded personnel.

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 Treatment Periods 2, 3, 4, or 5

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

If withdrawn from study drug, the patient will continue study visits to the end of Treatment Period 6. 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, 3, 4, or 5, 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, 3, 4, or 5, 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 a protocol deviation occurs in Treatment Period 6 such that the patient was unable to have an EOS visit performed within the visit window, 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.

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, regardless of reason, the patient will continue study visits including during the follow-up phase.

3.4. Patient Selection

Planned Enrollment: Approximately 141 patients randomized (total) and treated per trial:

- SEL-212A: approximately 47 patients
- SEL-212B: approximately 47 patients
- Placebo: approximately 47 patients

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

3.4.1. 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;

3.4.2. Exclusion Criteria

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

1. Has a history of anaphylaxis or 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®), pegaptanib (Macugen®) 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 (and other antifungals), nicardipine (and other calcium channel blockers), 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

- Glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2
- Urine albumen 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 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 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 virus 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

3.5. Determination of Sample Size

The sample size estimation is performed for the main estimand for the primary efficacy endpoint from V5.0 of the protocol ‘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’ which defined in Section 6.1. This estimand

considered the following as treatment failures: patients who discontinue study treatment due to lack of efficacy (eg, meeting stopping rule), patients who discontinue study treatment due to treatment-related or non-treatment related AEs, patients who take prohibited medication that lowers sUA, or patients who are lost to follow up or withdraw consent for reasons other than COVID-19.

Based on the Phase 2 (protocol SEL-212/201) results 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 treated 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, 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. In addition, the ongoing conflict in Ukraine may lead to treatment discontinuations and/or loss to follow-up; under the main estimand for the primary endpoint, these will also be treated as treatment failures. As both these factors 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 and treatment discontinuation/loss to follow-up due to the conflict in Ukraine 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. Furthermore, an additional 21 patients have been added to the original study sample size to account for the treatment discontinuation/loss to follow-up due to the conflict in Ukraine. The two additions to the sample size from the original sample size calculation results in approximately 141 patients (i.e., 47:47:47) to be randomized and dosed to demonstrate efficacy. This controls the power of each comparison vs. placebo at approximately 90%, even if the placebo arm were to be unaffected with respect to response probability by the conflict in Ukraine, with a response percentage of 5%, and the active treatment arm response percentage were to drop to 37%.

Sample size calculations were performed with the software package nQuery 8, Version 8.5.0.0 and updated using R software version 4.04.

3.6. Treatment Assignment & Blinding

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. Randomization

is permitted at any time between Day -7 to Day 0 inclusive. Uricase activity levels and sUA will be assessed through additional post-infusion blood samples at pre-determined time points by unblinded personnel. Also, anti-uricase and anti-pegadricase antibody levels will be assessed by unblinded personnel only in patients in active treatment arms. Antibody data will be saved in a project folder with restricted access by the unblinded team.

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

3.7. Administration of Study Medication

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) orally approximately 24 (± 12) hours prior to dosing
  - Fexofenadine 180 mg oral (PO) approximately 12 (± 2) hours prior to dosing (i.e., the evening before dosing Day 0)
  - 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 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 beginning 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 pre-medications will be given prior to placebo as well to maintain the blind.

3.8. Study Procedures and Flowchart

Scheduled assessment are presented by the following 4 tables / appendices on the following pages:

- Table A: Schedule of Assessment
- Table B: Schedule of Assessments: Dosing, sUA, and Uricase Activity During the Treatment Phase
- Table C: Dosing, serum uric acid, and Uricase Activity Assessment Schedule (Treatment Periods 1, 2, 3, 4, and 5)
- Table D: Dosing, serum uric acid, and Uricase Activity Assessment Schedule (Treatment Period 6)

Statistical Analysis Plan
Sponsor: Selecta Biosciences
Protocol No.: SEL-212/302

TABLE A: SCHEDULE OF ASSESSMENTS

Assessment	Scr. - 45 d to D0 (Pre-dose)[3]	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		
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 Protocol 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							
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

TABLE A: SCHEDULE OF ASSESSMENTS, CONTINUED

Assessment	**Scr. - 45 d to D0 (Pre-dose)[3]**	**Treatment Phase**															**EOS[1]**	**ET**
		TP1[2]		**TP2[2]**		**TP3[2]**		**TP4[2]**		**TP5[2]**		**TP6[2]**						
Day		**D0**	**D21**	**D0[5]**	**D21**	**D0[5]**	**D21**	**D0[5]**	**D21**	**D0[5]**	**D21**	**D0[5]**	**D7[4]**	**D14[4]**	**D21[4]**	**D28**		
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[23]																X
Joint Assessment (tenderness, swelling)		X						X								X		X
Health Questionnaires[24]		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 Protocol 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, 3, 4, or 5 in the D21 visit window or subsequent up to the rescheduled dosing visit. If a protocol deviation occurs in Treatment Period 6 such that the patient was unable to have an EOS visit performed within the visit window, 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.
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 1-5.
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 medication.
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 samples prior to study drug dosing.
22. Gout flares assessed based on validated gout flare definition (Gaffo 2018)
23. Start gout flare diary at Day 0 of Treatment Period 1.
24. Refer to Protocol Section 11.3 for Health Questionnaires.

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

TABLE B:
SCHEDULE OF ASSESSMENTS: DOSING, SUA, AND URICASE ACTIVITY DURING THE 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.
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 medication.
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 SEL-212A and SEL-110.36 at 0.15 mg/kg for patients randomized to SEL-212B or will be placebo.
8. Before starting infusion with Component 2, a period of up to 30 minutes is permitted after completion of infusion of Component 1.
9. Component 2 will be SEL-037 for patients randomized to either SEL-212A or to SEL-212B or will be placebo for patients randomized to placebo.

TABLE C: DOSING, SERUM URIC ACID, AND URICASE ACTIVITY ASSESSMENT SCHEDULE (TREATMENT PERIODS 1, 2, 3, 4, AND 5)

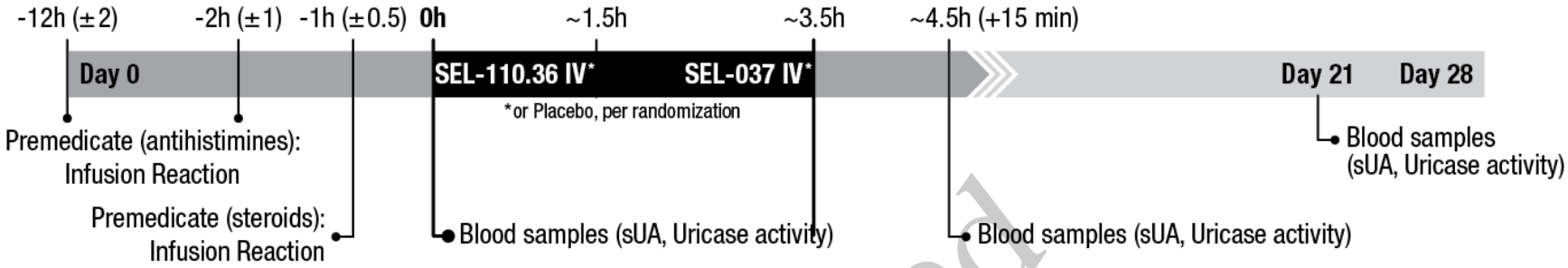
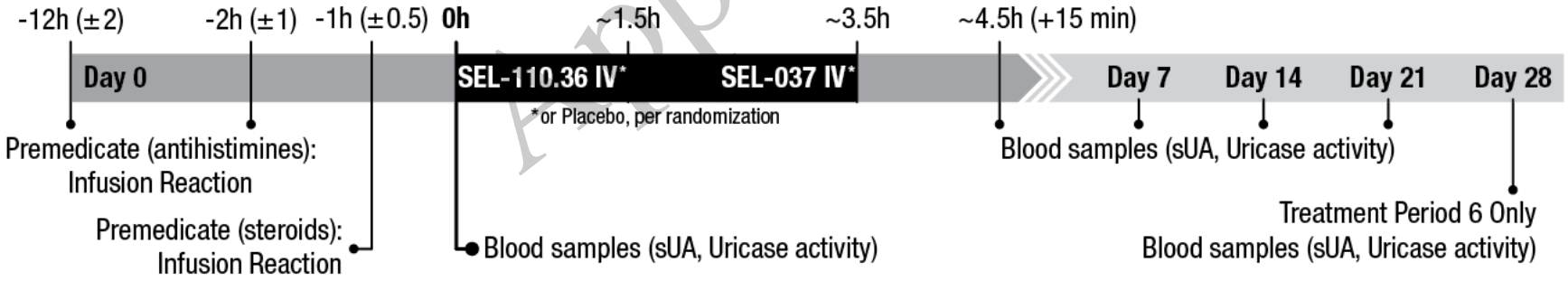


