# Statistical Analysis Plan

**Sponsor Name:** Selecta Biosciences

**Protocol Number:** SEL-212/202

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

**Protocol Version and Date: 1.0,** 24 January 2019
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**Syneos Health Project Code:** 7000459

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## Revision History

| Version # | Date (DD-Mmm-YYYY) | Document Owner | Revision Summary |
|---|---|---|---|
| 1.0 | 17-Apr-2019 | [redacted] | First Signed Version |
| 2.0 | 16-Dec-2019 | [redacted] | • Added clarification of unblinding for Selecta during interim analysis<br>• Added specified rules for primary response calculation, TEAE definition and Summary for tophus<br>• Incorporated some edits per Selecta review comments including summarie for period 3 SUA response |
| 2.1 | 18-Apr-2020 | [redacted] | • Updated per protocol 2.1<br>• Incorporated comments and requested additional analyses due to COVID-19 Pandemic |
| 2.2 | 22-May-2020 | [redacted] | • Redefined primary efficacy population as ITT set and modified imputation for primary endpoint<br>• Added clarification for PP population and major protocol deviation affecting efficacy |
| 3.0 | 09-Jun-2020 | [redacted] | • Updated per protocol 3.0 and Incorporated some edits per Selecta review comments |
| 3.1 | 04-Sep-2020 | [redacted] | • Added secondary efficacy endpoints related to mean SUA (sections 4.2, 7.2.1)<br>• Added some clarification for PD (section 5.6)<br>• Add missing data listing due to Covid-19 (section 5.9)<br>• Add log-rank test for subgroup patients with present and absence of tophus (section 6.1) |
| 4.0 | 08-Sep-2020 | [redacted] | • Updated signature page by replacing [redacted] with [redacted] |

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

## Approvals

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## Table of Contents

# 1. Glossary of Abbreviations

| Abbreviation | Description |
|---|---|
| Ab | Antibody |
| AE | Adverse event |
| AESIs | Adverse events of special interest |
| aPTT | Activated partial thromboplastin time |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| ATC | Anatomical Therapeutic Classification |
| eCRF | Electronic Case report form |
| CMH | Cochran-Mantel-Haenszel |
| CYP3A4 | Cytochrome P450, family 3, subfamily A |
| d | Day, Study day |
| dL | Deciliter |
| DSMC | Data and Safety Monitoring Committee |
| ECG | Electrocardiogram |
| EOS | End of Study |
| ET | Early Termination |
| g | gram |
| G6PD | Glucose-6-phosphate dehydrogenase |
| GFR | Glomerular Filtration Rate |
| h | Hour |
| HAQ-DI | Health Assessment Questionnaire-Disability Index |
| Hct | Hematocrit |
| HDL | High-density Lipoprotein |
| Hgb | Hemoglobin |
| HIV | Human immunodeficiency virus |
| HbA1c | Hemoglobin-A1c |
| ICF | Informed consent form |
| LDL | Low-density Lipoprotein |
| INR | International normalized ratio |
| ITT | Intent-to-Treat |
| kg | Kilograms |
| MCH | Mean Corpuscular Hemoglobin |
| MCHC | Mean Corpuscular Hemoglobin Concentration |
| MCV | Mean Corpuscular Volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligrams |
| mITT | Modified Intent-to-Treat |
| ml | Milliliters |
| MPV | Mean Platelet Volume |
| NIAID | National Institute of Allergy and Infectious Diseases |
| PEG | Polyethylene glycol |
| Plt | Platelet |
| PrGA | The Provider Global Assessment of Disease Activity |

| Abbreviation | Description |
|---|---|
| PP | Per Protocol |
| PT | Preferred Term |
| QD | Once Daily |
| QoL | Quality of life |
| RBC | Red Blood Cell |
| RCTC | Rheumatology Common Toxicity Criteria |
| RDW | Red Cell Distribution Width |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| Scr | Screening Period |
| SF-36 | Short Form Health Survey 36 |
| SUA | Serum Uric Acid |
| SOC | System Organ Class |
| SS | Safety Set |
| TEAE | Treatment-emergent adverse events |
| TLFs | Tables, Listings and Figures |
| TP | Treatment Period |
| ULN | Upper limit of normal |
| ULT | Uric acid lowering therapy |
| WHO-DD | World Health Organization Drug Dictionary |
| WBC | White Blood Cell |

