STUDY DRUG: SEL-212 (a combination of SEL-037 and SEL-110.36)
STUDY NUMBER: SEL-212/202
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A STUDY TO COMPARE THE EFFICACY OF SEL-212 TO KRYSTEXXA® IN GOUT PATIENTS REFRACTORY TO CONVENTIONAL THERAPY

Sponsor Selecta Biosciences
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	[redacted]. on behalf of [redacted]	
[redacted]	[redacted]	8June2020

SELECTA BIOSCIENCES CLINICAL STUDY PROTOCOL

A STUDY TO COMPARE THE EFFICACY OF SEL-212 TO KRYSTEXXA® IN GOUT PATIENTS REFRACTORY TO CONVENTIONAL THERAPY

STUDY NUMBER: SEL-212/202

CONTACT INFORMATION

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INVESTIGATOR'S AGREEMENT

I agree:

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

Hence, I:

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

Printed Name of Investigator

Signature of Investigator

Date

2. SYNOPSIS

Name of Sponsor/Company: Selecta Biosciences 65 Grove Street Watertown, MA 02472, USA
Name of Investigational Product: SEL-212 (a combination of SEL-037 and SEL-110.36) **Name of Comparator Product:** **KRYSTEXXA® (pegloticase)**
Name of Active Ingredient in Investigational Product: SEL-037 (pegadricase, recombinant pegylated candida urate oxidase) SEL-110.36 (a nanoparticle composed of PLA [poly{D,L-lactide}] and PLA-PEG [poly{D,L—lactide}-block-poly {ethylene-glycol}] encapsulating rapamycin)
Title of Study: A Study to Compare the Efficacy of SEL-212 to KRYSTEXXA® in Gout Patients Refractory to Conventional Therapy
Study Center(s): approximately 60 study centers in the United States
Studied Period (years): Estimated date first patient enrolled: 28 February 2019 Estimated date last patient completed: 31 July 2020
Objectives: **Primary:** • To assess the reduction in serum uric acid (SUA) in patients treated with SEL-212 compared to KRYSTEXXA® **Secondary:** Secondary objectives are to assess improvement of the following parameters in patients treated with SEL-212 compared to KRYSTEXXA: • Gout flares • SUA control • Joint tenderness and swelling • Quality of life (QoL)
Methodology: This study is a randomized, open-label, parallel-arm study to compare the safety and efficacy profiles of SEL-212 and KRYSTEXXA. Approximately 150 patients will be randomized 1:1

prior to Baseline to receive treatment with SEL-212 or KRYSTEXXA for 6 months. Efficacy assessments, as measured by SUA levels, will be conducted at intervals that are appropriate to determine treatment effect differences, including at month 3 and month 6. Assessments of qualitative endpoints will be conducted on an assessor-blinded basis. Safety will be monitored throughout the study.

Screening Period

After providing written informed consent, the patient is considered enrolled in the study. Patients will be evaluated for inclusion during the Screening Period. For all patients, the standard Screening Period will be up to 45 days prior to Baseline. Concurrently with the Screening Period, a premedication period with colchicine of at least 7 days prior to Baseline for potential gout flare will be required for all subjects, and a washout period of at least 7 days will be required prior to Baseline for patients on any urate-lowering therapy (ULT).

Treatment Periods

The total duration of the treatment will be 6 months. Eligible patients will be randomized 1:1 prior to Baseline to receive SEL-212 or KRYSTEXXA.

Study patients in the SEL-212 arm will receive study drug every 28 days coinciding with Day 0 of each Treatment Period for a total of up to 6 infusions of SEL-212.

Study patients in the KRYSTEXXA arm will receive study drug according to the manufacturer's prescribing information, i.e., every 14 days coinciding with Day 0 and Day 14 of each Treatment Period for a total of up to 12 infusions of KRYSTEXXA.

Prior to infusion, all patients will receive a standardized regimen of 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 at least 1 hour for safety assessments.

With each dose, a blood sample will be drawn for assessment of SUA level immediately prior to infusion (ie, Time 0h) with SEL-212 or KRYSTEXXA, and 1 hour after the infusion of the second component of SEL-212 or of KRYSTEXXA is completed. SUA levels will be assessed through additional post-infusion blood samples at pre-determined time points. Every effort will be made to obtain blood samples at the same time of day of each study visit.

Gout flares will be assessed at every visit. QoL and joint swelling and tenderness will be assessed on Day 0 of Treatment Period 1 and 4, and at the end of Treatment Period 6. Assessments of qualitative endpoints (health questionnaires and joint assessment) will be conducted on an assessor-blinded basis.

On dosing days, safety laboratory samples will be collected pre-infusion and per Schedule of Events in both the SEL-212 arm and the KRYSTEXXA arm. Concomitant medications and procedures and adverse events (AEs) will be monitored continuously during the study.

Follow-Up Period

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. Patients who terminate the study prematurely will have all Early Termination assessments performed. Patients who terminate

the study prematurely who are unable to be on-site for the Early Termination visit will be contacted by telephone for safety follow-up.

Data and Safety Monitoring Committee (DSMC)

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

Stopping Rules

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

- In the SEL-212 arm: 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
- In the KRYSTEXXA arm: SUA level > 6.0 mg/dL measured on 2 consecutive pre-dose measurements

If withdrawn from study drug, the patient will continue study visits to the end of Treatment Period 6.

Number of Patients (Planned):

- Planned Enrollment: Approximately 150 patients randomized (total):
  - SEL-212: approximately 75 patients
  - KRYSTEXXA: approximately 75 patients

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

A patient must meet all of 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 a history of symptomatic gout defined as:
   a. ≥ 3 gout flares within 18 months of Screening or
   b. Presence of ≥ 1 tophus or
   c. Current diagnosis of gouty arthritis
4. At the Screening Visit: male age 21 – 80 years, inclusive, or female of non-childbearing potential age 21-80 years, inclusive, where non-childbearing potential is defined as:
   a. > 6 weeks after hysterectomy with or without surgical bilateral salpingo-oophorectomy or

b. Post-menopausal (> 24 months of natural amenorrhea or in the absence of > 24 months of amenorrhea, 1 documented confirmatory FSH measurement)

5. Has at Screening SUA ≥ 7 mg/dL, with chronic refractory gout defined as having failed to normalize SUA and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the medically appropriate dose, or these drugs are contraindicated for the subject;
6. Is negative for anti-PEG antibodies at Screening;
7. Has not participated in a clinical trial within 30 days of the Screening Visit and agrees not to participate in a clinical trial for the duration of the study;
8. Negative serology for HIV-1/-2 and negative antigen to hepatitis B and negative antibodies to hepatitis C;
9. Has adequate venous access and able to receive IV therapy;
10. If applicable, has sufficiently recovered from any prior surgery to allow for successful completion of study procedures.

Exclusion Criteria:

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

1. Prior exposure to any experimental or marketed uricase (e.g., pegloticase [Krystexxa®], pegadricase [SEL-037], rasburicase [Elitek, Fasturtec])
2. History of anaphylaxis or severe allergic reactions to medications;
3. History of any allergy to pegylated products, including, but not limited to, peginterferon alfa-2a (Pegasys®), peginterferon alfa-2b (PegIntron®), pegfilgrastim (Neulasta®), pegaptanib (Macugen®), pegaspargase (Oncaspar®), pegademase (Adagen®), peg-epoetin beta (Mircera®), pegvisomant (Somavert®) certolizumab pegol (Cimzia®), naloxegol (Movantik®), peginesatide (Omontys®), and doxorubicin liposome (Doxil®);
4. Known moderate and severe CYP3A4 inhibitors or inducers must be discontinued 14 days before dosing and patients must remain off the medication for the duration of the study, including natural products such as St. John's Wort or grapefruit juice.
5. Drugs known to interact with Rapamune® such as cyclosporine, diltiazem, erythromycin, ketoconazole (and other antifungals), nicardipine (and other calcium channel blockers), rifampin, verapamil unless they are stopped 2 weeks prior to starting the trial and will not be used during the trial.
6. Initiation or change in dose of hormone-replacement therapy for menopausal women less than 1 month prior to the Screening Visit or during the Screening Phase would be exclusionary. If after being on a stable dose of hormone-replacement therapy for 1 month the patient may be considered for the study if she continues to meet all other inclusion and exclusion criteria.
7. A gout flare during Screening that was resolved for less than 1 week prior to first treatment with study drug (exclusive of synovitis/arthritis), unless the patient has a history of inter-flare intervals < 1 week.

8. Uncontrolled diabetes at Screening with HbA1c ≥ 8%;
9. Fasting Screening glucose > 240 mg/dL
10. Fasting Screening triglyceride > 300 mg/dL;
11. Fasting Screening low-density lipoprotein (LDL) > 200 mg/dL;
12. Glucose-6-phosphate dehydrogenase (G6PD) deficiency;
13. Uncontrolled hypertension defined as blood pressure >170/100 mmHg at both Screening and 1 week prior to dosing
14. Individual laboratory values which are exclusionary
    - White blood cell count (WBC) < 3.0 x10^9/L
    - Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3x upper limit of normal (ULN)
    - Estimated glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2
    - Hemoglobin (Hgb) < 9 g/dL
    - Serum phosphate < 2.0 mg/dL
15. Patients whose arrhythmia is unstable on current treatment;
16. History of coronary artery disease, including myocardial infarction or unstable angina, within the last 6 months;
17. Congestive heart failure, New York Heart Association Class III or IV;
18. Unless clinically stable and/or appropriately treated, electrocardiogram (ECG) with evidence of prior myocardial infarction, clinically significant arrhythmia, or other abnormalities that, in the opinion of the investigator, are consistent with significant underlying cardiac disease;
19. History of significant hematological disorders or autoimmune disorders, and/or subject is immunosuppressed or immunocompromised;
20. Subject is currently taking dabigatran (Pradaxa®), rivaroxaban (Xarelto®), edoxaban (Savaysa®), warfarin (Coumadin®), or apixaban (Eliquis®);
21. Subject has received an inactivated vaccine in the previous 3 months with respect to the randomization date or has received a live virus vaccine in the previous 6 months with respect to the randomization date. Recombinant vaccines are excluded from this exclusion criterium.
22. Subject is planning to receive any live or attenuated virus vaccination during the study.
23. History of malignancy within the last 5 years other than basal skin cancer;
24. Any condition, that in the opinion of the investigator, would be negatively affected by rapamycin.
25. Subjects with a documented history of moderate or severe alcohol or substance use disorder within the 12 months prior to randomization.
26. Subjects who, in the opinion of the investigator, present with a condition that would compromise their safety or that would make study completion unlikely.

Investigational Product and Comparator Product, 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 for reconstitution with sterile water for injection.
  - SEL-037: pegadricase, a recombinant pegylated candida urate oxidase.

Dosage of Investigational Drug

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

Mode of Administration (SEL-212)

- Premedication for SEL-212 (prior to study drug administration)
  - 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 the 0.6 mg every day regimen. 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.
  - Prednisone 40 mg oral (PO) approximately 24 (± 12) hours
  - Fexofenadine 180 mg oral (PO) approximately 12 (± 2) hours
  - Fexofenadine 180 mg oral (PO) approximately 2 (± 1) hours
  - Methylprednisolone 40 mg (or equivalent) IV approximately 1 (± 0.5) hours
- SEL-110.36
  - IV infusion with a syringe infusion pump at a steady rate of 3.0 mL/hr for the first 30 minutes, then a rate sufficient to deliver the remaining dose volume over a period of 60 minutes concurrently with normal saline
- SEL-037
  - Administration initiated within 15 minutes after completion of the SEL-110.36 infusion.
  - Administered via infusion pump over a time period of no less than 120 minutes. If an infusion reaction occurs during the administration of SEL-037, the infusion may be slowed, or stopped and restarted at a slower rate at the discretion of the physician.

KRYSTEXXA

- Premedication for KRYSTEXXA (prior to study drug administration)
  - 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 the 0.6 mg every day regimen. 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.
- Prednisone 40 mg oral (PO) approximately 24 (± 12) hours
- Fexofenadine 180 mg oral (PO) approximately 12 (± 2) hours
- Fexofenadine 180 mg oral (PO) approximately 2 (± 1) hours
- Methylprednisolone 40 mg (or equivalent) IV approximately 1 (± 0.5) hours

- KRYSTEXXA (pegloticase injection) will consist of commercially available study drug administered at a dosage of 8 mg (uricase protein) given as an IV infusion every 2 weeks, consistent with the manufacturer's currently approved labeling (*KRYSTEXXA Prescribing Information 2018*).

Duration of Treatment:

All patients are planned to receive study drug during 6 months of treatment. The SEL-212 treatment arm will receive a total of up to 6 infusions, scheduled every 28 days. The KRYSTEXXA treatment arm will receive a total of up to 12 infusions, scheduled every 14 days, according to the manufacturer's currently approved label (*KRYSTEXXA Prescribing Information 2018*).