TABLE D: DOSING, SERUM URIC ACID, AND URICASE ACTIVITY ASSESSMENT SCHEDULE (TREATMENT PERIOD 6)



4. Endpoints

4.1. 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

4.2. Secondary Efficacy Endpoints

Key Secondary Endpoints:

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

- Reduction of mean sUA as computed by subtracting the Baseline sUA level from the mean sUA during Treatment Period 6
- Percent reduction of mean sUA as computed by subtracting the Baseline sUA level from the mean sUA 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 PR (as best response) in overall tophus response evaluation until Day 28 of Treatment Period TP6
- 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
- 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 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 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:

- Percentage of patients who achieve and maintain reduction of sUA < 6 mg/dL for 100% of the time during Treatment Period 6
- Number 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
- Percentage of patients with development of new tophi until Day 28 of Treatment Period TP6 in the subgroups of tophaceous patients and in non tophaceous patients at Baseline
- 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 TP4

- Change from baseline to Day 28 of TP6 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)
- Percentage of patients with (at least one) gout flare in Treatment Periods 1-3
- Percentage of patients with (at least one) gout flare in Treatment Periods 1-6
- Change from Baseline to Day 28 of Treatment Period TP6 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

4.3. Exploratory Endpoints

- 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 in the Treatment Periods 1-3 based on self-reported weekly gout flare diary
- Gout flare incidence in the 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
- 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

4.4. Safety Endpoints

- Safety and tolerability of SEL-212 as assessed by adverse events (AEs), AEs of special interest (AESIs), 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; vital signs; immunogenicity analyses; 12-lead ECGs; and physical examination findings.

5. Analysis Sets

5.1. Screened / Randomized Set

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

5.2. Safety Set

The Safety Set (SS) will include all patients who were administered any amount of study medication. Patients will be analyzed according to treatment received.

5.3. Intent-to-Treat Set

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

5.4. Modified Intent-to-Treat

A number of modified ITT (mITT) populations will be defined, as a result of either the COVID-19 pandemic or the conflict in Ukraine. The COVID-19 pandemic could potentially impact the ability to attend visits and/or receive treatment, whilst the conflict in Ukraine could potentially impact the logistics of the clinical trial in sites from Russia and Ukraine.

mITT1: will include all randomized patients who were dosed, except those who discontinued treatment due to a COVID-19 infection as defined in the study protocol or do not have at least 2 sUA measurements 7 days apart in TP6 due to a/multiple missed visit due to a COVID-19 infection or subsequent complications as defined in the study protocol.

mITT2 will include all randomized patients who were dosed, except those who were recruited in sites from Ukraine or Russia where the data quality are compromised due to logistical issues, defined as:

1. Those who received fewer than 6 treatment doses due to logistical issues, for example a patient who is unable to receive one or more doses within the 90 day window due to lack of IMP or site closure due to the conflict.

2. Those who have limited laboratory safety data available/reportable after February 24, 2022, for example missing data that result in major protocol deviations

3. Those whose data were not able to be monitored after February 24, 2022

mITT3: will include all randomized patients who were dosed, except those who were recruited in sites from Ukraine or Russia.

Patients will be analyzed according to randomized treatment..

5.5. Per Protocol Set

The Per Protocol Set (PPS) will include all patients who were administered at least one complete dose of study medication, 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.

5.6. All randomized Set

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

5.7. 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. Determination of whether the deviation is major or minor, or has impacts on primary efficacy assessment will be based on the biasing impact of the deviation on the safety and efficacy data and will be determined prior to database lock.

The use of following medications/thereapies during the trial is not allowed and will be considered as major protocol deviations impacting the primary efficacy assessments:

- Uric acid lowering therapy (ULT) including, but not limited to allopurinol, febuxostat (Uloric®), probenecid, lesinurad (Zurampic®, Duzallo®), losartan, pegloticase (Krystexxa®) and benzbromarone ULT. 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.
- The use of CYP3A4/P-gp severe inducers or CYP3A4/P-gp severe inhibitors are prohibited 14 days prior to dosing and during the trial.

5.8. Subgroup analyses

For analyses examining number of tender joints (see 6.2.6) and gout flare incidence (see 6.2.8), an additional subgroup analysis will be performed, stratifying by background medication taken in the seven days prior to Day 0 of Treatment Period 1. Three strata will be defined: i) those who took neither non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine at any point over the seven days prior to Day 0 of Treatment Period 1, ii) those who took NSAIDs and not colchicine at any point over the seven days prior to Day 0 of Treatment Period 1, and iii) those who took colchicine at any point over the seven days prior to Day 0 of Treatment Period 1. Participants who are took both NSAIDS and colchicine in the seven days prior to Day 0 of Treatment Preriod 1 will be classified into strata iii.

For the primary analysis, results will be presented stratified by age (≤50 years old / >50 years old), race (white / non-white).

6. Estimands for Primary and Key Secondary Efficacy Endpoints

6.1. Estimands for Primary Efficacy

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

- 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 response status, whereby a responder is defined as a patient who has sUA < 6 mg/dL for at least 80% of the time during TP6.
- Population-level summary: Difference in the percentage of treatment responders of each SEL-212 treatment group versus placebo.
- Intercurrent events:
    - Meeting the pre-defined treatment stopping criteria is considered as lack of efficacy and 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 considered as treatment failure 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 failure and will be treated according to the composite strategy
    - Use of prohibited medication that significantly lower sUA levels will be considered as treatment failure and will be treated 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 sUA in TP6 up to Day 28 will be used

The sample size estimation for the study is based on the main estimand for the primary efficacy endpoint from version 5.0 of the Protocol, but following an ammendment to version 6.0, which additionally included patients presenting severe or critical symptoms of COVID-19 with a positive COVID-19 test result, and patients who missed all sUA assessment during TP6, as non-responders, it was determined that the same sample size is justified for the modified estimand. The sample size increase due to the conflict in Ukraine following an amendment to version 7.0 should provide at least 90% power in each comparison vs. placebo despite a potentially lower responder rate in each arm.

A second estimand for the primary efficacy endpoint is defined using the same population, variable and

population-level summary as in the main estimand, but with applying the treatment policy strategy in case of all intercurrent events (i.e. all month 6 assessments until Day 28 will be used even for patients who have discontinued the study drug) with exception of deaths, where the composite strategy will be used.

A third estimand for the primary efficacy endpoint is defined using the same population, variable and population-level summary as in the main estimand, but applying the composite strategy for all intercurrent events, i.e. all of the above listed events will be considered as treatment failures.

A fourth estimand for the primary efficacy endpoint is defined using the same population, variable and population-level summary as in the main estimand, but the intercurrent event handling of premature stopping of study treatment due to a positive COVID-19 test result along with severe of critical symptoms of COVID-19 will be handled according to the treatment policy strategy.

The main, second and third estimands will be repeated five times, once with the population changed to each of the three defined mITT populations, once with the with the population changed to the all randomized set, and once with the population changed to the PP set.

6.2. Estimands for Key Secondary Efficacy

6.2.1. Estimands for 'Reduction of mean sUA as computed by subtracting the Baseline sUA level from the mean sUA during Treatment Period 6'

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 during Treatment Period 6' is defined as follows:

- 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: Continuous variable showing the difference between the mean sUA value recorded in TP6 and the baseline sUA value for each individual.
- Population-level summary: Difference in LS means between each SEL-212 treatment group vs. placebo.
- Intercurrent events:
    - All intercurrent events (as listed in 6.1 for the primary estimand) except deaths will be considered using the treatment policy strategy
    - For deaths the last available value will be used (while-on-treatment strategy), i.e. the baseline sUA value will be subtracted from mean sUA values across the most recently attended TP.

A second estimand for this key secondary endpoint will be defined similarly to the main estimand but with using the while-on-treatment strategy for all intercurrent events (as listed in 6.1 for the primary estimand).