# 2. Purpose

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

## 2.1. Responsibilities

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

## 2.2. Timings of Analyses

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

An interim analysis will be conducted when 100% of patients are scheduled to have completed 3 months of study treatment (ie. scheduled to have completed Treatment Period (TP) 4 Day 0 visit). Since this is an open label study, unblinding of Syneos personel is not applicable when performing interim analyses. Selecta is blinded to all post dose serum uric acid (SUA) values and the primary endpoint throughout the study except that Selecta will be unblinded to the primary endpoint results at delivery of the interim analysis. As such, the interim analysis will be performed so that the study data will be collected once the timepoint criteria above is met, but the study data will be held by Syneos as a mitigation against significant COVID-19 pandemic disruption in the dataset. The primary and secondary endpoints will not be calculated nor the interim analysis results delivered to Selecta until requested by Selecta due to significant disruption in the study or due to the last patient dosing having occurred in the study. Selecta will remain blinded to individual subject SUA data until the final analysis. Syneos's biostats and programming study team will prepare all report summaries for the interim analyses. The purpose of the interim analysis is for business planning and so a protocol update including sample size adjustment is not applicable.

# 3. Study Objectives

## 3.1. Primary Objective

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

## 3.2. Secondary Objective(s)

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)

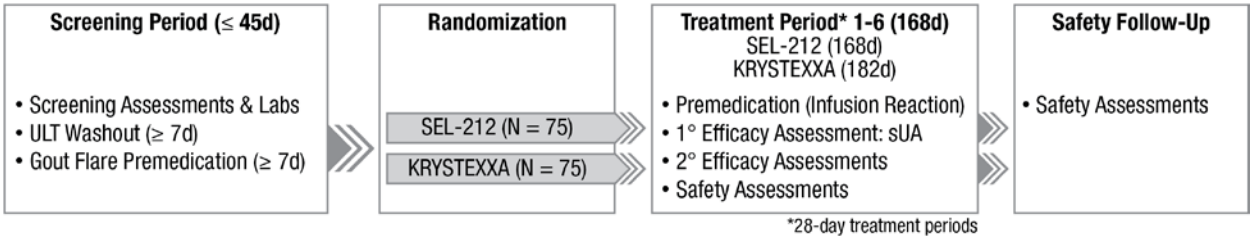
## 3.3. Overall Study Design

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 the figure below:

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 scheduled infusion on Study Day 154

## 3.4. Patient Selection

Approximately 150 patients will be selected to participate the study.

### 3.4.1. 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-ooporectomy or
   b. Postmenopausal (> 24 months of natural amenorrhea or in the absence of > 24 months of amenorrhea, 1 documented confirmatory FSH measurement)
5. Has at the Screening Visit 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.

### 3.4.2. 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. Patient 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. Patients with a documented history of moderate or severe alcohol or substance use disorder within the 12 months prior to randomization.
26. Patients who, in the opinion of the investigator, present with a condition that would compromise their safety or that would make study completion unlikely.

### 3.5. Determination of Sample Size

The primary efficacy criterion in this study is defined as the percentage of patients 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 patients per treatment group. Taking into account that some patients may be excluded from the mITT analyses, 75 patients 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 patient population.

### 3.6. Treatment Assignment & 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.

SEL-212 is comprised of 2 components: SEL-037 and SEL-110.36 with dose level 0.15 mg/kg and 0.2 mg/kg respectively based on patient's weight. The dose level for KRYSTEXXA® is 8 mg (uricase protein).

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

### 3.7. Administration of Study Medication

The designated site representative will prepare study drug on the day of treatment. For Treatment Period 1, patient's weight at screening will be used to determine actual dose level for SEL-212 cohort. 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 pre-dose measurements (KRYSTEXXA® cohort).

Before administration of SEL-212 or KRYSTEXXA®, patients will be premedicated with antihistamines and steroids for prevention of infusion reactions. Patients in the SEL-212 cohort will receive treatment with SEL-212 on Day 0 of each Treatment Period for a total of 6 doses of study drug. Patients in the KRYSTEXXA® cohort 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.