The total duration of participation in the study will range from approximately 26 to 31 weeks (184 to 219 days) for patients randomized to SEL-212 and approximately 28 to 33 weeks (198 to 233 days) for patients randomized to KRYSTEXXA as follows:

- Screening and/or washout and premedication period: up to 45 days (up to 6.5 weeks)
- Treatment: 168 days (24 weeks) for SEL-212 and KRYSTEXXA
- Safety Follow-Up: 30 (+ 4) days after the date of last infusion
  - SEL-212: Last scheduled infusion on Study Day 140
  - KRYSTEXXA: Last schedule infusion on Study Day 154

Criteria for Evaluation:

Efficacy:

Primary Endpoint:

- Comparison in the percentage of patients on SEL-212 vs. KRYSTEXXA who achieve and maintain reduction of SUA < 6 mg/dL for at least 80% of the time during Treatment Period 3 and Treatment Period 6

Secondary Endpoints:

- Comparison in the percentage of patients on SEL-212 vs. KRYSTEXXA who achieve and maintain reduction of SUA < 6 mg/dL for at least 80% of the time during Treatment Period 6

- Comparison in the percentage of patients on SEL-212 vs. KRYSTEXXA who achieve and maintain reduction of SUA < 6 mg/dL for 100% of the time during Treatment Period 6
- Comparison in the percentage of patients on SEL-212 vs. KRYSTEXXA who achieve and maintain reduction of SUA < 6 mg/dL for at least 80% of the time during Treatment Period 3
- Comparison in the percentage of patients on SEL-212 vs. KRYSTEXXA who achieve and maintain reduction of SUA < 6 mg/dL for 100% of the time during Treatment Period 3
- Comparison between patients on SEL-212 vs. KRYSTEXXA in pre-dose SUA values > 6 mg/dL during Treatment Periods 2-6. The pre-dose SUA is collected on the dosing day prior to the dosing administration or it is collected at the visit where dosing would have occurred had the patient not been previously withdrawn from study drug.
- Comparison between patients on SEL-212 vs. KRYSTEXXA of the change in health questionnaires
- Comparison between patients on SEL-212 vs. KRYSTEXXA of gout flare incidence per 3-month period (Treatment Periods 1-3 and Treatment Periods 4-6)
- Comparison between patients on SEL-212 vs. KRYSTEXXA of gout flare frequency per 3-month period (Treatment Periods 1-3 and Treatment Periods 4-6)
- Comparison between patients on SEL-212 vs. KRYSTEXXA of the change from Baseline to Treatment Period 6 in number of tender joints
- Comparison between patients on SEL-212 vs. KRYSTEXXA of the change from Baseline to Treatment Period 6 in number of swollen joints

Safety:

Safety Endpoints:

- Safety and tolerability of SEL-212 compared to KRYSTEXXA as assessed by AEs, 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; 12-lead ECGs; and physical examination findings.

Statistical Methods

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

Analysis Populations

- Screened / Randomized Set: The Screened Set will include all patients who signed an informed consent. The Randomized Set will include all patients randomized.
- Safety Set (SS): The Safety Set will include all patients who were administered any amount of study medication. Patients will be analyzed according to treatment received. The SS will be used for all analyses of safety endpoints and for the presentation of patients in all patient listings.
- Intent-to-Treat (ITT) Set: The Intent-to-Treat (ITT) Set will be used as the primary population for the analysis of efficacy. The ITT Set will include all randomized patients. Patients will be analyzed according to randomized treatment.
- Modified ITT (mITT) Set: The modified ITT (mITT) Set will include all randomized patients who were administered at least one complete dose of study medication and have at least one post-baseline assessment of SUA. Patients will be analyzed according to randomized treatment. The mITT will also be used for analyses of efficacy endpoints.
- Per Protocol (PP) Set: The Per Protocol Set (PPS) will include all patients who 1) were administered any amount of study medication, and 2) have completed at least 65% of the study dosing visits with or without receiving study drug (eg at least 4 of 6 TP Day 0 visits for patients receiving SEL-212 or at least 8 of 12 TP Day 0 or Day14 visits for patients receiving Krystexxa) unless early termination from the study occurred after study drug withdrawal due to meeting stopping rules or due to an adverse event, or due to PI discretion (for example where at least one pre-dose SUA was >6 mg/dL in the Krystexxa arm and patient was discontinued from study treatment), and 3) who have no major Protocol deviations affecting the primary efficacy assessments. Patients will be analyzed according to randomized treatment.

Efficacy Analyses

Primary Efficacy Analysis

The primary estimand will take into consideration the treatment policy strategy, ie, Treatment Period 6 (and also Treatment Period 3) assessments will be considered for all subjects in ITT independently whether the subject has completed the study treatment or has terminated early the study treatment. Additionally, the estimand based on the while-on-treatment strategy for dealing with study treatment terminators will be defined. For all used estimands of the primary efficacy, the estimator for the comparison between the treatment groups is defined as the difference in the proportion of responders between subjects receiving SEL-212 versus those receiving KRYSTEXXA during Treatment Periods 3 and 6. The statistical testing will be performed confirmatory using the Cochran-Mantel-Haenszel (CMH) test – considering the randomization stratum of tophus presence (yes/no) – with a one-sided type 1 error rate $\alpha = 5\%$. In addition, 90% two-sided confidence intervals for the overall treatment difference between SEL-212 and KRYSTEXXA treatment groups without stratification will be computed. The analysis of the estimands will be carried out based on the ITT primarily. Supportive analyses will be performed on the mITT and the PP. For each defined estimand sensitivity analyses will be performed using different imputation approaches for missing values. Details of the applied approaches will be presented in the Statistical Analysis Plan.

The SUA time curve will be used to estimate the proportion of time that the SUA level is below 6 mg/dL. Based on the serum samples collected during Treatment Periods 3 and 6, an estimate of the time with SUA < 6 mg/dL can be determined by connecting each two neighboring data points with a straight line. If the SUA time curve goes above 6 mg/dL the linear interpolation method will be used to estimate the point in time at which the SUA time curve intercepts the line between the last SUA value < 6 mg/dL and the first value ≥ 6 mg/dL.

The proportion of time that the SUA level is < 6 mg/dL will be computed by taking the ratio between the time during which the SUA level remains < 6 mg/dL (if necessary, using the linear interpolation method) and the entire time interval within Treatment Periods 3 and 6.

Let T1 be the total time interval in hours for Treatment Period 3 of which W1 hours is the time interval during which SUA level is < 6 mg/dL. Similarly, for Treatment Period 6, assume T2 is the total time interval in hours of which W2 hours is the time interval during which SUA level is < 6 mg/dL. For a subject to be considered a responder, the proportion of time that the SUA level is < 6 mg/dL during Treatment Periods 3 and 6 must be at least 80%. The proportion of time that the SUA level is < 6 mg/dL, i.e., percentage of non-hyperuricemic time, is calculated using the following formula:

$$Proportion = \frac{W1 + W2}{T1 + T2} \times 100$$

A logistic regression model controlling for the distribution of baseline characteristics will be performed as supportive analysis.

Summary tables of the percentage of responder (subjects who achieve and maintain reduction of SUA < 6 mg/dL for at least 80% of the time) in each treatment period will be provided by treatment group. Additionally, a summary table with the total time a subject has SUA values < 6 mg/dL will be provided for each treatment period by treatment group.

Summary tables of the actual values and change from baseline for SUA results will be provided for each scheduled sampling time point by treatment group. Additionally, mean SUA level, reduction in mean SUA and percent reduction in mean SUA from baseline during Treatment Period 3 or Treatment Period 6 will be presented by treatment group.

Secondary Efficacy Analyses

All statistical tests in secondary endpoints for the comparison between SEL-212 and KRYSTEXXA will be performed using one-sided tests at a type 1 error rate level of α=5%. In addition, 90% confidence intervals for treatment differences between SEL-212 and KRYSTEXXA treatment groups will be computed. The efficacy analyses will be carried out based on the ITT and PP Sets. mITT analyses will be performed if appropriate.

For assessment of SUA in the secondary efficacy analyses, summary tables of the number and percentage of subjects for each endpoint will be presented by treatment group, and the comparison between the treatment groups will be performed similar to the primary efficacy endpoint using a CMH-test considering the randomization stratum.

For the health questionnaires, comparison with regards to change from baseline in health questionnaires will be performed using an ANCOVA with the respective change from baseline value as dependent variable, treatment group and the randomization stratum as

independent fixed factors and the baseline value as independent covariate. For each health questionnaire, summary tables of total scores or domain scores and subscale scores will be provided for each scheduled assessment time by treatment group. Additionally, summaries of the changes from baseline will be provided.

The number and percentage of subjects reporting gout flares per 3-months period, i.e. Treatment Periods 1 to 3 and Treatment Periods 4 to 6, will be summarized by treatment group and will be tested using a CMH-test considering the randomization stratum. The frequency of gout flares will be summarized per 3-months period, i.e. for Treatment Periods 1 to 3 and Treatment Periods 4 to 6 for each treatment and will be compared using ANOVA considering the randomization stratum and treatment as fixed factors.

Comparison with regards to change of tender joints and swollen joints from baseline will be performed using an ANCOVA with the change from baseline value as dependent variable, treatment group and randomization stratum as independent fixed factors and the baseline number of tender joints and swollen joints as independent covariates, respectively. In case of non-normality, the non-parametric Wilcoxon test will be used for the comparison between the treatment groups. Summary tables of the number of tender joints and swollen joints for each assessment timepoint and for the change from baseline will be provided by treatment group, respectively.

A subgroup analysis will be conducted for patients who receive “additional gout flare treatment” in each arm for these objectives. Details of this subgroup analysis will be provided in the SAP.

Safety Analyses

All AEs will be coded and grouped into Preferred Terms (PT) by System Organ Class (SOC), using the most recent MedDRA Version. All AEs will be summarized by SOC and PT. An overall summary will be provided of the number and percentage of patients in each treatment group (SEL-212 and KRYSTEXXA) reporting TEAEs, serious TEAEs, treatment-related TEAEs, AESIs, TEAEs leading to withdrawal and TEAEs leading to death. The number and percentage of patients with TEAEs /serious TEAEs / AESIs / TEAEs leading to withdrawal / treatment-related TEAEs will be summarized by SOC and PT for each treatment group (SEL-212 and KRYSTEXXA). TEAEs will also be summarized by maximum intensity and causality.

Laboratory data will be summarized by the type of laboratory test and will be presented for each scheduled visit stratified by treatment group (SEL-212 and KRYSTEXXA). Normal reference ranges and markedly abnormal results will be used in the summary of laboratory data. Data will be flagged according to the reference limits (High or Low), if applicable. Changes from baseline will be presented for each post-baseline visit. Shift tables of the number of patients with low/normal/high values at each scheduled post-baseline visit compared to the low/normal/high categorization at baseline will be provided by treatment group (SEL-212 and KRYSTEXXA).

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

For each 12-lead ECG variable the actual value and the change from baseline will be summarized for the scheduled visits by treatment group (SEL-212 and KRYSTEXXA).

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

Sample Size Determination

The primary efficacy criterion in this study is defined as the percentage of subjects who achieve and maintain reduction of SUA < 6 mg/dL for at least 80% of the time during Treatment Period 3 and Treatment Period 6. The percentage of responders according to the above criterion is assumed to be 65% in the SEL-212 arm and 44% in the KRYSTEXXA arm. Using the Chi-square test for comparison between the SEL-212 arm and the KRYSTEXXA arm, and considering a one-sided α=5% and the statistical power of 80%, results in 69 subjects per treatment group. Taking into account that some subjects may be excluded from the mITT analyses, 75 subjects per treatment group will be randomized. For the sample size estimation, Chi-square test, instead of the Cochran-Mantel-Haenszel test, is used 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 subject population.