The main and second estimands will be repeated five times, once with the population changed to each of the three defined mITT populations, once with the with the population changed to the all randomized set, and once with the population changed to the PP set.

6.2.2. Estimands for 'Percent reduction of mean sUA as computed by subtracting the Baseline sUA level from the mean sUA during Treatment Period 6'

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' is defined as follows:

- 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: Continuous variable showing the percentage difference between the mean sUA value recorded in TP6 and the baseline sUA value for each individual, i.e. the (mean TP6 sUA value – baseline sUA value) ÷ baseline sUA value × 100.
- Population-level summary: Difference in LS means between each SEL-212 treatment group vs. placebo.
- Intercurrent events:
    - All intercurrent events (as listed in 6.1 for the primary estimand) except deaths will be considered using the treatment policy strategy
    - For deaths the last available value will be used (while-on-treatment strategy), i.e. the baseline sUA value will be subtracted from mean sUA values across the most recently attended TP ÷ baseline sUA value × 100.

A second estimand for this key secondary endpoint will be defined similarly to the main estimand but with using the while-on-treatment strategy for all intercurrent events (as listed in 6.1 for the primary estimand).

The main and second estimands will be repeated five times, once with the population changed to each of the three defined mITT populations, once with the with the population changed to the all randomized set, and once with the population changed to the PP set.

6.2.3. Estimands for 'The change from Baseline to Day 28 of Treatment Period 6 in the physical summary score of the Short Form Health Survey (SF-36)'

The main estimand for the key secondary efficacy endpoint 'Change from Baseline to Day 28 of TP6 of the Physical Summary Score of the Short Form Health Survey (SF-36)' is defined as follows:

- 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: Continuous variable showing the change from Baseline to 6 months after start of study treatment (D28 of Treatment Period 6).
- Population-level summary: Difference in LS means between each SEL-212 treatment group versus placebo in the change from baseline in summary score of SF-36 questionnaire.
- Intercurrent events:
    - All intercurrent events (as listed in 6.1 for the primary estimand) except deaths will be considered using the treatment policy strategy

- For deaths the last available value will be used (while-on-treatment strategy)

A second estimand for this key secondary efficacy endpoint will be defined similarly to the main estimand but with using the while-on-treatment strategy for all intercurrent events (as listed in 6.1 for the primary estimand).

The main and second estimands will be repeated five times, once with the population changed to each of the three defined mITT populations, once with the with the population changed to the all randomized set, and once with the population changed to the PP set.

6.2.4. Estimands for '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 TP6'

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 D28 of TP6 in patients with tophi at baseline' is defined as follows:

- 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, who were dosed (ITT population) and had tophi at baseline.
- Variable: Binary variable indicating whether the patient had experienced at least a PR (as best response) or not in overall tophus response until Day 28 of TP6. This variable corresponds to the assessment of tophus reduction compared to baseline.
- Population-level summary: Difference in the percentage of patients with at least PR (as best response) in overall tophus response between each SEL-212 treatment group versus placebo.
- Intercurrent events:
  - All intercurrent events (as listed in 6.1 for the primary estimand) except deaths will be considered using the treatment policy strategy
  - For deaths the last available tophus response assessment will be used (while-on-treatment strategy)

A second estimand for this key secondary endpoint will be defined similarly to the main estimand but with using the while-on-treatment strategy for all intercurrent events (as listed in 6.1 for the primary estimand).

The main and second estimands will be repeated five times, once with the population changed to each of the three defined mITT populations, once with the with the population changed to the all randomized set, and once with the population changed to the PP set, restricted each time to those who had tophi at baseline.

6.2.5. Estimands for 'Percentage of patients who achieve and maintain reduction of sUA < 6 mg/dL for at least 80% of the time during Treatment Period TP6 in subset of patients with tophi at baseline'

The main estimand for the key secondary efficacy endpoint 'Percentage of patients who achieve and maintain reduction of sUA < 6 mg/dL for at least 80% of the time during Treatment Period TP6 in subset of patients with tophi at baseline' is defined as follows:

- 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, who were dosed (ITT population) and had tophi at baseline.

- Variable: 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 TP6.
- Population-level summary: Difference in the percentage of treatment responders of each SEL-212 treatment group versus placebo.
- Intercurrent events:
    - All intercurrent events will be handled in the same way as the main estimand for the primary endpoint (as listed in 6.1 for the main estimand).

A second estimand for this key secondary endpoint will be defined similarly to the main estimand but with intercurrent events handled as per the second estimand for the primary endpoint (as listed in 6.1 for the primary estimand).

The main and second estimands will be repeated five times, once with the population changed to each of the three defined mITT populations, once with the with the population changed to the all randomized set, and once with the population changed to the PP set, restricted each time to those who had tophi at baseline

6.2.6. Estimands for 'The change from Baseline to day 28 of Treatment Period 6 in Number of Tender Joints'

The main estimand for the key secondary efficacy endpoint 'the change from Baseline to D28 of Treatment Period 6 in number of tender joints' is defined as follows:

- 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: Continuous variable showing the absolute Change in number of tender joints from Baseline to 6 months after start of study treatment (D28 of Treatment Period 6).
- Population-level summary: Difference in LS mean change from baseline in number of tender joints between each SEL-212 treatment group versus placebo.
- Intercurrent events:
    - All intercurrent events (as listed in 6.1 for the primary estimand) except deaths will be considered using the treatment policy strategy
    - For deaths the last available value will be used (while-on-treatment strategy)

A second estimand for this key secondary endpoint will be defined similarly to the main estimand but with using the while-on-treatment strategy for all intercurrent events (as listed in 6.1 for the primary estimand).

The main and second estimands will be repeated five times, once with the population changed to each of the three defined mITT populations, once with the with the population changed to the all randomized set, and once with the population changed to the PP set.

These analyses will be repeated for each background medication subgroup: i) no NSAIDs of colchicine, ii) NSAIDs no colchicine, and iii) colchicine.

6.2.7. Estimands for 'The change from Baseline to Day 28 of Treatment Period 6 in the total score of the Health Assessment Questionnaire (HAQ-DI)'

The main estimand for the key secondary efficacy endpoint 'Change from Baseline to Day 28 of TP6 of the Total Score of the Health Assessment Questionnaire (HAQ-DI)' is defined as follows:

- 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: Continuous variable showing change from Baseline to 6 months after start of study treatment (D28 of Treatment Period 6)
- Population-level summary: Difference in mean change from baseline in total score of the HAQ-DI questionnaire between each SEL-212 treatment group versus placebo.
- Intercurrent events:
    - All intercurrent events (as listed in 6.1 for the primary estimand) except deaths will be considered using the treatment policy strategy
    - For deaths the last available value will be used (while-on-treatment strategy)

A second estimand for this key secondary efficacy endpoint will be defined similarly to the main estimand but with using the while-on-treatment strategy for all intercurrent events (as listed in 6.1 for the primary estimand).

The main and second estimands will be repeated five times, once with the population changed to each of the three defined mITT populations, once with the with the population changed to the all randomized set, and once with the population changed to the PP set.

6.2.8. Estimands for 'Gout Flare Incidence during Treatment Periods 1-6'

The main estimand for the key secondary efficacy endpoint 'gout flare incidence in TP1 to 6' is defined as follows:

- 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: Incidence of gout flare during the whole treatment period from start of treatment until end of month 6. 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.
- Population-level summary: Difference in the incidence of gout flares between each SEL-212 treatment group versus placebo for the whole treatment period (start of treatment until end of Treatment Period 6).
- Intercurrent events:
    - All intercurrent events (as listed in 6.1 for the primary estimand) except deaths will be considered using the treatment policy strategy
    - For deaths the while-on-treatment strategy will be used

A second estimand for this key secondary endpoint will be defined similarly to the main estimand but with using the while-on-treatment strategy for all intercurrent events (as listed in 6.1 for the primary estimand).

The main and second estimands will be repeated five times, once with the population changed to each of the three defined mITT populations, once with the with the population changed to the all randomized set, and once with the population changed to the PP set.

These analyses will be repeated for each background medication subgroup: i) no NSAIDs of colchicine, ii) NSAIDs no colchicine, and iii) colchicine.