### 3.8. Study Procedures and Flowchart

Scheduled assessment are presented by the following 4 tables on next a few pages:

- Table A: schedule of assessment for patients randomized to SEL-212
- Table B: schedule of assessments: SEL-212 dosing and SUA during the treatment period
- Table C: schedule of assessment for patients randomized to KRYSTEXXA®
- Table D: schedule of assessments: KRYSTEXXA® dosing and SUA during the treatment period

## TABLE 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 |

## Table 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 Table B for SUA Sample Collection during Treatment Period | | | | | | | | | | | | | | | | | | X |
| Study Drug Administration | | | Refer to Schedule of Assessments in Table 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 day 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 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, 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 protocol 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

## TABLE 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----------X[7] | | | | | X----------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.

# TABLE 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 |

## TABLE 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 Table D for SUA Sample Collection during Treatment Period | | | | | | | | | | | | | | | | | | X |
| Study Drug Administration | | | Refer to Schedule of Assessments in Table 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 Day 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 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, 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 protocol 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

## TABLE 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.

# 4. Endpoints

## 4.1. Primary Efficacy Endpoint

Primary Endpoint:

- 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 3.8 tables B and D.

## 4.2. Secondary Efficacy Endpoints

Secondary Endpoints:

- Reduction of mean SUA in patients on SEL-212 vs. KRYSTEXXA® as computed by subtracting baseline SUA level from the mean SUA (area under the SUA time curve) during Treatment Period 3 and Treatment Period 6
- Percent reduction of mean SUA in patients on SEL-212 vs. KRYSTEXXA® as computed as the mean SUA level during treatment period (area under the SUA time curve) minus baseline SUA level divided by baseline SUA level multiplied by 100 during Treatment Period 3 and Treatment Period 6
- 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
- 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
- Reduction of mean SUA in patients on SEL-212 vs. KRYSTEXXA® as computed by subtracting baseline SUA level from the mean SUA (area under the SUA time curve) during Treatment Period 6
- Percent reduction of mean SUA in patients on SEL-212 vs. KRYSTEXXA® as computed as the mean SUA level during treatment period (area under the SUA time curve) minus baseline SUA level divided by baseline SUA level multiplied by 100 during Treatment Period 6
- Percentage of patients who achieve and maintain reduction of SUA < 6 mg/dL for at least 80% of the time during Treatment Period 3
- A summary table of the number and percentage of patients who achieve and maintain reduction of SUA < 6 mg/dL for 100% of the time during Treatment Period 3 will be provided by treatment group.
- Reduction of mean SUA in patients on SEL-212 vs. KRYSTEXXA® as computed by subtracting baseline SUA level from the mean SUA (area under the SUA time curve) during Treatment Period 3
- Percent reduction of mean SUA in patients on SEL-212 vs. KRYSTEXXA® as computed as the mean SUA level during treatment period (area under the SUA time curve) minus baseline SUA level divided by baseline SUA level multiplied by 100 during Treatment Period 3
- Percent of 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 for those patients who have been withdrawn from study drug.

- Change in health questionnaires to end of treatment period 3 and 6:
  - Health Assessment Questionnaire-Disability Index (HAQ-DI)
  - The Provider Global Assessment of Disease Activity (PrGA)
  - Short Form Health Survey 36 (SF-36)
- Percent of patients on SEL-212 vs. KRYSTEXXA® of gout flare incidence per 3-month period (Treatment Periods 1-3 and Treatment Periods 4-6)
- Percent of patients on SEL-212 vs. KRYSTEXXA® of gout flare frequency per 3-month period (Treatment Periods 1-3 and Treatment Periods 4-6)
- Change from Baseline to Treatment Period 6 in number of tender joints
- Change from Baseline to Treatment Period 6 in number of swollen joints

### 4.3. Safety Endpoints

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.

# 5. Analysis Sets

## 5.1. Screened / Randomized Set

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

## 5.2. Safety Set

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

## 5.3. Intent-to-Treat 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. ITT set is same as randomized set by its definition and will be referred as so in this SAP.

## 5.4. Modified Intent-to-Treat

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.

## 5.5. Per Protocol Set

The Per Protocol (PP) Set 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 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.