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

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Definition or Explanation
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
cm	centimeter
CR	Complete Response
CRF	case report form
CRO	contract research organization
CT	computed tomography
CYP3A4	Cytochrome P450, family 3, subfamily A
d	day
dL	deciliter
DSMC	Data and Safety Monitoring Committee
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EEA	European Economic Area
EOS	End-of-Study
ET	Early Termination
FAAN	Food Allergy & Anaphylaxis Network
FAS	Full Analysis Set
FSH	Follicle Stimulating Hormone
G6PD	glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
GFR	glomerular filtration rate
h	hour
HAQ-DI	Health Assessment Questionnaire-Disability Index
HbA1c	hemoglobin A1c
HBsAg	hepatitis-B surface antigen
hCG	human chorionic gonadotropin
Hct	hematocrit
HCVAb	hepatitis-C antibody
HDL	high density lipoprotein
Hgb	hemoglobin

Abbreviation or Specialist Term	Definition or Explanation
HIV	human immunodeficiency virus
I	Improved
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	International Ethics Committee
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
ITT	Intent to Treat
IUD	intrauterine device
IUS	intrauterine hormone releasing system
IV	intravenous
kg	kilogram
LDL	low-density lipoprotein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
mg	milligram
mmHg	millimeters of mercury
MPV	mean platelet volume
MR	Marked Response
ms	millisecond
mTOR	mammalian target of rapamycin
NIAID	National Institute of Allergy and Infectious Diseases
NSAID	non-steroidal anti-inflammatory drug
PD	pharmacodynamics
PD	Progressive Disease
PEG	polyethylene glycol
PLA	poly [D,L-lactide]
Plt	platelet
PPS	Per Protocol Set
PR	Partial Response
PrGA	Provider Global Assessment of Disease Activity
PT	Preferred Term
PT	prothrombin time
QD	once daily
RA	rheumatoid arthritis
RBC	red blood cell
RCTC	Rheumatology Common Toxicity Criteria

Abbreviation or Specialist Term	Definition or Explanation
RDW	red cell distribution width
SAE	serious adverse event
SAP	statistical analysis plan
Scr	Screening Period
SD	Stable Disease
SEL-212H	high dose of SEL-212
SEL-212L	low dose of SEL-212
SF-36	Short Form Health Survey
SOC	System Organ Class
SS	Safety Set
SUA	serum uric acid
SVP	Synthetic Vaccine Particle
TEAE	treatment-emergent adverse event
TID	three times daily
UE	Unable to Evaluate
ULN	upper limit of normal
ULT	urate lowering therapy
US	ultrasound
US FDA	United States Food and Drug Administration
USP	United States Pharmacopeia
WBC	white blood cell

5. INTRODUCTION

5.1 Gout and Refractory Gout

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

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

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

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

Refractory gout is a serious condition affecting approximately 50,000 patients in the United States and is characterized by uric acid levels that are not adequately controlled by approved therapies.

5.2 Symptoms of Gout

Symptoms and their development have a broad spectrum of severity. Most symptoms present as intermittent attacks or flares while others present as more severe, chronic disease affecting one or more joints with tophi, sometimes referred to as chronic tophaceous gouty arthropathy (*Khanna 2012a*). In chronic gout, tophi commonly develop in the fingers, hands, and feet around the olecranon, and under the skin on the ears, but may also develop in other tissues and organs such as the kidneys and heart valves (*Ryan 2016*). Pro-inflammatory cytokines and white cell debris are usually present in tophi, which suggest a state of chronic monosodium urate-crystal-stimulated inflammation (*Dalbeth 2011*). These tophi can erupt through the skin, become inflamed and painful, and discharge urate crystals and eventually may cause deformities and secondary osteoarthritis (*Ryan 2016*). They can infiltrate into the bone, causing bone erosion and joint damage (*Dalbeth 2011*). Additional complications include obstruction of the joint and infection as well as urolithiasis with uric acid stones or calcium oxalate stones (*Ryan 2016*). The presence of tophi is associated with more frequent flares, which may be so painful and

debilitating that they lead to joint replacement or surgical excision. Over time, flares become polyarticular, additive, and increase in severity (*Brook 2010*).

5.3 Gout and Hyperuricemia: Exacerbation of Existing Comorbidities

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

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

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

5.4 Impact on Quality of Life

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

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

experienced worse physical functioning. Notably, their scores did not improve over the 52-week period despite undergoing maximal medical management (*Strand 2012*).

There is also evidence that gout affects workplace productivity, as studies in patients with chronic, refractory gout self-report work absences due to flares, losing 25.1 workdays on average per year. Another study specifically found employees with gout missed 4.56 more days of work per year than those without gout (*Edwards 2011*).

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

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

5.5 Approved Therapies for Chronic Gout Refractory to Conventional Therapy

An estimated 160,000 gout patients fail to normalize their levels of SUA, have symptoms that are uncontrolled with the currently available treatments aimed at lowering urate levels, or suffer from comorbidities that preclude their use of conventional therapies (*Richette 2013*, *Strand 2012*). Lack of treatment options leads to unabated disease progression.

Currently, conventional therapies for the treatment of gout involve the inhibition of uric acid production and the improvement of uric acid renal clearance. The administration of exogenous uricase, an enzyme not present in humans that converts uric acid into the water-soluble compound, allantoin, is used only in instances of gout that is refractory to first and second lines of therapy (*Dalbeth 2011*).

There are 2 uricase products currently used to treat hyperuricemia: rasburicase (ELITEK®) and pegloticase (Krystexxa®).

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

Pegloticase is a pegylated recombinant porcine- or baboon-derived uricase. It is currently the only FDA-approved product for the treatment of chronic gout refractory to conventional therapy (*KRYSTEXXA Prescribing Information 2018*). While its use is associated with improvements in musculoskeletal function, quality of life, and pain, only approximately 42% of patients maintain a target serum urate level less than 6 mg/dL after 6 months of the approved dose regimen of 8 mg once every 2 weeks. The vast majority of patients (92%) develop anti-pegloticase antibodies. High titer antibodies appear to adversely affect the pharmacokinetics and pharmacodynamics of the enzyme and are associated with a decrease in therapeutic response and increased risk of infusion reactions. Approximately 26% of patients taking Krystexxa report infusion reactions, 6.5% experience anaphylaxis, and the incidence of infusion reactions correlate with high anti-pegloticase antibody titer. These adverse events are typically preceded by a loss of urate-lowering effects.

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

The high rate of treatment failure and the potential for anaphylactic reactions have resulted in limited use of Krystexxa since its approval.

5.6 Unmet Medical Need

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

Selecta Biosciences has developed SEL-212, the first drug product designed to reduce or prevent an immunologic response and improve efficacy, safety, and tolerability of a uricase enzyme (pegadricase) in patients who require long-term treatment to manage symptoms and progression of chronic refractory gout. Selecta uses its proprietary, antigen-specific Synthetic Vaccine Particle (SVP) platform to encapsulate the approved immunomodulatory drug, rapamycin, to mitigate formation of anti-drug antibodies by inducing antigen-specific regulatory T cells. Selecta is leveraging its nanoparticle technology encapsulating rapamycin (SVP-rapamycin) with the goal of inducing durable antigen-specific immune tolerance to pegadricase, a pegylated uricase. Specifically, SEL-212, in its current formulation, is a combination intravenous drug product that consists of a pegylated recombinant uricase (pegadricase; SEL-037) and a

biodegradable nanoparticle containing rapamycin (SEL-110.36), a small molecule inhibitor of the mammalian target of rapamycin (mTOR) pathway. Pegadricase is derived from *Candida utilis* and metabolizes poorly soluble uric acid to the more soluble metabolite, allantoin. Administration of SEL-110.36 just prior to pegadricase is intended to induce immune tolerance to prevent the formation of anti-uricase antibodies that may compromise efficacy or safety of pegadricase.

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

6. STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objective

The primary objective of this study is to assess the reduction in SUA in patients treated with SEL-212 compared to KRYSTEXXA.

6.1.2 Secondary Objectives

The secondary objectives of this study are to assess improvement of the following parameters in patients treated with SEL-212 compared to KRYSTEXXA:

- Gout flares
- SUA control
- Joint tenderness and swelling
- Quality of Life (QoL)

6.2 Study Endpoints

6.2.1 Primary Endpoint

The primary endpoint of this study is the comparison in the percentage of patients on SEL-212 vs. KRYSTEXXA who achieve and maintain reduction of SUA < 6 mg/dL for at least 80% of the time during Treatment Period 3 and Treatment Period 6

6.2.2 Secondary Endpoints

The secondary endpoints of this study are:

- Comparison in the percentage of patients on SEL-212 vs. KRYSTEXXA who achieve and maintain reduction of SUA < 6 mg/dL for at least 80% of the time during Treatment Period 6
- Comparison in the percentage of patients on SEL-212 vs. KRYSTEXXA who achieve and maintain reduction of SUA < 6 mg/dL for 100% of the time during Treatment Period 6
- Comparison between patients on SEL-212 vs. KRYSTEXXA in pre-dose SUA values > 6 mg/dL during Treatment Periods 2-6
- Comparison between patients on SEL-212 vs. KRYSTEXXA of the change in health questionnaires
- Comparison between patients on SEL-212 vs. KRYSTEXXA of gout flare incidence per 3-month period (Treatment Periods 1-3 and Treatment Periods 4-6)
- Comparison between patients on SEL-212 vs. KRYSTEXXA of gout flare frequency per 3-month period (Treatment Periods 1-3 and Treatment Periods 4-6)
- Comparison between patients on SEL-212 vs. KRYSTEXXA of the change from Baseline to Treatment Period 6 in number of tender joints
- Comparison between patients on SEL-212 vs. KRYSTEXXA of the change from Baseline to Treatment Period 6 in number of swollen joints

6.2.3 Safety Endpoints

The safety endpoints of this study are:

- Safety and tolerability of SEL-212 compared to KRYSTEXXA as assessed by AEs, 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; 12-lead ECGs; and physical examination findings.

7. INVESTIGATIONAL PLAN

7.1 Overall Study Design

This study is a randomized, open-label, parallel-arm study to compare the safety and efficacy profiles of SEL-212 and KRYSTEXXA. Approximately 150 patients will be randomized 1:1 prior to Baseline to receive treatment with SEL-212 or KRYSTEXXA for 6 months. Efficacy assessments, as measured by SUA levels, will be conducted at intervals that are appropriate to determine treatment effect differences, including at month 3 and month 6. Assessments of qualitative endpoints will be conducted on an assessor-blinded basis. Safety will be monitored throughout the study.

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

The total duration of participation in the study will range from approximately 26 to 31 weeks (184 to 219 days) for patients randomized to SEL-212 and approximately 28 to 33 weeks (198 to 233 days) for patients randomized to KRYSTEXXA as follows:

- Screening and/or washout and premedication period: up to 45 days (up to 6.5 weeks)
- Treatment: 168 days (24 weeks) for SEL-212 KRYSTEXXA
- Safety Follow-Up: 30 (+ 4) days after the date of last infusion
  - SEL-212: Last scheduled infusion on Study Day 140
  - KRYSTEXXA: Last schedule infusion on Study Day 154

7.1.1 Screening Period

After providing written informed consent, the patient is considered enrolled in the study. Patients will be evaluated for inclusion during the Screening Period. For all patients, the standard Screening Period will be up to 45 days prior to Baseline. Concurrently with the Screening Period, a premedication period with colchicine of at least 7 days prior to Baseline for potential gout flare will be required for all subjects, and a washout period of at least 7 days will be required prior to Baseline for patients on any urate-lowering therapy (ULT).

7.1.2 Treatment Period

The total duration of treatment will be 6 months. Eligible patients will be randomized 1:1 prior to Baseline to receive SEL-212 or KRYSTEXXA.

Study patients in the SEL-212 arm will receive study drug every 28 days coinciding with Day 0 of each Treatment Period for a total of up to 6 infusions of SEL-212.

Study patients in the KRYSTEXXA arm will receive study drug according to the manufacturer's prescribing information, i.e., every 14 days coinciding with Day 0 and Day 14 of each Treatment Period for a total of up to 12 infusions of KRYSTEXXA.

Prior to infusion, all patients will receive a standardized regimen of 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 at least 1 hour for safety assessments.

Refer to Section 10 for details about study drug administration.

With each dose, a blood sample will be drawn for assessment of SUA level immediately prior to infusion (ie, Time 0h) with SEL-212 or KRYSTEXXA, 1 hour after the infusion of the second component of SEL-212 or of KRYSTEXXA is completed. SUA levels will be assessed through additional post-infusion blood samples at pre-determined time points. Every effort will be made to obtain blood samples at the same time of day of each study visit.

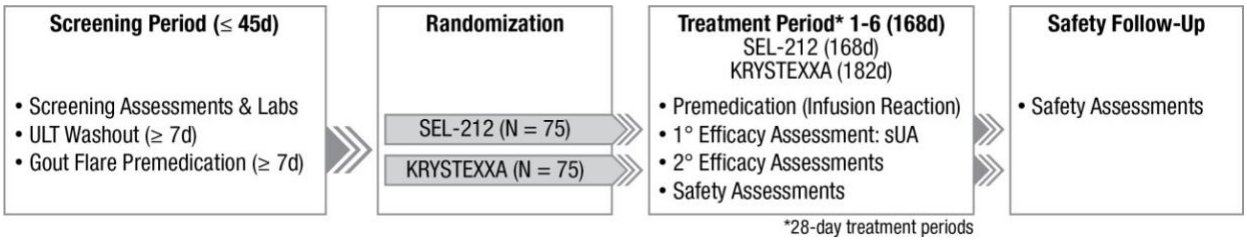
Gout flares will be assessed at every visit. QoL and joint swelling and tenderness will be assessed on Day 0 of Treatment Period 1 and 4, and at the end of Treatment Period 6. Assessments of qualitative endpoints (health questionnaires and joint assessment) will be conducted on an assessor-blinded basis.