6.2.9. Estimands for 'Gout Flare Incidence during Treatment Periods 1-3'

The main estimand for the key secondary efficacy endpoint 'gout flare incidence in TP1 to 3' is defined as follows:

- 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: Incidence of gout flare during the whole treatment period from start of treatment until end of month 3. 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.
- Population-level summary: Difference in the incidence of gout flares between each SEL-212 treatment group versus placebo for the whole treatment period (start of treatment until end of Treatment Period 3).
- Intercurrent events:
    - All intercurrent events (as listed in 6.1 for the primary estimand) except deaths will be considered using the treatment policy strategy
    - For deaths the while-on-treatment strategy will be used

A second estimand for this key secondary endpoint will be defined similarly to the main estimand but with using the while-on-treatment strategy for all intercurrent events (as listed in 6.1 for the primary estimand).

The main and second estimands will be repeated five times, once with the population changed to each of the three defined mITT populations, once with the with the population changed to the all randomized set, and once with the population changed to the PP set.

These analyses will be repeated for each background medication subgroup: i) no NSAIDs of colchicine, ii) NSAIDs no colchicine, and iii) colchicine.

7. General Aspects for Statistical Analysis

7.1. General Methods

SAS® version 9.4 or higher will be used for all statistical analyses and tabulations.

In general, summaries will present data by treatment group and overall for each scheduled assessment time where appropriate.

Unless stated otherwise, descriptive summaries will include n, mean, standard deviation, median, minimum and maximum for continuous variables, and n and percent for categorical variables. If there are multiple assessments collected for the same scheduled time the first assessment post-baseline will be used. The last available assessment before start of study treatment will be used as baseline.

Adverse events and medical history will be coded according to the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be coded using the most recent WHO Drug Dictionary version. The actual version of MedDRA and WHO drug used will be noted in the footnote of the respective output.

7.2. Key Definitions

Baseline is defined as the last non-missing value prior to the start date and time of the study drug. For Health questionnaires (including HAQ-DI, SF-36, and PGA), gout flare assessment, tender joint assessment and swollen joint assessment, if no assessment is available prior to the start time of the study drug, assessments post the start of study drug but on the date of first study drug administration may be considered as Baseline. Tophus status at baseline in the study will be based on IRT.

Day 0 of Treatment Period 1 is defined as the first date of study drug administration.

Overall study day will be calculated as date of event/collection – first dose date of the study.

Study day within each treatment period will be calculated as date of event/collection – first dose date at each treatment period to be consistent with protocol which defines the day of dosing in each treatment period as day 0.

7.3. Missing Data

Missing data will be imputed for the primary efficacy and key secondary efficacy variables as described in Section 9.

Missing or incomplete dates in safety data: In all listings, missing or incomplete dates will be left as they have been recorded. However, for calculation and sorting based on dates and for consideration in summary tables, the following method will be used: The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing or incomplete, it is assumed to have occurred during the study treatment phase (i.e. a TEAE for AEs) except if the partial onset date indicates differently). A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.

Missing TEAE relationship will be imputed by ‘related’ for tabulation.

7.4. Unscheduled visits

Unscheduled visit measurements will be included in analyses and treatment summaries in the following circumstances:

i) If there are missing data at a scheduled visit, but data available at an unscheduled visit that occurred after the previous scheduled visit, and prior to the next scheduled visit.
   a. In the event there are more than one unscheduled visit between the previous scheduled visit and the next scheduled visit, the closest measurement to the missed target day will be used.
   b. If there are multiple records within the same distance from the target day, the latest record will be used.

ii) Derivations of baseline/last-on-treatment measurements.

iii) For all safety parameters, if there are multiple measurements within a visit window, then the record closest to the target day will be used.
   a. In the event there are more than one unscheduled visit between the previous scheduled visit and the next scheduled visit, the closest measurement to the missed target day will be used.
   b. If there are multiple records within the same distance from the target day, the latest record will be used.

Otherwise, data collected at unscheduled visits will be included in the data listings but will not be included in the analyses or in treatment summaries.

8. Demographic, Other Baseline Characteristics and Medication

8.1. Patient Disposition and Withdrawals

Patient disposition data will be listed. Summary tables reflecting the number of patients for the following will be presented:

- Screened (or enrolled) patients
- ITT, SS, mITT, all randomized, and PP patients
- Patients who complete the study treatment
- Patients who early terminate study treatment overall and by treatment period together with reasons
- Patients who complete the study
- Patients who early terminate the study overall and by treatment period together with reasons

Screen Failure subjects will be listed with reason for failure.

A figure of the percentage of patients who discontinued the study treatment will be presented by treatment and period. Additionally, a figure of the percentage of patients who discontinued the study treatment because of the stopping rule will be presented by treatment and period.

8.2. Demographic and Other Baseline Characteristics

Demographic characteristics such as gender, age, race, ethnicity, height, weight, BMI, time since first gout diagnosis and estimated glomerular filtration rate (eGFR) will be summarized for the ITT and the SS population, by treatment and overall. Demographic characteristics will be listed for all randomized patients.

Age (years) will be calculated based on date of signed informed consent as:

(Date of informed consent - date of birth) / 365.25 and truncated to complete years.

BMI (kg/m^2) will be calculated as: Weight (kg)/[Height(cm)/100]^2.

8.3. Medical History

Medical history will be coded using current version of Medical Dictionary for Regulatory Activities (MedDRA®). Medical history will be listed for all randomized patients. No summaries will be provided.

8.4. Other Baseline Characteristics

Tophus assessment at screening, gout flare assessment at screening and baseline and the number of tender and swollen joints at baseline will be summarized by treatment group, overall SEL-212 and total. In addition, sUA at screening and baseline (Day 0 pre-dose) will be summarized by treatment group, as well as the change in sUA from screening to baseline.

8.5. Medication

Prior medication is defined as any medication which has an end date prior to the date of first dose of study drug administration.

Concomitant medication is defined as any medication which has an end date or is continuing after the date of first dose of study drug administration or has a missing end date.

The original verbatim terms collected in the eCRF for prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD current version).

Listings will include the therapeutic (i.e., the second level of Anatomical Therapeutic Chemical [ATC] classification system code, that is, corresponding to the first 3 figures), preferred name (the fourth level of the ATC code, that is, corresponding to the first 5 figures) and verbatim text. The listings will be sorted by treatment group, patient id, chronological start date, stop date, therapeutic class, preferred name and verbatim name and will contain all randomized patients.

A frequency table of the number and percentage of patients will be provided for prior medications and concomitant medications by therapeutic class and preferred name for each treatment group and overall on the ITT population.

Premedication for gout flare and premedication against infusion reactions (provided before start of dosing in each treatment period) will be summarized separately by treatment group and period, if applicable.

8.6. Summary of sUA from screening to baseline, stratified by ULT at screening

An additional baseline summary will be produced, stratifying all randomised individuals by whether they were on ULT at screening or not. A summary of sUA at screening and baseline (Day 0 pre-dose) will be summarized by treatment group, as well as the change in sUA from screening to baseline.

9. Efficacy

9.1. Assessment of sUA Time Curve and Summaries

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 in TP6 will be used to estimate the proportion of time that the sUA level is below 6 mg/dL by Day 28. Based on the serum samples collected during TP6 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 TP6 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. For example, if a patient had their Day 28 assessment on Day 30 then a straight line will connect Day 30 and their previous assessment, but the percentage of time the time curve is < 6 mg/dL will be derived only up to Day 28. 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 EOS will be used to interpolate the curve up to Day 28. This can include the use of unscheduled sUA assessments. However, note that no sUA assessments are scheduled for EOS as this is conducted via phone call. For example, if a patient is missing their Day 28 assessment, and the next assessment is at Day 40 of TP6 (e.g., once their mild-moderate COVID-19 resolve) then this additional timepoint will be plotted and a straight line will be connected between this and their previous assessment in TP6 prior to Day 28 (as Day 40 is now the next available assessment between Day 28 and up to, and including EOS) and the percentage of time the time curve is < 6 mg/dL will again be derived up to Day 28. 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. For example if a patient has all scheduled assessments during TP6 up to Day 21, with no assessments on or after Day 28, up to and including EOS, but has an unscheduled assessment on Day 25 then the percentage of time with sUA level < 6 mg/dL for TP6 would be taken to be the percentage of time the sUA levels were < 6 mg/dL from Day 0 to Day 25. If only 2 or fewer assessments are available (allowing for the use of assessments after Day 28 up to, and including EOS, 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. For a patient to be considered a responder in TP6, 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 (or last available assessment prior to Day 28 if no assessments are available from Day 28 up to, and including EOS) must be at least 80%.