## 5.6. 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, or has impacts on primary efficacy assessment will be based on the biasing impact of the deviation on the safety and efficacy data. Major protocol deviations affecting the primary efficacy assessments include: 1) major protocol deviations that lead to premature study drug discontinuation; 2) major protocol deviations that lead to patients receiving study drug treatment in treatment periods 3 or 6 that they would not otherwise have received (such as incorrect application of the protocol stopping rules that allow a patient to continue dosing despite having met the stopping criteria); and 3) protocol deviations that involve out of window sampling of SUA due to a) visits occurring outside of the protocol visit window for dosing days (where dosing days refer to dosing visits of patients still on study drug who have not previously been withdrawn from study drug) in Treatment period 3 and 6, b) visits occurring outside of the protocol visit

window for visits within TP3 or TP6 scheduled 1 week prior to the dosing days, c) visits occurring outside of the protocol visit window for TP6 D21 for patients who have not been withdrawn from study drug and for dosing day TP4D0, or d) visits occurring 35 days or more beyond TP6D0 for the TP6D28 visit for patients who have not been withdrawn from study drug, where the protocol visit window above refers to the current protocol window allowed at the time of analysis. Major protocol deviations affecting the primary efficacy assessments will be reviewed and determined periodically during clinical and medical review of protocol deviations during the study.

Protocol deviations related to Covid-19 will be identified and flagged.

## 5.7. General Methods

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

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

Unless stated otherwise, descriptive summaries will include n, mean, standard deviation, median, minimum and maximum for continuous variables, and n and percent for categorical variables. If there are multiple assessments collected on the same scheduled time within the visit windows defined for each assessment, the average of these assessments will be used. For tabulated safety summaries, only the scheduled assessments will be included in the summary tables.

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

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

## 5.8. Key Definitions

Baseline is defined as the last non-missing value prior to the start of infusion of SEL-212 or KRYSTEXXA®.

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

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

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

## 5.9. Missing Data

Missing data will not be imputed unless specified otherwise. Missing eCRF data due to Covid-19 will be listed.

# 6. Demographic, Other Baseline Characteristics and Medication

## 6.1. Patient Disposition and Withdrawals

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

- Screened (or Enrolled) patients
- ITT, SS, mITT, and PP patients
- Patients who complete the study treatment
- Patients who early terminate the study treatment and reasons for early termination
- Patients who early terminate the study and reasons for early termination

Screen Failure patients will be listed.

Kaplan-Meier (KM) figures of the time to early termination of the study by treatment group and by presence of tophus will be provided.

Kaplan-Meier (KM) figures of the time to early termination of the study due to adverse event by treatment group and by presence of tophus will be provided.

Kaplan-Meier (KM) figures of the time to early study treatment discontinuation by treatment group and by presence of tophus will be provided.

Kaplan-Meier (KM) figures of the time to early study treatment discontinuation due to stopping rules by treatment group and by presence of tophus will be provided.

Kaplan-Meier (KM) figures of the time to early study treatment discontinuation due to stopping rules or due to Infusion-related reactions including infusion reaction, allergic reaction to pre-med or one of drug components and anaphylaxis, by treatment group and by presence of tophus will be provided.

In addition, stratified Log-rank test will be used to test treatment difference with presence of tophus as stratification factor for those time to event endpoint mentioned above. Unstratified Log-rank test will be used to test treatment difference for patients with presence of tophus and for patients with absence of tophus.

## 6.2. Demographic and Other Baseline Characteristics

Demographic characteristics such as gender, age, race and ethnicity will be summarized for all ITT patients, by treatment and overall. Demographic characteristics will be also summarized using MITT and PP set patients.

Age will be calculated based on date of signed informed consent as below:

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

## 6.3. Medical History

No summaries will be provided. Medical history will be coded using current version of Medical Dictionary for Regulatory Activities (MedDRA®). The version number will be noted on the actual data listing for medical

history. Medical history will be listed by treatment and patient including coded terms for system organ class and preferred term.

## 6.4. Concomitant Medication and Therapy

Concomitant medications are permitted during this study unless otherwise restricted. Medications used in the 3 months prior to screening and during the study will be recorded on the Concomitant Medications electronic case report form (eCRF). The reported medications will be reviewed and evaluated by the investigator or designee to determine if they affect a patient's eligibility to participate or continue to participate in the study.

### 6.4.1. Prior Medication

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

Prior medication will be listed.

### 6.4.2. Concomitant Medication

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

The original verbatim terms collected in the eCRF for prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD current version) into drug class (Anatomical Therapeutic Classification [ATC] level 4) and preferred term.