On dosing days, safety laboratory samples will be collected pre-infusion and per Schedule of Events in both the SEL-212 arm and the KRYSTEXXA arm. Concomitant medications and procedures and adverse events (AEs) will be monitored continuously during the study.

7.1.3 Follow-Up Period

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. Patients who terminate the study prematurely will have all Early Termination assessments performed. Patients who terminate the study prematurely who are unable to be on-site for the Early Termination visit will be contacted by telephone for safety follow-up.

Figure 1: Study Schematic



7.2 Number of Patients

The study will randomize approximately 150 patients with chronic refractory gout.

7.3 Treatment Assignment

Patients will be randomized 1:1 to receive open-label treatment with SEL-212 or KRYSTEXXA.

7.4 Dose Adjustment Criteria

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

7.4.1 Safety Criteria for Adjustment or Stopping Doses

7.4.1.1 SEL-212

A patient randomized to treatment with SEL-212 will be withdrawn from study drug for meeting the following stopping rule:

- In the SEL-212 arm: 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

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 may 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 withdrawn from study drug, the patient will continue study visits to the end of Treatment Period 6. At the discretion of the Investigator, the patient will be permitted to return to urate lowering therapy 60 days after the patient's last study drug treatment. Urate lowering therapy shall not be SEL-212 or KRYSTEXXA.

7.4.1.2 KRYSTEXXA

A patient randomized to treatment with KRYSTEXXA and who has started receiving treatment with study drug will be withdrawn from study drug for meeting the following stopping rule:

- In the KRYSTEXXA arm: SUA level > 6.0 mg/dL measured on 2 consecutive pre-dose measurements, based on the following assessments:
  - If a pre-dose SUA level is > 6.0 mg/dL, then the Investigator will have the option to schedule a second SUA measurement to occur 2 days before the next scheduled KRYSTEXXA dosing day. The pre-dose SUA collected on Day 0 of Treatment Period 1 shall not be used in determining whether to invoke the stopping rule.
  - If the second measured SUA level is > 6.0 mg/dL, then the Investigator will withdraw the patient from study drug per the stopping rule.

- If the second measured SUA level is ≤ 6.0 mg/dL, the patient can proceed to dosing with KRYSTEXXA. However, SUA will be assessed on the day of dosing, per protocol, to be used determining consecutive pre-dose measurements for future stopping rules.

If withdrawn from study drug, the patient will continue study visits to the end of Treatment Period 6. At the discretion of the Investigator, the patient will be permitted to return to urate lowering therapy 60 days after the patient's last study drug treatment. Urate lowering therapy shall not be SEL-212 or KRYSTEXXA.

7.4.2 Criteria for Adjustment or Stopping Doses

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

7.5 Criteria for Study Termination

The study can be terminated at any time at the Sponsor's sole discretion. Otherwise, the study will be terminated when all patients have completed follow-up assessments (Section 20) or the Sponsor or regulatory agency(ies) have determined there is an unacceptable risk to patients or additional dosing or procedures are not warranted or necessary.

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

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

7.6 Study Rationale

7.6.1 Rationale for the Study Design

Study SEL-212/202 is a randomized, open-label, parallel-arm study to compare the safety and efficacy profiles of SEL-212 to KRYSTEXXA.

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

The study will be conducted on an open-label treatment basis; therefore, all patients, Investigators, study personnel, and Sponsor personnel involved in the conduct of the study will

have access to the randomized treatment assignments. Only the assessments of qualitative endpoints (health questionnaires and joint assessment) will be conducted on an assessor-blinded basis. The open-label design was selected because of the substantial differences in administration of SEL-212 and KRYSTEXXA (Section 10) and the practicality of maintaining the treatment blind. The parallel arms involving active treatment will permit adequate statistical comparison of the groups for efficacy and safety signal detection.

KRYSTEXXA was selected as the active comparator because it is approved for this patient population and because the exogenous protein carries similar risks to the SEL-037 component of SEL-212.

7.6.2 Rationale for the Study Population

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

7.6.3 Rationale for the Selected Dose

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

Doses of KRYSTEXXA selected for this study are based on the manufacturer's approved labeling (*KRYSTEXXA Prescribing Information 2018*).

7.6.3.1 Phase 1b Study with SEL-212

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

In the Phase 1b study, patients (N = 64) with a serum uric acid level ≥ 6 mg/dL, with or without a history of gout, were administered SVP-rapamycin alone, pegadricase alone, or SEL-212 as an intravenous infusion. Mitigation of ADAs and a dose-dependent reduction in SUA levels occurred from study Day 1 to Day 30 in patients administered SEL-212 (data on file). There was no effect of SVP-rapamycin alone on SUA levels, and patients administered pegadricase alone developed ADAs that resulted in loss of SUA control by Day 14. SEL-212 was generally well tolerated at all dose levels. The maximum tolerated dose of SVP-rapamycin was determined to be 0.3 mg/kg. Data from this study were used to select additional dose levels of each component of SEL-212 for evaluation in the currently ongoing Phase 2 study SEL-212/201.

7.6.3.2 Phase 2 Study with SEL-212

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

Overall, in the currently ongoing Phase 2 study with SEL-212, SUA levels have remained consistently below 6 mg/dL in 70% to 89% of evaluable Part A patients administered SEL-212 once monthly for 3 months. Similarly, in Part C where SEL-212 was administered once monthly for 5 months, SUA levels have remained below 6 mg/dL in 61% to 75% of evaluable patients through the end of the fifth treatment period. All evaluable Part C patients who had SUA levels below 6 mg/dL at week 12 also had SUA below 6 mg/dL at Week 24. The control of SUA has occurred in the context of low incidences of infusion reactions, anaphylaxis, and gout flares as well as treatment-emergent adverse events (TEAEs) known to be potentially associated with sirolimus (Rapamune®). Data support a once monthly dosing regimen.

7.6.4 Rationale for the Primary Efficacy Endpoint

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

Based on a proposed indication of treatment of chronic gout refractory to conventional therapy, the objectives of this study design are to assess the reduction in SUA in cohorts of adult subjects treated with SEL-212 compared to KRYSTEXXA. The proposed primary endpoint is

comparison in the percentage of patients on SEL-212 vs. KRYSTEXXA who achieve and maintain reduction of SUA < 6 mg/dL for at least 80% of the time during Treatment Period 3 and Treatment Period 6.

7.6.5 Rationale for Secondary Efficacy Endpoints

Secondary endpoints were selected based on symptoms of chronic gout as well as quality of life as a consequence of chronic gout. Patients with severe, chronic gout are often refractory to oral therapies and often present with swollen or tender joints. Exacerbation of gout (flare) and joint tenderness and swelling impact a patients' ability to maintain physical activity and functioning and correspond to quality of life. Several instruments will be used to assess quality of life and will include patient-reported outcomes, provider-reported assessments, and generalized assessments of overall quality of life.

7.7 Benefits and Risks

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

- Substantially increased percentage of patients that maintain control of SUA while on therapy
- Substantially reduced gout flare rate during therapy
- Substantially reduced risk of infusion reactions
- More convenient to and greater compliance by patients because of once monthly therapy
- Acceptable safety at the doses to be studied in this Phase 2 study

SEL-212 has the potential to be an unprecedented safe and effective treatment option for patients for which other treatment options are inadequate. The overall balance between benefits and risks appears acceptable for the SEL-202/202 study of SEL-212 in the intended population of patients with chronic gout refractory to conventional therapy.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1 Patient Inclusion Criteria

A patient must meet all of 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 a history of symptomatic gout defined as:
   a. ≥ 3 gout flares within 18 months of Screening or
   b. Presence of ≥ 1 tophus or
   c. Current diagnosis of gouty arthritis
4. At the Screening Visit: male age 21 – 80 years, inclusive, or female of non-childbearing potential age 21-80 years, inclusive, where non-childbearing potential is defined as:
   a. > 6 weeks after hysterectomy with or without surgical bilateral salpingo-oophorectomy or
   b. Post-menopausal (> 24 months of natural amenorrhea or in the absence of > 24 months of amenorrhea, 1 documented confirmatory FSH measurement)
5. Has at Screening SUA ≥ 7 mg/dL, with chronic refractory gout defined as having failed to normalize SUA and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the medically appropriate dose, or these drugs are contraindicated for the subject;
6. Is negative for anti-PEG antibodies at Screening;
7. Has not participated in a clinical trial within 30 days of the Screening Visit and agrees not to participate in a clinical trial for the duration of the study;
8. Negative serology for HIV-1/-2 and negative antigen to hepatitis B and negative antibodies to hepatitis C;
9. Has adequate venous access and able to receive IV therapy;
10. If applicable, has sufficiently recovered from any prior surgery to allow for successful completion of study procedures.

8.2 Patient Exclusion Criteria

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

1. Prior exposure to any experimental or marketed uricase (e.g., pegloticase [Krystexxa®], pegadricase [SEL-037], rasburicase [Elitek, Fasturtec]);
2. History of anaphylaxis or severe allergic reactions to medications;
3. History of any allergy to pegylated products, including, but not limited to, peginterferon alfa-2a (Pegasys®), peginterferon alfa-2b (PegIntron®), pegfilgrastim (Neulasta®), pegaptanib (Macugen®), pegaspargase (Oncaspar®), pegademase (Adagen®), peg-epoetin

beta (Mircera®), pegvisomant (Somavert®) certolizumab pegol (Cimzia®), naloxegol (Movantik®), peginesatide (Omontys®), and doxorubicin liposome (Doxil®);

4. Known moderate and severe CYP3A4 inhibitors or inducers must be discontinued 14 days before dosing and patients must remain off the medication for the duration of the study, including natural products such as St. John's Wort or grapefruit juice;
5. Drugs known to interact with Rapamune® such as cyclosporine, diltiazem, erythromycin, ketoconazole (and other antifungals), nicardipine (and other calcium channel blockers), rifampin, verapamil unless they are stopped 2 weeks prior to starting the trial and will not be used during the trial;
6. Initiation or change in dose of hormone-replacement therapy for menopausal women less than 1 month prior to the Screening Visit or during the Screening Phase would be exclusionary. If after being on a stable dose of hormone-replacement therapy for 1 month the patient may be considered for the study if she continues to meet all other inclusion and exclusion criteria;
7. A gout flare during Screening that was resolved for less than 1 week prior to first treatment with study drug (exclusive of synovitis/arthritis), unless the patient has a history of inter-flare intervals < 1 week;
8. Uncontrolled diabetes at Screening with HbA1c ≥ 8%;
9. Fasting Screening glucose > 240 mg/dL;
10. Fasting Screening triglyceride > 300 mg/dL;
11. Fasting Screening low-density lipoprotein (LDL) > 200 mg/dL;
12. Glucose-6-phosphate dehydrogenase (G6PD) deficiency;
13. Uncontrolled hypertension defined as blood pressure >170/100 mmHg at both Screening and 1 week prior to dosing;
14. Individual laboratory values which are exclusionary
    - White blood cell count (WBC) < 3.0 x10^9/L
    - Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3x upper limit of normal (ULN)
    - Estimated glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2
    - Hemoglobin (Hgb) < 9 g/dL
    - Serum phosphate < 2.0 mg/dL
15. Patients whose arrhythmia is unstable on current treatment;
16. History of coronary artery disease, including myocardial infarction or unstable angina, within the last 6 months;
17. Congestive heart failure, New York Heart Association Class III or IV;
18. Unless clinically stable and/or appropriately treated, electrocardiogram (ECG) with evidence of prior myocardial infarction, clinically significant arrhythmia, or other abnormalities that, in the opinion of the investigator, are consistent with significant underlying cardiac disease;

19. History of significant hematological disorders or autoimmune disorders, and/or subject is immunosuppressed or immunocompromised;
20. Subject is currently taking dabigatran (Pradaxa®), rivaroxaban (Xarelto®), edoxaban (Savaysa®), warfarin (Coumadin®), or apixaban (Eliquis®);
21. Subject has received an inactivated vaccine in the previous 3 months with respect to the randomization date or has received a live virus vaccine in the previous 6 months with respect to the randomization date. Recombinant vaccines are excluded from this exclusion criterium;
22. Subject is planning to receive any live or attenuated virus vaccination during the study.
23. History of malignancy within the last 5 years other than basal skin cancer;
24. Any condition, that in the opinion of the investigator, would be negatively affected by rapamycin;
25. Subjects with a documented history of moderate or severe alcohol or substance use disorder within the 12 months prior to randomization;
26. Subjects who, in the opinion of the investigator, present with a condition that would compromise their safety or that would make study completion unlikely.