For example, if a patient only has measurements on both Day 0 assessments and Day 8 (planned assessment for Day 7) then percentage of time with sUA level < 6 mg/dL for TP6 would be taken to be the percentage of time the sUA levels were < 6 mg/dL from Day 0 to Day 8. However, if the Day 7 planned assessment was taken on Day 6 then this patient would have a missing value for their response.

A frequency table of the percentage of responders in TP6 will be provided by treatment group in overall and stratified by tophus status at baseline for the ITT population. Additionally, a summary table with the total

and percentage of time a patient has sUA values < 6 mg/dL in TP6 will be provided by treatment group in overall and stratified by tophus status at baseline for the ITT.

Summary table of the actual values and change from baseline (Day 0 TP1) 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 TP6 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

The sUA levels will be visualized in a box-plot by assessment time and treatment.

9.2. Analyses of Primary Efficacy Estimands

The statistical testing of each SEL-212 treatment group versus placebo in all four estimands 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 α = 2.5% to adjust for the two comparisons against placebo. Only the test results of the main estimand will be considered as confirmatory.

In addition, a logistic regression model will be fitted, with response as the outcome variable, tophus presence (yes/no) at baseline, treatment group included as covariates.

The analysis of all four estimands will be carried out based on the ITT population, and analyses on the main, second and third estimand will be performed, but the population will be each of the defined mITT populations, the PP and the all randomized set as opposed to the ITT. For missing response evaluation data in TP6 (see also Section 9.1) values will be multiple imputed. The logistic method considering the tophus status at baseline and the treatment group will be applied for the multiple imputation. For the main, second and fourth estimand of primary efficacy, sensitivity analysis will be performed using the tipping-point analysis for binary response, to investigate the sensitivity to departures from missing-at-random (MAR). For patients with missing response status, the underlying response probability will be varied systematically and comprehensively such that, should one exist, a tipping point can be identified where if the probability of being a non-responder in the treatment group is higher than in the placebo group, the statistical significance switches from treatment effect p-value <0.025 to treatment effect p-value ≥0.025. For each arm, the following scenarios will be explored, where the true underlying response probability amongst those with missing response status will have the following probabilities:

0.01, 0.11, 0.21, 0.31, 0.41, 0.51, 0.61, 0.71, 0.81, 0.91, 0.99.

The analysis will be performed in each combination of placebo probability to SEL-212 active treatment arm probability, with the most extreme cases being when one arm in the comparison has a response probability of 0.99 and the other has a response probability of 0.01. Once a tipping point has been established, scenarios that make the treatment effect more favorable to the placebo arm will not be examined. Responses for those with missing response data will be imputed multiple times for each scenario, with responses drawn with the probabilities listed above. In each scenario, the results across multiply imputed

datasets will be combined in the same way as the multiple imputation analysis, but the response probabilities will be pre-specified as opposed to generated from a logistic regression.

An 11 × 11 table will be displayed for each SEL-212 active arm vs. placebo comparison where the p-values from the tipping point analysis under each combination of underlying response probabilities for those with missing data are shown.

A table with number and type/reason of missing values in the primary efficacy variable will be provided by treatment group on the ITT population for each estimand.

Frequency table of the treatment responders considering the responder definition in Section 9.1 but also the definitions in Section 6 for the estimands of interest will be provided by treatment group for all three estimands defined in Section 6, and the difference in proportions between each SEL-212 treatment group and placebo will be presented together with 97.5% confidence intervals. The treatment effect odds ratio and 97.5% confidence intervals will be presented from the logistic regression.

9.3. Key Secondary Efficacy Estimands and Analyses

9.3.1. Hierarchical Testing Approach of Key Secondary Efficacy Estimands

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 as defined in Section 6.2. The test result of the n^{th} 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.

9.3.2. Key Secondary Efficacy Analyses

9.3.2.1. *Reduction of mean sUA as computed by subtracting the Baseline sUA level from the mean sUA during Treatment Period 6*

Both estimands, as well as the estimands where the ITT is replaced by each mITT, all randomized and PP sets, for this key secondary efficacy will be tested between each SEL-212 treatment group versus placebo using an ANCOVA, with reduction of mean sUA at TP6 from baseline as the dependent variable, treatment and randomization stratum as fixed effects, and baseline sUA value as covariates. Missing values of change from baseline will be multiple imputed by using the RPMM method considering tophus status at baseline and treatment group. 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.

The change from baseline in mean sUA across TP6 will be summarized by treatment group on the ITT, the defined mITT populations, all randomized and the PP population.

9.3.2.2. *Percent reduction of mean sUA as computed by subtracting the Baseline sUA level from the mean sUA during Treatment Period 6*

Both estimands, as well as the estimands where the ITT is replaced by each mITT, all randomized and PP sets for this key secondary efficacy will be tested between each SEL-212 treatment group versus placebo using an ANCOVA, with percentage change of mean sUA at TP6 from baseline as the dependent variable,

treatment and randomization stratum as fixed effects, and baseline sUA value as covariates. Missing values of % change from baseline will be multiple imputed by using the RPMM method considering tophus status at baseline and treatment group. 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.

However, residuals from this model will be checked for conformity to normality assumptions. Differences from normality in these residuals will result in the dependent variable being log-transformed and the ANCOVA applied to this outcome, adjusting for the same covariates. This model will then be considered the primary analysis for this estimand.

The percentage change from baseline in mean sUA across TP6 will be summarized by treatment group on the ITT, the defined mITT populations, the all randomized and the PP population.

9.3.2.3. *The change from Baseline to Day 28 of Treatment Period 6 in the physical summary score of the Short Form Health Survey 36 (SF-36)*

Both estimands, as well as the estimands where the ITT is replaced by each mITT, all randomized and PP sets, for this key secondary efficacy endpoint will be tested between each SEL-212 treatment group versus placebo using MMRM with change in SF-36 summary score as dependent variable and treatment, period, treatment-by-period interaction, randomization stratum and baseline value of SF-36 summary score as fixed effect variables. The unstructured covariance structure will be used for the MMRM. The LSMean difference between each SEL-212 and placebo treatments groups will be estimated on the treatment-by-period interaction at TP6-Day 28 visit, along with its 97.5% confidence interval, and 2-sided p-values.

A sensitivity analysis will be performed for the main estimand: missing values of SF-36 summary score at TP6-D28 will be multiple imputed by using the RPMM method considering tophus status at baseline and treatment group, and the change from baseline to Day 28 of TP6 in SF-36 summary score will be analyzed using an ANCOVA with treatment and randomization stratum as fixed effects and the baseline value of SF-36 summary score as covariate.

The SF-36 summary score at scheduled visits and the change from baseline will be summarized by treatment group and period, on the ITT, the defined mITT populations, all randomized population and the PP population.

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.

The SF-36 consists of 8 scaled domain scores with range 0-100 with higher score indicating better health and 2 component scores (physical component and mental component). The 8 domains are:

- Vitality
- Physical functioning
- Bodily Pain
- General Health Perceptions

- Physical Role Functioning
- Emotional Role Functioning
- Social Role Functioning
- Mental Health

9.3.2.4. *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 TP6*

This efficacy endpoint considers the patients with tophi at baseline and compares between each SEL-212 and placebo the percentage of patients with at least PR (as best response) in the overall tophus response evaluation until Day 28 of TP6. The statistical testing of each SEL-212 treatment group versus placebo in both estimands, as well as the estimands where the ITT is replaced by each mITT, all randomized and PP sets, of this key secondary efficacy will be performed using the Chi-square test with continuity correction with a two-sided type 1 error rate $\alpha = 2.5\%$ to adjust for the two comparisons against placebo. In the main estimand, patients with missing information on tophus response until Day 28 of TP6 will be multiple imputed using the logistic method considering the treatment group.

Frequency table of tophaceous patients at baseline with best response in the overall tophus evaluation resulting in at least PR / stable disease progressive disease will be provided by treatment group and period on the ITT, the defined mITT populations, all randomized and the PP population.