Concomitant medication will be summarized by treatment, ATC4 and preferred term for SS patients and will be listed for all SS patients.

# 7. Efficacy

## 7.1. Primary Efficacy Endpoint Analysis

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 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. SUA values collected at unscheduled visits within period 3 and period 6 will be included for the SUA time curve. 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. For period 3, entire time interval is between time of day 0 SUV assessment for period 3 and period 4. For Period 6, the entire time interval is between time of day 0 and day 28 assessment.

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 patient 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 (p) of non-hyperuricemic time, is calculated using the following formula:

$$Percentage\ (p) = \frac{W1 + W2}{T1 + T2} \times 100$$

Missing scheduled assessments of SUA will be imputed as follows: If SUA is missing at day 0 (predose) for periods 3, 4 and 6 and day 28 for period 6 in the SEL-212 cohort, baseline SUA will be used for calculation. If SUA is missing at day 0 (predose) for periods 3, 4 and 6 and day 28 for period 6 or day 14 (pre-dose) for treatment periods 3 and 6 in the Krystexxa cohort, baseline SUA will be used for calculation. Day 0 predose time point is the same as day 28 of previous treatment period. For example, period 4 predose is same as period 3 day 28. If SUA is missing at the post-dose timepoint on dosing days (ie post-treatment on Day 0 in SEL-212 cohort or post-treatment on either D0 or D14 in Krystexxa cohort) in either Treatment period 3 or 6 or is missing at Day 21 of treatment period 3 or 6 for the SEL-212 cohort for a patient, it will be imputed by the mean of the available assessments at the respective time from the prior Treatment Periods (ie from Treatment periods 1 and 2 for missing data in TP3 and from Treatment periods 1 to 5 for missing data in TP6) of this patient. Missing SUA assessments at Day 7 and Day 14 in the SEL-212 cohort and missing SUA assessments at Day 7 and 21 in the Krystexxa cohort will not be imputed, but SUA time curve will be determined by interpolation.

If the duration of the Treatment Period 3 or 6 has been extended by more than 6 days beyond its nominal 28 day duration due to study visits occurring beyond their protocol windows, the corresponding TP4 day 0 (predose) or TP6 day 28 value will be imputed by the baseline value for the patient at the timepoint of 28 days after the previous Day 0 timepoint (TP3 or TP6) and only those SUA values drawn within 28 days of the respective day 0 (ie. TP3 or TP6) will be used in calculating the proportion of time that the SUA level is below 6 mg/dL.

The primary estimand will take into consideration the treatment policy strategy, ie, Treatment Period 3 and 6 assessments will be considered for all patients in ITT independently whether the patient has completed the study treatment or has terminated the study treatment early. If a subject withdraws from study before completing period 6 or is put back on ULTs, the subject will be considered as a non-responder for the primary efficacy endpoint. The return of ULTs is a confounding factor for subsequent SUA efficacy.

The estimator for the comparison between the treatment groups is defined as the difference in the proportion of responders between patients 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.

A logistic regression model to compare treatment difference controlling for presence of tophus will be performed as supportive analysis.

In addition, a sensitivity analysis will be performed as below for the primary endpoint:

- If a subject withdraws from study treatment before completing period 6 due to stopping rules met for treatment, the subject will be considered as a non-responder for the primary efficacy endpoint.
- If a subject withdraws from the study before completing period 6 or the study terminates prior to a subject completing period 6, the primary efficacy endpoint is based on SUA assessment for period 3 where 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:

$$Percentage\ (p) = \frac{W1}{T1} \times 100$$

Summary tables of the percentage of responders (patients who achieve and maintain reduction of SUA < 6 mg/dL for at least 80% of the time) will be provided by treatment group. Additionally, a summary table with the total time a patient has SUA values < 6 mg/dL will be provided for treatment period 3 and treatment period 6 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 Periods 3 and 6, during Treatment 3, and during Treatment Period 6 will be summarized by treatment group respectively and will be compared for treatment difference using ANOVA model with presence of tophus and treatment group as fixed factors

- 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

## 7.2. Secondary Efficacy Endpoint Analyses

There is no hierarchical ordering of the secondary endpoints. All secondary endpoint will be included for analyses as described.