8.2.1 Patient Completion and Withdrawal Criteria

8.2.1.1 Screen Failures

A patient is considered enrolled in the study at the time of ICF signature. Any patient that is screened but not dosed will be considered a screen failure and the reason for failure will be documented. Within the 45-day screening window, out-of-range laboratory tests may be repeated up to 2 times before declaring a screen failure. After the 45-day screening window, patients can be re-screened once.

8.2.1.2 Patient Completion

A patient will be considered to have completed the study when the patient has completed Safety Follow-up that occurs 30 (+ 4) days after the final dose of study drug. Enrolled patients who prematurely discontinue for any reason before completion of the study will be treated as outlined below in Section 8.2.1.3.1.

8.2.1.3 Enrolled Patient Withdrawal and Discontinuations

8.2.1.3.1 Withdrawal Procedures

Early termination from the study occurs when an enrolled patient withdraws consent or the Investigator terminates a patient. The reason for withdrawal will be evaluated and recorded in the case report form (CRF) and source documents. Patients that withdraw will not be replaced.

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

assessments completed (i.e., End of Study assessments) (Section 20), if the assessments pose no risk to the patient and the patient allows such assessments.

The Investigator should consult with the Sponsor/medical monitor prior to withdrawing any patient from the study. Since this is a multiple-dose study, once dosed, patients generally should not be terminated by the Investigator and should be followed through the end of Treatment Period 6, unless the patient withdraws consent or is lost to follow-up. In situations where continued participation in certain aspects of the study pose a risk to the patient, with consultation with the medical monitor, the Investigator should discontinue those procedures that pose a risk and should continue to collect data and conduct those assessments that do not put the patient at risk through the end of Treatment Period 6. Patients with compliance issues or major deviations that effect data quality will also continue to be followed through the end of Treatment Period 6 collecting as much data on the patient as possible, unless otherwise indicated by the Sponsor.

8.2.1.3.2 Patients Lost To Follow-Up

For patients to be considered as lost to follow-up, at least 3 contact attempts must be documented, of which the last must be a letter sent by a service that requires a delivery signature record (e.g., US Postal Service certified letter or Federal Express/UPS letter that requires signature of delivery). If the letter is undeliverable or no response is received within 7 days, the patient will be considered terminated due to lost to follow-up.

9. TREATMENT OF PATIENTS

9.1 Description of Study Drug

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

Table 1: Investigational Product

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

9.2 Concomitant Medications and Therapies

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

9.2.1 Uric Acid Lowering Therapy

Uric acid lowering therapy (ULT) including, but not limited to allopurinol, febuxostat (Uloric®), probenecid, lesinurad (Zurampic®, Duzallo®), and benzbromarone ULT, are not permitted for use during the study. Patients will undergo a ULT washout period prior to dosing with study drug according to the schedules described in Section 20.

Patients cannot have any prior exposure to or be presently be taking any experimental or marketed uricase therapy, as defined in Exclusion Criterion 1 (Section 8.2).

9.2.2 Anticoagulants Use

Anticoagulant use, as defined in Exclusion Criterion 20 (Section 8.2) is prohibited during the study.

9.2.3 Hormone Replacement Therapy

Hormone replacement therapy in menopausal women should remain stable throughout the study.

9.2.4 CYP3A4 Inducers and Inhibitors

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

9.2.5 Other Concomitant Medications

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

9.3 Treatment Compliance

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

9.4 Randomization and Blinding

This is a randomized, open-label treatment study. Patients will be randomized 1:1 to receive SEL-212 or KRYSTEXXA. Randomization preferably should occur 7 days prior to the first dose of study drug (ie, Day -7). The randomization will be stratified for tophus presence (yes/no). Assessments of qualitative endpoints will be conducted on an assessor-blinded basis.

Prior to study drug administration in Treatment Periods 2 through 6, the Investigator will determine a patient's eligibility for treatment with study drug by evaluating the patient's SUA level measured from the blood sample obtained from Day 21 of the most recently completed Treatment Period (SEL-212 cohort) or from the previous 2 measurements (KRYSTEXXA cohort).

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

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1 Study Drug

This is a randomized, open-label treatment study. The designated site representative will prepare study drug on the day of treatment. Prior to study drug administration in Treatment Periods 2 through 6, the Investigator will determine a patient's eligibility for treatment with study drug by evaluating the patient's SUA level measured from the blood sample obtained from Day 21 of the most recently completed Treatment Period (SEL-212 cohort) or from the previous 2 measurements (KRYSTEXXA cohort).

10.1.1 SEL-212

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

The dose level to be investigated in this study will be:

- SEL-212: consisting of 0.15 mg/kg SEL-110.36 and 0.2 mg/kg SEL-037

10.1.2 KRYSTEXXA

KRYSTEXXA (pegloticase injection) will consist of commercially available study drug.

The dose level to be investigated in this study will be:

- KRYSTEXXA: 8 mg (uricase protein) (*KRYSTEXXA Prescribing Information 2018*)

10.2 Study Drug Packaging and Labeling

SEL-212 will be supplied in vials in individual cartons with cartons and vials unassigned to a patient. KRYSTEXXA will be packaged according to the manufacturer's specifications.

10.3 Study Drug Storage

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

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

KRYSTEXXA will be handled and stored according to the manufacturer's currently approved labeling (*KRYSTEXXA Prescribing Information 2018*).

10.4 Study Drug Preparation

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

Treatment Periods, the patient's weight at the Day 21 visit from the preceding Treatment Period will be used for dose calculation. Detailed procedures and examples of dose calculations and study drug preparation are provided in the Study Operations Manual.

10.4.1 SEL-037 Preparation

Each vial of SEL-037 will be reconstituted with 6.9 mL of sterile water for injection, USP (United States Pharmacopeia or equivalent) which forms a 6 mg/mL concentrated solution and then the appropriate dose diluted for administration in 100 mL of room temperature 0.9% sodium chloride for injection, USP. The full resultant volume of the SEL-037-normal saline solution (100 mL saline + required volume of reconstituted SEL-037 + saline bag manufacturing overfill) will be administered in the allotted time. Reconstituted SEL-037 is stable at room temperature for 18 hours and the diluted SEL-037-normal saline solution for infusing should be used (i.e., infusion completed) within 6 hours of dilution. If not administered immediately, store refrigerated. The SEL-037 dose administration must be completed within 12 hours of the start of reconstitution.

10.4.2 SEL-110.36 Preparation

Each vial of SEL-110.36 will be reconstituted with 4.9 mL of sterile water for injection, USP (United States Pharmacopeia or equivalent) which forms a 2 mg/mL suspension before being drawn into appropriate size syringe/syringes for IV infusion with syringe pump. Reconstituted SEL-110.36 is stable for 24 hours at room temperature at normal light conditions. SEL-110.36 should be administered on the same day and as soon as possible after reconstitution. If not administered immediately, store refrigerated. The SEL-110.36 dose must be completely administered within 12 hours of the start of reconstitution.

10.4.3 KRYSTEXXA Preparation

Doses of KRYSTEXXA will be calculated and prepared based on the manufacturer's currently approved labeling (*KRYSTEXXA Prescribing Information 2018*).

Under appropriate aseptic technique, 1 mL of KRYSTEXXA will be withdrawn from the vial and injected into a single 250 mL bag of 0.9% Sodium Chloride Injection, USP or 0.45% Sodium Chloride Injection USP for IV infusion. The solution will not be mixed or diluted with other drugs. Thorough mixing will be by inversion, not shaking. The diluted solution may be kept for 4 hours at 2°C to 8°C (36°F to 46°F) and at room temperature (20°C to 25°C, 68°F to 77°F). It is recommended that diluted solutions be stored under refrigeration, not frozen, protected from light, and used within 4 hours of dilution.

Detailed procedures for study drug preparation are provided in the Study Operations Manual.

10.5 Premedication

10.5.1 Gout Flares (Prevention and Treatment)

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

Patients not already taking colchicine will receive colchicine 1.2 mg as a single loading dose followed by 0.6 mg QD for the remainder of participation in the trial. If the patient cannot tolerate the loading dose level of 1.2 mg, then the patient will initiate and maintain colchicine at 0.6 mg. Patients with a documented medical reason that describes a contraindication to colchicine will receive ibuprofen 600 mg TID or an equivalent NSAID unless the patient has a contraindication to NSAID. At the discretion of the Investigator, a proton pump inhibitor may be prescribed with the NSAID as gastric prophylaxis. Patients with documented medical reasons that describe contraindications to both colchicine and NSAIDs will receive no premedication for gout flare.

Patients who began receiving a NSAID as gout flare prevention medication due to a contraindication to colchicine should continue to receive the NSAID during study participation. These medications will be supplied by the clinic.

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

10.5.2 Premedication with Antihistamines and Steroids

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

- Prednisone (40 mg) orally approximately 24 (± 12) hours prior to dosing (morning before study drug dosing on Day 0)
- Fexofenadine (180 mg) orally approximately 12 (± 2) hours prior to dosing (evening before study drug dosing on Day 0)
- Fexofenadine (180 mg) orally approximately 2 (± 1) hours prior to dosing (day of study drug dosing)
- Methylprednisolone (40 mg) (or equivalent) IV approximately 1 (± 0.5) hours prior to dosing (day of study drug dosing)

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

10.6 Administration

10.6.1 SEL-212

Before administration of SEL-212, patients will be premedicated with antihistamines and steroids as described in Section 10.5.

Patients will receive treatment with SEL-212 on Day 0 of each Treatment Period for a total of 6 doses of study drug.

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

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

The reconstituted SEL-110.36 will be withdrawn from the vial and dosed via IV infusion with a syringe infusion pump utilizing an appropriately sized syringe. SEL-110.36 will be infused at a rate of 3.0 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 125 mL normal saline. Following the infusion of SEL-110.36, the main IV line must be flushed with normal saline prior to the start of the SEL-037 infusion. Refer to the Study Operations Manual for instructions regarding infusions for patients with medical history involving cardiovascular comorbidities.

SEL-037 infusion will start within 15 minutes after completion of the SEL-110.36 infusion. SEL-037 will be infused via infusion pump over a time period of no less than 120 minutes. If an infusion reaction occurs during the administration of SEL-037, the infusion may be slowed, or stopped and restarted at a slower rate at the discretion of the physician. Following the infusion of SEL-037, the main IV line must be flushed with normal saline.

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

10.6.2 KRYSTEXXA

Before administration of KRYSTEXXA, patients will be premedicated with antihistamines and steroids as described in Section 10.5.

Patients will receive treatment with KRYSTEXXA on Day 0 and Day 14 of each Treatment Period for a total of 12 doses of study drug.

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

KRYSTEXXA will administered based on the manufacturer's currently approved labeling (*KRYSTEXXA Prescribing Information 2018*). Detailed instructions for study drug administration are provided in the Study Operations Manual.

Before administration, the diluted solution of KRYSTEXXA should be allowed to reach room temperature, but never exposed to artificial heating (eg, hot water, microwave). The diluted solution of KRYSTEXXA should be administered by IV infusion via gravity feed, syringe-type pump, or infusion pump over no less than 120 minutes. Following the infusion of KRYSTEXXA, the main IV line must be flushed with normal saline.

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

10.7 Study Drug Accountability

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

10.8 Study Drug Handling and Disposal

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

11. ASSESSMENT OF EFFICACY

11.1 Activity Assessment

11.1.1 Serum Uric Acid Assessment

The primary endpoint of this study is the comparison in the percentage of patients on SEL-212 vs. KRYSTEXXA who achieve and maintain reduction of SUA < 6 mg/dL for at least 80% of the time during Treatment Period 3 and Treatment Period 6.

Serum samples for measurement of SUA will be collected according to the schedules described in Section 20. Methods used for processing samples and for measurement of SUA levels are described in the Study Operations Manual.

11.2 Gout Assessment

11.2.1 Gout Flare Assessment

Gout flare will be assessed as part of TEAE collection with severity determined as described in Section 12.2.2.3.

11.2.2 Joint Assessment

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

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

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

The HAQ-DI will be administered according to the schedules described in Section 20.

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.

11.3.2 Provider Global Assessment of Disease Activity

The Provider Global Assessment of Disease Activity (PrGA) will be conducted according to the schedules described in Section 20. The PrGA 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.

11.3.3 Short Form Health Survey 36 (SF-36)

The SF-36 will be administered according to the schedules described in Section 20.

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.

12. ASSESSMENT OF SAFETY

12.1 Safety Parameters

12.1.1 Demographic/Medical History

Demographic and significant medical history will be documented according to the schedules described in Section 20. Medical history will be recorded up to the time of dosing.

12.1.2 Concomitant Medications and Procedures

Concomitant medications and procedures will be documented according to the schedules described in Section 20.

12.1.3 Vital Signs

Vital signs will be documented according to the schedules described in Section 20.

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.

12.1.4 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed according to the schedules described in Section 20.