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 for tophaceous patients at baseline in the ITT, the defined mITT populations, all randomized and the PP population. Tophus photography can be repeated on TP1D0 or until 14 days post TP1D0 if initial images submitted to the Central Reader were not collected per acquisition guidelines.

9.3.2.5. *Percentage of patients who achieve and maintain reduction of sUA < 6 mg/dL for at least 80% of the time during Treatment Period TP6 in subset of patients with tophi at baseline*

Both estimands, as well as the estimands where the ITT is replaced by each mITT, all randomized and PP sets, for this key secondary endpoint will be analysed in the same way as the primary endpoint, except a Chi-square test with continuity correction will be performed, given only patients with tophus at baseline will be included in the analysis. In addition, the logistic model used to carry out multiple imputation for missing response evaluation data in TP6 will only include the treatment group in the model (and not tophus status at baseline), as only patients with tophus at baseline will be included in the analysis.

9.3.2.6. *The change from Baseline to Day 28 of Treatment Period 6 in number of tender joints*

Both estimands, as well as the estimands where the ITT is replaced by each mITT, all randomized and PP sets, for this key secondary efficacy will be tested between each SEL-212 treatment group versus placebo using the mixed model for repeated measures (MMRM) with change in tender joints from baseline as dependent variable and treatment, period, treatment-by-period interaction, randomization stratum and baseline value of tender joints as fixed effect variables. The unstructured covariance structure will be used for the MMRM. The Least Square (LS) Mean difference between each SEL-212 and placebo treatments groups will be estimated on the treatment-by-visit interaction at TP6-Day 28 visit, along with its 97.5% confidence interval, and 2-sided p-values.

A sensitivity analysis will be performed for the main estimand: missing values of number of tender joints at Day 28 TP6 will be multiple imputed by using the regression and predictive mean matching (RPMM) method considering tophus status at baseline and treatment group. The change from baseline to Day 28 of TP6 in tender joints will be analyzed using an ANCOVA with treatment and randomization stratum as fixed effects and the baseline value of tender joints as covariate.

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

9.3.2.7. *The change from Baseline to Day 28 of Treatment Period 6 in the total score of the Health Assessment Questionnaire*

Both estimands, as well as the estimands where the ITT is replaced by each mITT, all randomized and PP sets, for this key secondary efficacy will be tested between each SEL-212 treatment group versus placebo using MMRM with change in HAQ-DI total score as dependent variable and treatment, period, treatment-by-period interaction, randomization stratum and baseline value of HAQ-DI total score as fixed effect variables. The unstructured covariance structure will be used for the MMRM. LSMean difference between each SEL-212 and placebo treatments groups will be estimated on the treatment-by-visit interaction at TP6-Day 28 visit, along with its 97.5% confidence interval, and 2-sided p-values.

A sensitivity analysis will be performed for the main estimand: missing values of HAQ-DI total score at TP6-Day 28 will be multiple imputed by using the RPMM method considering tophus status at baseline and treatment group, and the change from baseline to Day 28 of TP6 in HAQ-DI total score will be analyzed using an ANCOVA with treatment and randomization stratum as fixed effects and the baseline value of HAQ-DI total score as covariate.

The HAQ-DI total score at scheduled visits and the change from baseline will be summarized by treatment group and period on the ITT, the defined mITT populations, all randomized and the PP population.

The HAQ-DI, which includes the patient global assessment and pain scale, 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.

Eight (8) categories will be assessed by the HAQ-DI: 1) dressing and grooming, 2) arising, 3) eating, 4) walking, 5) hygiene, 6) reaching, 7) gripping, and 8) common daily activities. There are 2 or 3 questions for each section. Scoring within each section is on a 4-point Likert scale from 0 (without any difficulty) to 3 (unable to do). The score given to each section is the worst (highest) score within the section (ie, if one question is scored 1 and another 2, then the score for the section is 2). In addition, if an aid or device is used or if help is required from another individual, then the minimum score for that section is 2. If the section score is already 2 or more then no modification is made. The sum of the 8 scores of the 8 sections will be divided by 8 to obtain the HAQ-DI total score. In the event that one section is not

completed by a patient then the summed score would be divided by 7. The HAQ-DI total score will be calculated if 6 or more sections are available, otherwise it will be defined at missing.

9.3.2.8. *Gout Flare Incidence During Treatment Periods 1-6*

The 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. Both estimands, as well as the estimands where the ITT is replaced by each mITT, all randomized and PP sets for this key secondary efficacy will be tested between each SEL-212 treatment group versus placebo using ANOVA model with incidence of gout flares as dependent variable and treatment and randomization stratum as fixed effect variables. Missing values of gout flare incidence by TP6-Day 28 will be multiple imputed by using the RPMM method considering tophus status at baseline and treatment group.The LSMean difference between each SEL-212 and placebo treatments groups will be provided along with its 97.5% confidence interval, and 2-sided p-values.

In a supportive analysis, for each defined estimand the comparison between each SEL-212 treatment group and placebo will be performed using MMRM with the dependent variable 'incidence of gout flares in the study (TP1-6)' and treatment, 3-month period (months 1-3 versus months 4-6), treatment-by-3-month period interaction and randomization stratum as fixed effects. The LSMean difference between each SEL-212 and placebo treatment groups will be presented for each 3-month period, along with its 97.5% confidence interval, and 2-sided p-values.
In a further supportive analysis, the total number of gout flares by TP6-Day 28 will be analyzed. Missing values of total number of gout flares by TP6-Day 28 will be multiple imputed by using the RPMM method considering tophus status at baseline and treatment group. The total number of gout flares will be analyzed using an ANOVA with treatment and randomization stratum as fixed effects.

A summary table of the incidence of gout flares during the study and stratified by 3 months period (month 1-3 and month 4-6 after start of study treatment) will be provided by treatment group on the ITT, mITT, all randomized and PP populations. Summary tables of the total number of gout flares during the study will be provided by treatment group in overall and additionally stratified by severity on the ITT, mITT and PP populations. Summary tables of the number of gout flares during the first 3 months (TP1-3) and the next three months (TP4-6) will be provided by treatment group in overall and additionally stratified by severity on the ITT, mITT, all randomized and PP populations.

9.3.2.9. *Gout Flare Incidence During Treatment Periods 1-3*

The 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. Both estimands, as well as the estimands where the ITT is replaced by each mITT, all randomized and PP sets, for this key secondary efficacy will be tested between each SEL-212 treatment group versus placebo using ANOVA model with incidence of gout flares as dependent variable and treatment and randomization stratum as fixed effect variables. Missing values of gout flare incidence by TP3-Day 28 will be multiple imputed by using the RPMM method considering tophus status at baseline and treatment group. The LSMean difference between each SEL-212 and placebo treatments groups will be provided along with its 97.5% confidence interval, and 2-sided p-values.

In a supportive analysis, the total number of gout flares by TP3-Day 28 will be analyzed. Missing values of total number of gout flares by TP3-Day 28 will be multiple imputed by using the RPMM method considering tophus status at baseline and treatment group. The total number of gout flares will be analyzed using an ANOVA with treatment and randomization stratum as fixed effects.

9.3.3. Additional Secondary Efficacy Endpoints and Analyses

- Percentage of patients who achieve and maintain reduction of sUA < 6 mg/dL for 100% of the time during TP6:

  A frequency table of number and percentage of patients who achieve and maintain reduction of sUA < 6 mg/dL for 100% of the time during TP6 will be provided on the ITT population. Each SEL-212 treatment group will be compared versus placebo using the MH estimate and test for common risk difference considering the randomization stratum of tophus presence (yes/no) on the ITT population. In addition, 95% confidence intervals for treatment differences between each SEL-212 treatment group and placebo will be computed.

- Number with pre-dose sUA values < 6 mg/dL during TPs 2-6 for each patient:

  A summary table of the mean number of TPs with pre-dose sUA values < 6 mg/dL during TP2 to TP6 will be provided by treatment group on the ITT population. Each SEL-212 treatment group will be compared versus placebo using ANCOVA model with the number of pre-dose values < 6 mg/dL during TPs 2-6 for each patient as dependent variable and treatment group as independent fixed effect variable. 95% confidence intervals for treatment differences between each SEL-212 treatment group and placebo will be presented.

- Anti-pegadricase and anti-uricase antibody formation and levels, pre-treatment for each treatment period in the SEL-212 active treatment arms:

  Summary table of pre-treatment values of each variable will be provided by treatment period and by SEL-212 treatment group on the ITT population.