12.1.5 Weight and Height

Weight (kg) and height (cm) will be performed according to the schedules described in Section 20. Height will be measured at Screening only. Weight will be used to calculate study drug dosage as described in Section 10.4.

12.1.6 Physical Examination

Physical examinations will be conducted according to the schedules described in Section 20. Breast, rectal, and urogenital exams are not required unless warranted based on the clinical judgment of the patient's medical history or current medical condition. The physical exam should be done by a physician or physician's assistant or similarly qualified individual.

12.1.7 Tophus Assessment

Assessment of the presence of tophi will be conducted according to the schedules described in Section 20. Patients will be stratified according to the presence of tophi (yes/no).

At the time of tophus assessment (Section 20), selected investigational sites will photograph tophi on the hands and feet in a subset of subjects for illustrative purposes. Detailed procedures for conducting the photography are provided in the Study Operations Manual.

12.1.8 Laboratory Assessments

All laboratory assessment will be conducted according to the schedules described in Section 20. Procedures for processing samples are included in the study operations manual.

12.1.8.1 Hematology

Hematology assessments will include white blood cells (WBC) count with differential, red blood cell (RBC) count, hematocrit (Hct), hemoglobin (Hgb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelet (Plt) count, mean platelet volume (MPV).

12.1.8.2 Blood Chemistry

Clinical chemistry assessments will include alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, blood urea nitrogen (BUN), creatinine, fibrinogen, glucose (fasting), phosphorous, and electrolytes (sodium, potassium, chloride, bi-carbonate, phosphate, and magnesium).

The following clinical laboratory assessments will be conducted only during Screening to determine eligibility for study participation: anti-PEG antibodies and G6PD.

12.1.8.3 Lipids

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

12.1.8.4 Coagulation

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

12.1.8.5 Urinalysis

Urinalysis will include assessment of urinary protein, albumin, creatinine, pH, specific gravity, blood, glucose, ketones, bilirubin, leukocyte, esterase, WBC, RBC, crystals, casts (cast types), epithelial cells (renal and nonrenal), bacteria, mucus, and yeast.

At Screening only, urine will be collected for pregnancy testing (Section 12.1.8.8).

12.1.8.6 Anti-Drug-Antibodies

A blood sample for assessment of development of anti-drug-antibodies will be collected for possible future analysis.

12.1.8.7 Serology

Serology screening will include human immunodeficiency virus (HIV) antibodies 1 and 2, hepatitis-B surface antigen (HBsAg), and hepatitis-C antibody (HCVAb). If HCVAb is positive, then HCV virus level will be determined.

12.1.8.8 Pregnancy Screen

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

Female partners of male patients who are of childbearing potential are required to practice an acceptable form of birth control to continue in the study and for 30 days after the last study drug administration. Male patients of reproductive potential who are having intercourse with female partners of childbearing potential must agree to use 2 forms of contraception, 1 of which must be a barrier method, during the study and for 90 days after the last study drug administration. Acceptable barrier methods include a condom and diaphragm. Acceptable forms of birth control for female partners of childbearing potential are non-hormonal and hormonal intrauterine devices, hormonal birth control pills, hormonal birth control patches, hormonal birth control injections, hormonal birth control implants. Spermicide used alone is not an acceptable method and must be used with another acceptable form birth control method. Abstinence is acceptable if consistent with the patient's normal lifestyle.

If a patient becomes pregnant after she begins taking study drug, the procedures in Section 12.2.2.7 should be followed.

12.1.8.9 Definition of Childbearing Potential and Acceptable Contraceptive Methods

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

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

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

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

12.1.9 Premedication Regimen

Refer to Section 10.5 for procedures about premedication regimens to prevent infusion associated reactions and gout flare.

12.2 Adverse and Serious Adverse Events

12.2.1 Definition of Adverse Events

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

12.2.1.1 Adverse Event (AE)

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

Patients will be considered enrolled in the study upon signing the ICF. During the Screening Phase (from time informed consent is signed to immediately before dosing) any clinically significant changes in the patient's health will be recorded in the patient's medical history and will not be considered as AEs. AEs will be collected from the time the patient is dosed (infusion is started) until the end of the End of Study Visit. SAEs will be collected from the time the patient signs informed consent until the End of Study Visit.

12.2.1.2 Serious Adverse Event (SAE)

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

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

12.2.1.3 Suspected Adverse Reaction

A suspected adverse reaction is an AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse

reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

12.2.1.4 Unexpected Adverse Events and Unexpected Suspected Drug Reaction

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

12.2.1.5 Infusion Reactions / Adverse Events of Special Interest

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

Infusion reactions will be managed and treated as described below. In addition to premedication with antihistamines and steroids (Section 10.5.2), the following steps will be implemented in this protocol to either reduce the risk of infusion reactions or manage infusion reactions.

- Patients with immunoreactivity to PEG will be ineligible for the study
- Patients with prior exposure to uricase therapy will be ineligible
- Patients with a history of anaphylaxis or severe allergic reactions, angioedema, or previous infusion reactions will be excluded from the trial.
- Study drug will be administered at controlled rates only in a healthcare setting and by healthcare providers sufficiently equipped and prepared to manage infusion reactions including anaphylaxis.
- In case of infusion reaction, sites will perform specific assessments as specified in the Study Operations Manual.
- Each patient will be observed for infusion reactions after dosing of study drug in the clinic for approximately 1 hour after the end of study drug infusion. Patients will be informed about the signs or symptoms of infusion reactions and will be instructed to notify the Investigator immediately if they believe they are experiencing a reaction.
- Each patient shall remain for a minimum of 1 hour after the completion of infusion of study drug for a period of safety observation.
- Only sites with immediate capability to appropriately respond to a reaction of this severity will be allowed to participate in the trial to reduce the risk to any patient.

Adverse events of special interest (AESI) will be recorded specifically for occurrences of: gout flares, infections, viral infections, interstitial lung disease, stomatitis, infusion-related reactions including anaphylaxis, malignancies, renal failure; and the following lab tests, if deemed

clinically significant by the PI: hyperlipidemia, worsening of renal function tests, proteinuria, and leukopenia.

12.2.2 Recording Adverse Events

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

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

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

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

12.2.2.1 Adverse Event Term/Name/Description

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

12.2.2.2 Relationship to Study Drug

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

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

- Not Related: If no valid reason exists for suggesting a relationship to study drug or the AE was more likely explained by causes other than study drug.
- Unlikely to be Related: Onset of the event has a reasonable temporal relationship to study drug administration and although a causal relationship is unlikely, it is biologically plausible.

- Possibly Related: Onset of the event has a strong temporal relationship to administration of the study drug and a causal relationship is biologically plausible
- Related: The study drug dosing and AE were closely related in time and the AE may be explained by exposure to study product: e.g., known pharmacological effect or recurrence on re-challenge.

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

12.2.2.3 Adverse Event Intensity/Severity Grading

AEs will be classified according to the Rheumatology Common Toxicity Criteria, version 2.0 (*Woodworth 2007*). Additional details of the criteria can be found in the study operations manual.

- Grade 1 (mild): AE that is usually transient of short duration; or involves mild or minor symptoms which are of marginal clinical relevance; or is asymptomatic consisting of clinical or diagnostic observations alone; no intervention or only minimal treatment with non-prescription intervention was required. The event does not generally interfere with usual activities of daily living.
- Grade 2 (moderate): AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living (e.g., shopping, laundry, transportation, or ability to conduct finances), causing discomfort but poses no significant or permanent risk or harm to the patient.
- Grade 3 (severe): AE that is medically significant/important but not life-threatening; may require brief hospitalization to prevent the event from worsening; interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
- Grade 4 (life-threatening): An AE, and/or its immediate sequelae, which is associated with an imminent risk of death or which is associated with physical or mental disabilities that affect or limit the ability of a person to perform activities of daily living (eating, ambulation, toileting, etc.); disability may be persistent or result in significant disability, incapacity or limitation of self-care activities.

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

12.2.2.4 Assessment of Outcome

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

- Fatal

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

12.2.2.5 Action Taken with Study Drug

The action taken with reference to study drug will be assessed by the investigator as:

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

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

12.2.2.6 Laboratory and Diagnostic Abnormalities as Adverse Events

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

12.2.2.7 Pregnancy

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

The Investigator, or his/her designee, will collect pregnancy information on every female who becomes pregnant while enrolled in this study and on every female partner of a male patient who becomes pregnant while the male partner is enrolled in this study. The Investigator will report to the Sponsor or Sponsor's designee within 24 hours of learning of a patient's or female partner of a patient's pregnancy. In the case of a female partner of a male patient enrolled in the study becoming pregnant while the male patient is enrolled in this study, a separate pregnancy partner informed consent form will be completed by the patient's partner. The patient or female partner

of a patient must also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor or Sponsor Designee, as appropriate. Follow-up on the child will be to the first well-child visit. Any premature termination of the pregnancy will be reported.

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

12.2.3 Reporting Adverse Events

12.2.3.1 Adverse Event Reporting Period

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

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

12.2.3.2 SAE Reporting Procedures

If SAEs occur, all Investigators should immediately, but not later than 24 hours of observing or learning of the event, complete and fax the SAE form to Syneos Health and Pharmacovigilance.

Facsimile (for SAE only): [redacted]

Email (for SAE only): [redacted]

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

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

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

facsimile or email to Syneos Health and Pharmacovigilance within 24 hours of receipt of the information.

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

12.2.3.3 Regulatory Reporting Requirements for SAEs

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

12.2.3.4 Reporting Safety Information to the IRB/IEC

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

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

12.2.4 Follow-up of Adverse Events

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

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

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

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

13. STATISTICS

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

13.1 Sample Size Determination

The primary efficacy criterion in this study is defined as the percentage of subjects who achieve and maintain reduction of SUA < 6 mg/dL for at least 80% of the time during Treatment Period 3 and Treatment Period 6.

The percentage of responders according to the above criterion is assumed to be 65% in the SEL-212 arm and 44% in the KRYSTEXXA arm.

Using the Chi-square test for comparison between the SEL-212 arm and the KRYSTEXXA arm, and considering a one-sided alpha=5% and the statistical power of 80%, results in 69 subjects per treatment group. Taking into account that some subjects may be excluded from the modified Intent-to-Treat (mITT) analyses (Section 13.2.4), 75 subjects per treatment group will be randomized. For the sample size estimation, Chi-square test, instead of the Cochran-Mantel-Haenszel test, is used 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 subject population.

Sample size calculations were performed with the software package nQuery Advisor® Sample Size Calculator V. 8.2.1.0.

13.2 Analysis Populations

13.2.1 Screened / Randomized Set

The Screened Set will include all patients who signed an informed consent. The Randomized Set will include all patients randomized.

13.2.2 Safety Set (SS)

The Safety Set will include all patients who were administered any amount of study medication. Patients will be analyzed according to treatment received. The SS will be used for all analyses of safety endpoints and for the presentation of patients in all patient listings.

13.2.3 Intent-to-Treat (ITT) Set

The Intent-to-Treat (ITT) Set will be used as the primary population for the analysis of efficacy. The ITT Set will include all randomized patients. Patients will be analyzed according to randomized treatment.

13.2.4 Modified ITT (mITT) Set

The modified ITT (mITT) Set will include all randomized patients who were administered at least one complete dose of study medication and have at least one post-baseline assessment of SUA. Patients will be analyzed according to randomized treatment. The mITT will also be used for analyses of efficacy endpoints.

13.2.5 Per Protocol Set

The Per Protocol Set (PPS) will include all patients who 1) were administered any amount of study medication, and 2) have completed at least 65% of the study dosing visits with or without receiving study drug (eg at least 4 of 6 TP Day 0 visits for patients receiving SEL-212 or at least 8 of 12 TP Day 0 or Day14 visits for patients receiving Krystexxa) unless early termination from the study occurred after study drug withdrawal due to meeting stopping rules or due to an adverse event, or due to PI discretion (for example where at least one pre-dose SUA was >6 mg/dL in the Krystexxa arm and patient was discontinued from study treatment), and 3) who have no major Protocol deviations (Section 13.3) affecting the primary efficacy assessments. Patients will be analyzed according to randomized treatment.

13.3 Protocol Deviations

All protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management, dosing, and sampling procedures or patient assessment will be listed. The list of protocol deviations will be reviewed by the Sponsor, the principal investigator, the study statistician and the study pharmacokineticist and finalized before database lock. Determination of whether the deviation is major or minor will be based on the biasing impact of the deviation on the safety and efficacy data.