  A descriptive summary table of D21 anti-pegadricase and anti-uricase antibody titers, D21 uricase activity values and D21 SUA values at each treatment period, stratified by treatment arm and whether or not the D21 SUA was above or less than or equal to the stopping rule level for that TP (i.e. ≤1 mg/dL in TP1 and ≤6 mg/dL in TPs 2-6).

- 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 TP4

Pairwise comparison of each SEL-212 treatment group versus placebo will be performed using the Chi-square test with continuity correction. In addition, 95% confidence intervals for treatment differences between each SEL-212 treatment group and placebo will be computed.

Frequency table of tophaceous patients at baseline with best response in the overall tophus evaluation resulting in at least PR / stable disease progressive disease will be provided by treatment group and period on the ITT population.

The time until the first tophus reduction (i.e. the first time PR (as best response) is assessed in overall tophus response) will be summarized using descriptive statistics by treatment group for tophaceous patients at baseline in the ITT population.

- 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:

  A frequency table of number and percentage of patients will be provided by treatment group and tophus status at baseline on the ITT population who developed new tophi during the study until Day 28 of TP6, i.e. were classified as PD due to new tophi in the overall tophus response evaluation. Pairwise comparison of each SEL-212 treatment group versus placebo will be performed using the Chi-square test with continuity correction. In addition, 95% confidence intervals for treatment differences between each SEL-212 treatment group and placebo will be computed.

  The actual value and the change from baseline of the total number of tophi will be summarized for each scheduled visit by treatment group. Location of tophus, palpation and appearance will be summarized by category, as appropriate, by treatment group for each scheduled visit.

- Change from baseline to Day 28 of TP6 in subscales of Health Assessment Questionnaire (HAQ-DI), in subscales of Short Form Health Survey (SF-36) and in Provider Global Assessment of Disease Activity (PGA)

  Summary table of actual values and change from baseline will be provided for all subscales of HAQ-DI, for all subscales of SF-36, the two component scores of SF-36, and the PGA, by period and treatment group. Pairwise comparison of each SEL-212 treatment group versus placebo will be performed using MMRM with the change from baseline in the respective health assessment score as dependent variable and treatment, period, treatment by period interaction, randomization stratum, and baseline value of the respective health assessment as fixed effects. The LSMean difference between each SEL-212 and placebo treatments groups will be presented for TP6, along with its 95% confidence interval, and 2-sided p-values.

  HAQ-DI subscales and SF-36 subscales and component scores are described in Sections 9.3.2.5 and 9.3.2.3 of this SAP, respectively. The PGA will be administered to assess the severity of the patient's disease on a scale from 0 (patient feels "very well") to 100 (patient feels "very poor"). Lower scores indicate less severe disease.

- Percentage of Patients with Gout flares:

  Frequency table of the number and percentage of patients reporting at least one gout flare in the study until end of Month 6, in the first 3 months, and the next 3 months will be summarized by treatment group on the ITT population.

  The number and percentage of patients with at least one life-threatening / at least one severe but no life-threatening / at least one moderate but no severe or life-threatening / only mild gout flares will be presented for each treatment group for all 6 months, but also per 3-month period (first 3 months and next 3 months) on the ITT population.
  The percentage of patiens with gout flares will be compared between each SEL-212 treatment group versus placebo on the ITT population using the MH estimate and test for common risk difference considering the randomization stratum of tophus presence (yes/no). This analysis will be performed separately for the whole treatment period of 6 months and for the first 3 months after

start of study treatment. 95% confidence intervals for treatment differences in proportions between each SEL-212 treatment group and placebo will be computed.

- Change from Baseline to Day 28 of TP6 in number of swollen joints:

  The number of swollen joints at scheduled visits and the change from baseline will be summarized by treatment group on the ITT population. Pairwise comparison of each SEL-212 treatment group versus placebo will be performed using MMRM with the change from baseline in the number of swollen joints as dependent variable and treatment, period, treatment by period interaction, randomization stratum, and baseline number of swollen joints as fixed effects. The LSMean difference between each SEL-212 and placebo treatment groups will be presented for TP6, along with its 95% confidence interval, and 2-sided p-values.

- Length of time patients are anti-uricase antibody free or before induction of anti-uricase antibody levels above baseline in patients receiving SEL-212:

  A summary table will be provided for each SEL-212 treatment group on the ITT population.

- Length of time patients are anti-pegadricase antibody free or before induction of anti-pegadricase antibody levels above baseline in patients receiving SEL-212:

  A summary table will be provided for each SEL-212 treatment group on the ITT population.

9.3.4. Exploratory Endpoints

All exploratory endpoints will be summarized on the ITT population.

- Levels of uricase activity in patients receiving SEL-212:

  Summaries for each SEL-212 treatment group will be provided by period.

- Effect on monosodium urate crystal deposits and/or total body monosodium urate crystal deposits (imaging patients only):

  Frequencies and summaries will be provided by treatment group, and period, if appropriate.

- Levels of inflammatory and tolerogenic biomarkers:

  Frequencies and summaries will be provided by treatment group, and period, if appropriate..

- Changes in antibody production (anti-uricase and anti-pegadricase) in patients in the SEL-212 groups:

  Summaries for each SEL-212 treatment group will be provided by period.

- Gout flare incidence during Treatment Periods 4-6

  A summary table of incidence of gout flares during TPs 4-6 will be presented, based on the ITT population, but including only patients who were still being followed up at the start of TP 4. The incidence is defined as the total number of gout flares a patient experiences between TP4 day 0 and TP6 day 28, divided by the length of observation of the patient in this time period.

  An ANCOVA model will be performed with incidence of gout flares as the dependent variable, and treatment and randomization stratum as fixed effect variables. The LSMean difference between

each SEL-212 and placebo treatment group will be provided along with its 95% confidence interval, and 2-sided p-values.

- Gout flare incidence based on self-reported weekly gout flare diary:

  A summary table of the incidence of gout flares during the study and during the first 3 months and the next 3 months after start of study treatment based on weekly gout flare diary will be provided by treatment group on the ITT population. The incidence is defined as the total number of gout flares a patients experiences in respective time period divided by the length of observation of the patient in this time period. Additionally a summary table of the total number of gout flares during the study, and of the total number of grout flares during the first 3 months and the next 3 months after start of study treatment will be provided by treatment group and severity on the ITT population.

  An ANCOVA model will be performed with incidence of gout flares as dependent variable and treatment and randomization stratum as fixed effect variables for the whole treatment period (TP1 to 6) and for the first 3 months (TP1 to 3) on the ITT. The LSMean difference between each SEL-212 and placebo treatment group will be provided along with its 95% confidence interval, and 2-sided p-values.

  Additionally, a MMRM will be applied on the ITT with the dependent variable 'incidence of gout flares in the study (TP1-6)' and treatment, 3-month period (months 1-3 versus months 4-6), treatment-by-3-month period interaction, randomization stratum and baseline value of number of gout flares as fixed effects. The LSMean difference between each SEL-212 and placebo treatment group will be presented for each 3-month period, along with its 95% confidence interval, and 2-sided p-values.

- Association between multiomic markers of gout and treatment effect in patients treated with SEL-212

  The treatment effect at TP6, i.e., the number and percentage of patients with responses as defined for the primary efficacy variable (i.e. having sUA value < 6 mg/dL in more than 80% of the time in TP6) will be summarized for each class of multiomic markers by SEL-212 treatment group.

- Immune tolerance related multiomic markers in patients on SEL-212 who developed anti-uricase vs. those patients on SEL-212 that did not develop anti-uricase antibodies, and in patients on SEL-212 who developed anti-pegadricase antibodies vs. those patients on SEL-212 that did not develop anti-pegadricase antibodies:

  Summaries for each SEL-212 treatment group will be provided by period and by antibody status.

10. Safety

The population used for safety analyses will be the Safety Set (SS). All safety assessments will be listed by treatment group and patient ID. Visit-wise assessed safety parameters will be listed by treatment group, patient ID and visit/ timepoint. Unscheduled assessments will be flagged and presented in listings. Adverse events will be listed by treatment group, patient ID, start date/time and stop date/time.

10.1. Extent of Exposure

Number and percentage of patients who received all 6 cycles of study treatment (i.e., completed study treatment) and who received only 5, 4, 3, 2, or 1 cycles will be presented by treatment group and overall. The dose applied in in each treatment period will be summarised by treatment group and overall SEL-212.