13.4 Efficacy Analyses

13.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as:

- Comparison in the percentage of patients on SEL-212 vs. KRYSTEXXA who achieve and maintain reduction of SUA < 6 mg/dL for at least 80% of the time during Treatment Period 3 and Treatment Period 6

The primary estimand will take into consideration the treatment policy strategy, ie, Treatment Period 6 (and also Treatment Period 3) assessments will be considered for all subjects in ITT independently whether the subject has completed the study treatment or has terminated early the study treatment. Additionally, the estimand based on the while-on-treatment strategy for dealing with study treatment terminators will be defined. For all used estimands of the primary efficacy, the estimator for the comparison between the treatment groups is defined as the difference in the proportion of responders between subjects receiving SEL-212 versus those receiving KRYSTEXXA during Treatment Periods 3 and 6. The statistical testing will be performed confirmatory using the Cochran-Mantel-Haenszel (CMH) test – considering the randomization

stratum of tophus presence (yes/no) – with a one-sided type 1 error rate α = 5%. In addition, 90% two-sided confidence intervals for the overall treatment difference between SEL-212 and KRYSTEXXA treatment groups without stratification will be computed. The analysis of the estimands will be carried out based on the ITT primarily. Supportive analyses will be performed on the mITT and the PP. For each defined estimand sensitivity analyses will be performed using different imputation approaches for missing values. Details of the applied approaches will be presented in the Statistical Analysis Plan.

The SUA time curve will be used to estimate the proportion of time that the SUA level is below 6 mg/dL. Based on the serum samples collected during Treatment Periods 3 and 6, an estimate of the time with SUA < 6 mg/dL can be determined by connecting each two neighboring data points with a straight line. If the SUA time curve goes above 6 mg/dL the linear interpolation method will be used to estimate the point in time at which the SUA time curve intercepts the line between the last SUA value < 6 mg/dL and the first value ≥ 6 mg/dL.

The proportion of time that the SUA level is < 6 mg/dL will be computed by taking the ratio between the time during which the SUA level remains < 6 mg/dL (if necessary, using the linear interpolation method) and the entire time interval within Treatment Periods 3 and 6.

Let T1 be the total time interval in hours for Treatment Period 3 of which W1 hours is the time interval during which SUA level is < 6 mg/dL. Similarly, for Treatment Period 6, assume T2 is the total time interval in hours of which W2 hours is the time interval during which SUA level is < 6 mg/dL. For a subject to be considered a responder, the proportion of time that the SUA level is < 6 mg/dL during Treatment Periods 3 and 6 must be at least 80%. The proportion of time that the SUA level is < 6 mg/dL, i.e., percentage of non-hyperuricemic time, is calculated using the following formula:

$$Proportion = \frac{W1 + W2}{T1 + T2} \times 100$$

A logistic regression model controlling for the distribution of baseline characteristics will be performed as supportive analysis.

Summary tables of the percentage of responder (subjects who achieve and maintain reduction of SUA < 6 mg/dL for at least 80% of the time) in each treatment period will be provided by treatment group. Additionally, a summary table with the total time a subject has SUA values < 6 mg/dL will be provided for each treatment period by treatment group.

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

Additionally, mean SUA level, reduction in mean SUA and percent reduction in mean SUA from baseline during Treatment Period 3 or Treatment Period 6 will be presented by treatment group.

- Mean SUA level is defined as the area under the SUA time curve (computed using the linear trapezoidal rule during Treatment Periods 3 and 6) divided by the corresponding time interval.
- Reduction in mean SUA is computed by subtracting baseline SUA level from mean SUA during Treatment Period 3 and 6.
- Percent reduction in the mean SUA from baseline is computed as the mean SUA level during Treatment Periods 3 and 6 minus baseline SUA level divided by baseline SUA level multiplied by 100

13.4.2 Secondary Efficacy Endpoints and Analyses

The secondary endpoints of this study are:

- Comparison in the percentage of patients on SEL-212 vs. KRYSTEXXA who achieve and maintain reduction of SUA < 6 mg/dL for at least 80% of the time during Treatment Period 6
- Comparison in the percentage of patients on SEL-212 vs. KRYSTEXXA who achieve and maintain reduction of SUA < 6 mg/dL for 100% of the time during Treatment Period 6
- Comparison in the percentage of patients on SEL-212 vs. KRYSTEXXA who achieve and maintain reduction of SUA < 6 mg/dL for at least 80% of the time during Treatment Period 3
- Comparison in the percentage of patients on SEL-212 vs. KRYSTEXXA who achieve and maintain reduction of SUA < 6 mg/dL for 100% of the time during Treatment Period 3
- Comparison between patients on SEL-212 vs. KRYSTEXXA in pre-dose SUA values > 6 mg/dL during Treatment Periods 2-6. The pre-dose SUA is collected on the dosing day prior to the dosing administration or it is collected at the visit where dosing would have occurred had the patient not been previously withdrawn from study drug.
- Comparison between patients on SEL-212 vs. KRYSTEXXA of the change in health questionnaires
- Comparison between patients on SEL-212 vs. KRYSTEXXA of gout flare incidence per 3-month period (Treatment Periods 1-3 and Treatment Periods 4-6)
- Comparison between patients on SEL-212 vs. KRYSTEXXA of gout flare frequency per 3-month period (Treatment Periods 1-3 and Treatment Periods 4-6)
- Comparison between patients on SEL-212 vs. KRYSTEXXA of the change from Baseline to Treatment Period 6 in number of tender joints
- Comparison between patients on SEL-212 vs. KRYSTEXXA of the change from Baseline to Treatment Period 6 in number of swollen joints

All statistical tests in secondary endpoints for the comparison between SEL-212 and KRYSTEXXA will be performed using one-sided tests at a type 1 error rate level of α=5%. In addition, 90% confidence intervals for treatment differences between SEL-212 and

KRYSTEXXA treatment groups will be computed. The efficacy analyses will be carried out based on the ITT and PP Sets. mITT analyses will be performed if appropriate.

Summary table of the number and percentage of subjects who achieve and maintain reduction of SUA < 6 mg/dL for at least 80% of the time during Treatment Period 6 will be provided by treatment group. The comparison between the treatment groups will be performed similar to the primary efficacy endpoint using a CMH-test considering the randomization stratum.

Summary table of the number and percentage of subjects who achieve and maintain reduction of SUA < 6 mg/dL for 100% of the time during Treatment Period 6 will be provided by treatment group. The comparison between the treatment groups will be performed similar to the primary efficacy endpoint using a CMH-test considering the randomization stratum.

Summary table of the number and percentage of subjects with pre-dose SUA values > 6 mg/dL during Treatment Periods 2-6 will be provided by treatment group. The comparison between the treatment groups will be performed similar to the primary efficacy endpoint using a CMH-test considering the randomization stratum.

For the health questionnaires, comparison with regards to change from baseline in health questionnaires will be performed using an ANCOVA with the respective change from baseline value as dependent variable, treatment group and the randomization stratum as independent fixed factors and the baseline value as independent covariate.

For each health questionnaire, summary tables of total scores or domain scores and subscale scores will be provided for each scheduled assessment time by treatment group. Additionally, summaries of the changes from baseline will be provided.

The number and percentage of subjects reporting gout flares per 3-months period and overall, i.e. Treatment Periods 1-3 and Treatment Periods 4-6 and Period 1-6, will be summarized by treatment group and will be tested using a CMH-test considering the randomization stratum.

The frequency of gout flares will be summarized per 3-months period and overall and by severity for each treatment and will be compared using ANOVA model with presences of tophus and treatment as fixed factors. In addition for periods 4-6 and 1-6, poisson regression model will be used with number of gout flares as independent variable, treatment and presence of tophus as fixed factor, and length of follow-up for each corresponding treatment period as covariate.

Comparison with regards to change of tender joints from baseline will be performed using an ANCOVA with the change from baseline value as dependent variable, treatment group and randomization stratum as independent fixed factors and the baseline number of tender joints as independent covariate. In case of non-normality the non-parametric Wilcoxon test will be used for the comparison between the treatment groups. Summary tables of the number of tender joints

for each assessment timepoint and for the change from baseline will be provided by treatment group.

Comparison with regards to change of swollen joints from baseline will be performed using an ANCOVA with the change from baseline value as dependent variable, treatment group and randomization stratum as independent fixed factors and the baseline number of swollen joints as independent covariate. In case of non-normality, the non-parametric Wilcoxon test will be used for the comparison between the treatment groups. Summary tables of the number of swollen joints for each assessment timepoint and for the change from baseline will be provided by treatment group.

13.4.3 Subgroup Analyses

In the event of a prolonged gout flare which is not successfully managed, Investigators will most likely treat patients with corticosteroids which will have a downstream effect on the duration of flares, swollen/tender joint counts and QOL assessments. In order to better extrapolate the results, a subgroup analysis will be conducted for patients who receive "additional gout flare treatment" in each arm for these objectives. Details of this subgroup analysis will be provided in the SAP.

13.5 Safety Analyses

13.5.1 Extent of exposure:

Frequency counts of number of patients who received all doses (i.e., completed study treatment) and descriptive statistics of doses and total cumulative doses by treatment group (SEL-212 or KRYSTEXXA) will be presented.

13.5.2 Adverse Events / Adverse Drug Reactions:

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

An overall summary will be provided of the number and percentage of patients reporting TEAEs, serious TEAEs, treatment-related TEAEs, AESIs, TEAEs leading to withdrawal, and TEAEs leading to death.

The number and percentage of patients with TEAEs / serious TEAEs / TEAEs leading to withdrawal/treatment-related TEAEs will be summarized by SOC and PT for each treatment group (SEL-212 or KRYSTEXXA). AESIs will also be summarized.

TEAEs will also be summarized by maximum intensity and causality.

13.5.3 Laboratory Assessments

Laboratory data will be summarized by the type of laboratory test and will be presented for each scheduled visit stratified by treatment group (SEL-212 or KRYSTEXXA). Normal reference

ranges and markedly abnormal results will be used in the summary of laboratory data. Data will be flagged according to the reference limits (High or Low), if applicable. Changes from baseline will be presented for each post-baseline visit. Shift tables of the number of patients with low/normal/high values at each scheduled post-baseline visit compared to the low/normal/high categorization at baseline will be provided by treatment group (SEL-212 or KRYSTEXXA).

13.5.4 Vital Signs

Summary tables of the actual values and changes from baseline will be provided for each vital sign parameter at each scheduled visit by treatment group (SEL-212 or KRYSTEXXA).

13.5.5 ECG

For each 12-lead ECG variable the actual value and the change from baseline will be summarized for the scheduled visits by treatment group (SEL-212 or KRYSTEXXA).

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

13.5.6 Tophus Assessment

For each tophus assessment variable (including total number, location, palpation and appearance) the actual value and the change from baseline will be summarized for the scheduled visits by treatment group (SEL-212 or KRYSTEXXA).

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Study Monitoring

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

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

15.2 Audits and Inspections

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

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

15.3 Protocol Modifications

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

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

16. ETHICS AND GOOD CLINICAL PRACTICE COMPLIANCE

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

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

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

17. DATA HANDLING AND RECORDKEEPING

17.1 Data Management

17.1.1 Case Report Forms

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

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

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

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

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

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

17.1.2 Retention of Records

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

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

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

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

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

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

18. REPORTING STUDY RESULTS AND PUBLICATION POLICY

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

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

19. LIST OF REFERENCES

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20. APPENDICES

APPENDIX A SCHEDULE OF ASSESSMENTS FOR PATIENTS RANDOMIZED TO SEL-212

Assessment	Scr.		Treatment Period (TP)																	EOS[1]	ET
			TP1[2]		TP2[2]		TP3[2]				TP4[2]		TP5[2]		TP6[2]						
Day	- 45 d	-7 d[3]	D0	D21	D0[4]	D21	D0[4]	D7	D14	D21	D0[4]	D21	D0[4]	D21	D0[4]	D7	D14	D21	D28[20]		
Informed Consent	X																				
Demographics	X																				
Inclusion/Exclusion	X																				
Medical History	X																				
Physical Examinations	X[5]		X[6]		X[6]		X[6]				X[6]		X[6]		X[6]				X[5]		X[5]
Vital Signs	X	X	X[7]		X[7]		X[7]				X[7]		X[7]		X[7]			X	X		X
Weight and Height[8]	X	X		X		X				X		X		X				X	X		X
Tophus Assessment	X																		X		X
12-Lead ECG	X																		X		X
Screening Labs[9]	X																				
Screening Lab: Anti-PEG-Ab	X																				
Urine Pregnancy Test	X																				
Washout: ULTs		X[10]	Patients will abstain from ULT use after the ULT washout period																		
Document ULTs Discontinued		X																			
Dispense Premedication: Gout Flare and Infusion Reaction		X																			
Premedication: Gout Flare		X[11]	Continuously																		
Premedication: Infusion Reaction			X[12]		X[12]		X[12]				X[12]		X[12]		X[12]						
Safety Labs: Chemistry[13]	X		X	X		X				X		X		X				X	X		X
Safety Labs: Hematology[14]	X		X	X		X				X		X		X				X	X		X
Safety Labs: Coagulation[15]	X		X	X		X				X		X		X				X	X		X
Safety Labs: Lipids[16]	X		X	X		X				X		X		X				X	X		X
Safety Labs: Urinalysis[17]	X		X	X		X				X		X		X				X	X		X
Safety Labs: Anti-drug-Ab																			X		X
Gout Flare Assessment	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Joint Assessment (tenderness, swelling)			X								X								X		X

Appendix A SCHEDULE OF ASSESSMENTS FOR PATIENTS RANDOMIZED TO SEL-212, CONTINUED

Assessment	Scr.		Treatment Period (TP)																	EOS[1]	ET
			TP1[2]		TP2[2]		TP3[2]				TP4[2]		TP5[2]		TP6[2]						
Day	- 45 d	-7 d[3]	D0	D21	D0[4]	D21	D0[4]	D7	D14	D21	D0[4]	D21	D0[4]	D21	D0[4]	D7	D14	D21	D28[20]		
Health Questionnaires[18]			X								X								X		X
Collect Sample for SUA	X		Refer to Schedule of Assessments in Appendix B for SUA Sample Collection during Treatment Period																		X
Study Drug Administration			Refer to Schedule of Assessments in Appendix B for Study Drug Administration during the Treatment Period																		
Concomitant Medications / Procedures			Continuously																	X	X
AE/SAE Collection	X[19]	X[19]	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 days to +1 day.
3. Visit window is -2 days.
4. Study drug dosing to occur 28 days from the previous dose with a window of -4 days to +3 days of the intended dosing day.
5. Full physical exam
6. Directed physical exam
7. 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.
8. Height measured once during Screening only.
9. Screening labs to include: SUA, anti-PEG-antibodies, hepatitis B and C antibodies, human immunodeficiency virus 1/2 (HIV1/2), hemoglobin-A1c (HbA1c), glucose, triglycerides, LDL, glucose-6-phosphate dehydrogenase (G6PD), WBC, AST, ALT, Hgb, serum creatinine, and serum phosphate, urinalysis
10. Begin ULT washout at least 7 days prior to Day 0 of Treatment Period 1.
11. Begin colchicine 0.6 mg QD premedication at least 7 days prior to Day 0 of Treatment Period 1. Patients not already taking colchicine will receive colchicine 1.2 mg as a single loading dose followed by the 0.6 mg every day regimen. 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.
12. Pretreatment to minimize potential infusion reactions: oral steroids at 24 (± 12) hours and oral antihistamines at 12 (± 2) hours and 2 (± 1) hours and IV steroids at 1 (± 0.5) hours prior to study medication.
13. Chemistry labs to include: Alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, blood urea nitrogen (BUN), creatinine, fibrinogen, glucose (fasting), phosphorous, electrolytes (sodium, potassium, chloride, bi-carbonate, phosphate and magnesium).
14. Hematology labs to include: white blood cells (WBC) count with differential, red blood cell (RBC) count, hematocrit (Hct), hemoglobin (Hgb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelet (Plt) count, mean platelet volume (MPV)
15. Coagulation labs to include: prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR)
16. Lipid labs to include: total cholesterol, HDL, LDL, triglycerides
17. Urinalysis to include: urinary protein, albumin, creatinine, pH, specific gravity, blood, glucose, ketones, bilirubin, leukocyte, esterase, WBC, RBC, crystals, casts (cast types), epithelial cells (renal and nonrenal), bacteria, mucus, and yeast.
18. Refer to Section 11.3 for Health Questionnaires.
19. During Screening, SAE collection begins at time of signing informed consent. Non-serious AE will not be collected during Screening.
20. Visit window is -2 days to +6 days

Abbreviations: Ab: antibody; D (d): day; ECG: electrocardiogram; EOS: end of study; ET: early termination; h: hour; RCTC: Rheumatology Common Toxicity Criteria; Scr: Screening Period; SUA: serum uric acid; TP: treatment period; ULT: urate lowering therapy

APPENDIX B SCHEDULE OF ASSESSMENTS: SEL-212 DOSING AND SUA DURING THE TREATMENT PERIOD

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

1. Study drug dosing to occur 28 days from the previous dose with a window of -4 days to +3 days of the intended dosing day.
2. Treatment Period 6 only.
3. Pretreatment to minimize potential infusion reactions: oral steroids at 24 (± 12) hours and oral antihistamines at 12 (± 2) hours and 2 (± 1) hours and IV steroids at 1 (± 0.5) hours prior to study medication.
4. Obtain sample prior to study drug infusion.
5. Obtain sample 1 (± 0.25) hour after completion of infusion of Component 2.
6. Component 1 will be SEL-110.36 for patients randomized to treatment with SEL-212.
7. Before starting infusion with Component 2, a period of up to 15 minutes is permitted after completion of infusion of Component 1.
8. Component 2 will be SEL-037 for patients randomized to treatment with SEL-212.

APPENDIX C SCHEDULE OF ASSESSMENTS FOR PATIENTS RANDOMIZED TO KRYSTEXXA

Assessment	Scr.		Treatment Period (TP)																	EOS[1]	ET
			TP1[2]		TP2[2]		TP3[2]				TP4[2]		TP5[2]		TP6[2]						
Day	- 45 d	-7 d[3]	D0	D14	D0[4]	D14	D0[4]	D7	D14	D21	D0[4]	D14	D0[4]	D14	D0[4]	D7	D14	D21	D28[20]		
Informed Consent	X																				
Demographics	X																				
Inclusion/Exclusion	X																				
Medical History	X																				
Physical Examinations	X[5]		X[6]		X[6]		X[6]				X[6]		X[6]		X[6]				X[5]		X[5]
Vital Signs	X	X	X[7]	X[7]	X[7]	X[7]	X[7]		X[7]		X[7]	X[7]	X[7]	X[7]	X[7]		X[7]	X	X		X
Weight and Height[8]	X	X		X		X			X			X		X			X		X		X
Tophus Assessment	X																		X		X
12-Lead ECG	X																		X		X
Screening Labs[9]	X																				
Screening Lab: Anti-PEG-Ab	X																				
Urine Pregnancy Test	X																				
Washout: ULTs		X[10]	Patients will abstain from ULT use after the ULT washout period																		
Document ULTs Discontinued		X																			
Dispense Premedication: Gout Flare and Infusion Reaction		X																			
Premedication: Gout Flare		X[11]	Continuously																		
Premedication: Infusion Reaction			X[12]	X[12]	X[12]	X[12]	X[12]		X[12]		X[12]	X[12]	X[12]	X[12]	X[12]		X[12]				
Safety Labs: Chemistry[13]	X		X	X		X			X			X		X			X		X		X
Safety Labs: Hematology[14]	X		X	X		X			X			X		X			X		X		X
Safety Labs: Coagulation[15]	X		X	X		X			X			X		X			X		X		X
Safety Labs: Lipids[16]	X		X	X		X			X			X		X			X		X		X
Safety Labs: Urinalysis[17]	X		X	X		X			X			X		X			X		X		X
Safety Labs: Anti-drug-Ab																			X		X
Gout Flare Assessment	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Joint Assessment (tenderness, swelling)			X								X								X		X
Health Questionnaires[18]			X								X								X		X

Appendix C, SCHEDULE OF ASSESSMENTS FOR PATIENTS RANDOMIZED TO KRYSTEXXA, CONTINUED

Assessment	Scr.		Treatment Period (TP)																	EOS[1]	ET
			TP1[2]		TP2[2]		TP3[2]				TP4[2]		TP5[2]		TP6[2]						
Day	- 45 d	-7 d[3]	D0	D14	D0[4]	D14	D0[4]	D7	D14	D21	D0[4]	D14	D0[4]	D14	D0[4]	D7	D14	D21	D28[20]		
Collect Sample for SUA	X		Refer to Schedule of Assessments in Appendix D for SUA Sample Collection during Treatment Period																		X
Study Drug Administration			Refer to Schedule of Assessments in Appendix D for Study Drug Administration during the Treatment Period																		
Concomitant Medications / Procedures			Continuously																	X	X
AE/SAE Collection	X[19]	X[19]	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 14 of each Treatment Period is -2 days to +3 days; visit window at Day 7 and 21 of TP3 and TP6 is -2 days to +3 days.
3. Visit window is -2 days.
4. Study drug dosing to occur 14 days from the previous dose with a window of -2 days to +3 days of the intended dosing day.
5. Full physical exam
6. Directed physical exam
7. Assess vital signs on Day 0 and 14 at Time 0 (pre-dose), and 1 hour (+ 5 minutes) after completion of infusion.
8. Height measured once during Screening only.
9. Screening labs to include: SUA, anti-PEG-antibodies, hepatitis B and C antibodies, human immunodeficiency virus 1/2 (HIV1/2), hemoglobin-A1c (HbA1c), glucose, triglycerides, LDL, glucose-6-phosphate dehydrogenase (G6PD), WBC, AST, ALT, Hgb, serum creatinine, and serum phosphate
10. Begin ULT washout at least 7 days prior to Day 0 of Treatment Period 1.
11. Begin colchicine 0.6 mg QD premedication at least 7 days prior to Day 0 of Treatment Period 1. Patients not already taking colchicine will receive colchicine 1.2 mg as a single loading dose followed by the 0.6 mg every day regimen. 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.
12. Pretreatment to minimize potential infusion reactions: oral steroids at 24 (± 12) hours and oral antihistamines at 12 (± 2) hours and 2 (± 1) hours and IV steroids at 1 (± 0.5) hours prior to study medication.
13. Chemistry labs to include: Alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, blood urea nitrogen (BUN), creatinine, fibrinogen, glucose (fasting), phosphorous, electrolytes (sodium, potassium, chloride, bi-carbonate, phosphate and magnesium).
14. Hematology labs to include: white blood cells (WBC) count with differential, red blood cell (RBC) count, hematocrit (Hct), hemoglobin (Hgb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelet (Plt) count, mean platelet volume (MPV)
15. Coagulation labs to include: prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR)
16. Lipid labs to include: total cholesterol, HDL, LDL, triglycerides
17. Urinalysis to include: urinary protein, albumin, creatinine, pH, specific gravity, blood, glucose, ketones, bilirubin, leukocyte, esterase, WBC, RBC, crystals, casts (cast types), epithelial cells (renal and nonrenal), bacteria, mucus, and yeast.
18. Refer to Section 11.3 for Health Questionnaires.
19. During Screening, SAE collection begins at time of signing informed consent. Non-serious AE will not be collected during Screening.
20. Visit window is -2 days to +6 days

Abbreviations: Ab: antibody; D (d): day; ECG: electrocardiogram; EOS: end of study; ET: early termination; h: hour; RCTC: Rheumatology Common Toxicity Criteria; Scr: Screening Period; SUA: serum uric acid; TP: treatment period; ULT: urate lowering therapy

APPENDIX D SCHEDULE OF ASSESSMENTS: KRYSTEXXA DOSING AND SUA DURING THE TREATMENT PERIOD

Assessments	**Treatment Periods: 1, 2, 4, and 5**						**Treatment Periods 3 and 6**								
Day	**D0[1]**			**D14**			**D0[1]**			**D7**	**D14**			**D21**	**D28[2]**
Timepoint	**0h**	**~2.0h**	**~3.0h**	**0h**	**~2.0h**	**~3.0h**	**0h**	**~2.0h**	**~3.0h**		**0h**	**~2.0h**	**~3.0h**		
Premedicate: Infusion Reaction	X[3]			X[3]			X				X[3]				
Blood Sample: SUA	X[4]		X[5]	X[4]		X[5]	X[4]		X[5]	X	X[4]		X[5]	X	X
Study Drug Infusion	X --------- X			X --------- X			X---------X				X --------- X				

1. Study drug dosing to occur 14 days from the previous dose with a window of -2 days to +3 days of the intended dosing day.
2. Treatment Period 6 only.
3. Pretreatment to minimize potential infusion reactions: oral steroids at 24 (± 12) hours and oral antihistamines at 12 (± 2) hours and 2 (± 1) hours and IV steroids at 1 (± 0.5) hours prior to study medication.
4. Obtain sample prior to study drug infusion.
5. Obtain sample 1 (± 0.25) hour after completion of infusion.

Revision History

Version	Reason for Change	Date
1.1	• Clarifications, administrative corrections	12 APR 2019
2.0	• Clarifications, administrative corrections • Updated study personnel information • Reduced Screening threshold SUA to 7 mg/dL to allow for enrollment of all patients with serum uric acid above the limit of solubility	14 MAY 2019
2.1	• Clarifications, administrative corrections • Updated study personnel information • Added oral steroid premedication 24hr prior to dose	03 FEB 2020
3.0	• Clarifications, administrative corrections • Updated study personnel information and sponsor address • Updated secondary endpoints • Updated statistical analysis population definitions • Updated primary efficacy population to be ITT • Updated statistical analysis approach for gout flare endpoint • Clarification of visit windows	08 JUN 2020