Number and percentage of patients who met the stopping rules will be summarized by treatment group, overall SEL-212 and treatment period. The percentage will be plotted versus treatment period by treatment group.

10.2. Treatment Compliance

Treatment compliance will be calculated for the two active components SEL-110.36 and SEL-037 for each SEL-212 treatment group separately in a first step. In a second step these compliances will be pooled to one overall compliance for each SEL-212 treatment group.

For each component SEL-110.36 and SEL-037 the following will be calculated for each patient in each of the SEL-212 treatment groups:

1) For each treatment period i and patient j: Compliance of SEL-xx in period i = 100% x (total volume infused in period i) / (total volume planned in period i).
2) For each treatment period i and patient j: Overall compliance in period i = (compliance of SEL-110.36 in period i + compliance of SEL-037) / 2;
3) Mean overall treatment compliance of patient j = Sum of overall compliances in all applied treatment periods of patient j divided by the number of applied treatment periods.

The overall treatment compliance for each period and the mean overall treatment compliance will be summarized and presented by SEL-212 treatment group.

Additionally the volume and infusion duration (defined as stop time of infusion – start time of infusion) in each treatment period will be summarized for each SEL-212 treatment group and for placebo.

10.3. Adverse Events / Adverse Drug Reactions

All adverse events (AEs) will be coded using the most recent MedDRA Version. All AEs will be summarized by system organ class (SOC) and preferred term (PT) for each treatment group, for overall SEL-212 and in total. 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).

Following AEs are considered as AESI: 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.

An overall summary will be provided of the number and percentage of patients reporting AEs, TEAEs, treatment-related (possibly related and related) TEAEs, serious TEAEs, treatment-related serious 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 study drug withdrawal and TEAEs leading to death. 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. 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. Any gout flare which occurs within 24 hours after initiation of study drug infusion will be listed as a gout flare and not as an infusion reaction.

The number and percentage of patients with TEAEs / treatment-related TEAEs / serious TEAEs / AESIs / TEAEs leading to study drug withdrawal/ will be summarized by SOC and PT for each treatment group, overall SEL-212 and total. TEAEs will also be summarized by SOC and PT for maximum intensity and maximum causality for each treatment group, overall SEL-212 and total.

Exposure-adjusted event rates based on i) patients and also based on ii) events by treatment group, overall SEL-212 and total will be provided for patients with at least one related TEAE, at least one SAE, at least one TEAE of special interest and also for specific TEAEs of special interest. For SAEs and AESIs that occur in ≥2% of individuals, as well as the most common TEAEs, the rate difference of exposure-adjusted event rates between the two treatment groups together with the 95% confidence interval will be provided; this will also be presented for the two treatment groups combined vs. placebo.

i) Exposure –adjusted event rate in treatment group A based on patients = Number of all patients with at least one event in treatment group A / Total sum of the treatment exposure time of all patients in treatment group A.

ii) Exposure –adjusted event rate in treatment group A based on events = Number of all events in treatment group A / Total sum of the treatment exposure time of all patients in treatment group A.

Listings of TEAEs and non-TEAEs will be provided.

10.4. Laboratory Evaluations

Laboratory data will be presented in separate tables for each laboratory test type (hematology, blood chemistry, coagulation, antibodies, lipids). Each laboratory parameter will be summarized by scheduled visit and by treatment group, overall SEL-212 and total, presenting actual values and change from baseline. The values from unscheduled visits will be included in analyses according to the rules set out in Section 7.4. Shift tables of the number and percentage of patients below normal range (low), within normal range (normal) and above normal range (high) at each scheduled post-baseline visit compared to the low/normal/high categorization at baseline will be provided by treatment group. A listing of clinically significant abnormal values will be provided in the tables section. Biomarkers and genetic markers will also be summarized by treatment group. Pregnancy test results and drug screen results will be listed only.

10.5. Vital Signs and Weight

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. Summary tables of the actual values and changes from baseline will be provided for each vital sign parameter and weight at each scheduled visit by treatment group, overall SEL-212 and total.

10.6. 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, overall SEL-212 and total.

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. A frequency table with number and percentage of patients with abnormal clinically significant overall interpretation will be presented for each scheduled visit by treatment group, overall SEL-212 and total. Additionally, a frequency table with number and percentage of patients with noteworthy QTcF/QTcB values (> 450, > 480 and > 500 ms) during the study and of patients noteworthy QTcF/QTcB changes from baseline (≥ 30 but <60; ≥ 60 ms) will be provided by treatment group, overall SEL-212 and total.

10.7. Physical Examination

Physical examination results will be presented in data listings, only.

11. DSMB / Interim Analysis

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

No Interim Analysis is planned in this study.

12. Deviation from Analyses Planned in Protocol

The key secondary endpoints for gout flare will be analyzed by ANOVA instead of ANCOVA as specified in the protocol, as adjustment for baseline is not possible given gout flare incidence is not assessed at baseline.

13. Reference List

ICH-E9 (R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials – to the Guideline on Statistical Principles for Clinical Trials. Final Version, 20 November 2019.

P. Berglund, S. Heeringa: Multiple Imputation of Missing Data Using SAS. SAS Institute Inc., July 2014.

Committee on National Statistics, Division of Behavioral and Social Sciences and Education, National Research Council: The Prevention and Treatment of Missing Data in Clinical Trials. Panle on Handling Missing Data in Clinical Trials. The National Academies Press, 2010

J.D. Dziura et al.: Missing Data in Clinical Trials From Design to Analysis. Yale Journal of Biology and Medicine 86 (2013), pp. 343-358.

14. Programming Considerations

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.4 (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

14.1. General Considerations

- Each output will be stored in a separate file.
- Output files will be delivered in Rich Text Format.
- Numbering of TFLs will follow ICH E3 guidance

14.2. Table, Listing, and Figure Format

14.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

14.2.2. Headers

- All output should have the following header at the top left of each page:

  SELECTA Biosciences
  Protocol SEL-212/302
  Draft/Final Run *<date>*

- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

14.2.3. Display Titles

- Each TFL is identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering will be applied. A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT Analysis Set)

14.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of patients in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

14.2.5. Body of the Data Display

14.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

14.2.5.2. *Table Conventions*

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 patient represented in 1 or more groups are included.
- An Unknown or Missing category is added to each parameter for which information is not available for 1 or more patients.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999
- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.
- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented by the body system, ATC class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated are reported as “-”.
- The percentage of patients is normally calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the

denominator, usually the appropriate number of patients exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of patients) where a patient can be included in more than one category, describe in a footnote or programming note if the patient are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.
- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

14.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, patient number, visit/collection day, and visit/collection time.
- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on patient listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the patient are output as "N/A", unless otherwise specified.
- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

14.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

14.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Patient specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').

15. Quality Control

SAS programs will be developed to produce all analysis datasets and statistical outputs. The programming and quality checks for these will be governed by Parexel SOP-GDO-WW-003-05.b.

Parexel SOP-GDO-WW-003-05.b: Statistical Programming Deliverables defines the processes and responsibilities for programming and Quality control (QC) of Statistical Programming deliverables, using SAS system and R. The programming deliverables include Study Data Tabulation Model (SDTM), Analysis datasets (ADs), Statistical Tables, Listings and Figures (TLFs) including these presenting Pharmacokinetic (PK) or Pharmacodynamic (PD) analysis results and Patient Profiles for Safety Narrative preparation as Clinical Study Report (CSR) components.

Approval Signatures

Document Name: Statistical Analysis Plan 23 Feb 2023 SEL-212/302

Document Number: VV-TMF-2453379

Parexel Version Number:

System Version Number: 2 .0

Document Approvals	
Reason for signing: Approved	Name: [redacted] Role [redacted] Date of signature: 22-Feb-2023 22:46:46 GMT+0000
Reason for signing: Approved	Name: [redacted] Role: [redacted] Date of signature: 23-Feb-2023 13:07:59 GMT+0000
Reason for signing: Approved	Name: [redacted] Role: [redacted] Date of signature: 23-Feb-2023 13:33:55 GMT+0000
Reason for signing: Approved	Name: [redacted] Role: [redacted] Date of signature: 23-Feb-2023 13:48:53 GMT+0000