### 7.2.1. Secondary Efficacy Endpoints based on SUA

For the following secondary endpoints, the comparison between SEL-212 and KRYSREXXA® will be done similar to the primary efficacy endpoint using a CMH-test considering the randomization stratum of tophus presence (yes/no) with one-sided 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 as supportive.

- percentage of patients who achieve and maintain reduction of SUA < 6 mg/dL for at least 80% of the time during Treatment Period 3
- percentage of patients who achieve and maintain reduction of SUA < 6 mg/dL for at least 80% of the time during Treatment Period 6
- percentage of patients who achieve and maintain reduction of SUA < 6 mg/dL for 100% of the time during Treatment Period 6
- percent of patients whose pre-dose SUA values > 6 mg/dL during Treatment Periods 2-6

A summary table of the number and percentage of patients 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.

A summary table of the number and percentage of patients who achieve and maintain reduction of SUA < 6 mg/dL for at least 80% of the time during Treatment Period 3 will be provided by treatment group.

A summary table of the number and percentage of patients 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.

A summary table of the number and percentage of patients who achieve and maintain reduction of SUA < 6 mg/dL for 100% of the time during Treatment Period 3 will be provided by treatment group.

A summary table of the number and percentage of patients with pre-dose SUA values > 6 mg/dL during Treatment Periods 2-6 will be provided by treatment group.

### 7.2.2. Change from baseline in HAQ-DI Total Score

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.

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

Comparison with regards to change from baseline 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.

Summary tables of total scores will be provided for each scheduled assessment time by treatment group. Additionally, summaries of the changes from baseline will be provided.

### 7.2.3. Provider Global Assessment of Disease Activity (PrGA)

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.

Comparison with regards to change from baseline in PrGA 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.

Summary tables of PrGA will be provided for each scheduled assessment time by treatment group. Additionally, summaries of the changes from baseline will be provided.

### 7.2.4. Short Form Health Survey 36 (SF-36)

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

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

- Vitality
- Physical functioning
- Bodily Pain
- General Health Perceptions
- Physical Role Functioning
- Emotional Role Functioning
- Social Role Functioning
- Mental Health

All domain scores and component scores will be derived and collected on eCRF.

For each domain and component scores, comparison with regards to change from baseline 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.

Summary tables of each domain and component score will be provided for each scheduled assessment time by treatment group. Additionally, summaries of the changes from baseline will be provided.

### 7.2.5. Gout Flares Incidence and Frequency

The number and percentage of patients reporting gout flares per 3-months period and overall, i.e. Treatment Periods 1-3, Treatment Periods 4-6 and Periods 1-6, will be summarized by treatment group and will be tested using a CMH-test considering the randomization stratum. The same analysis will also be performed by patient's maximum severity of gout flare experienced within each 3-months period.

The frequency of gout flares will be summarized per 3-months period and overall and by severity for each treatment group and will be compared using ANOVA model with presence of tophus and treatment group 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.

### 7.2.6. Change from Baseline to Treatment Period 6 in Number of Tender and Swollen Joints

Comparison with regards to change in number of tender joints from baseline to end of treatment period 3 (day 0 period 4) and period 6 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 time point and for the change from baseline will be provided by treatment group.

Comparison with regards to change of swollen joints from baseline to end of treatment period 3 (day 0 period 4) and 6 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 time point and for the change from baseline will be provided by treatment group.

## 7.3. 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 may be conducted for patients who receive “additional gout flare treatment”. The statistical analysis and summaries described in sections 7.2.2 through 7.2.6 may be repeated for the subgroup of patients who receive “additional gout flare treatment” as well as by primary efficacy endpoint (responder vs. non-responder).

## 7.4. Deviation from Analyses Planned in Protocol

### 7.4.1. Additional analyses

The following analyses are added even though they are not included in the protocol:

- Interim analysis.
- Subgroup analyses on the secondary endpoint by patient’s primary efficacy endpoint (responder vs. non-responder).

The following analyses have been added as a result of the impact of Covid-19 on the study which may result in a larger anticipated number of subjects not completing the study and therefore not undergoing the assessments required for the primary efficacy endpoint or the study being stopped prematurely by sponsor decision. This is in line with FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic Guidance for Industry, Investigators, and Institutional Review Boards.

- Additional analyses suggested to primary endpoint as sensitivity analyses to determine if the impact that these have on the conclusions of the study and to describe the impact of Covid-19 on the study performance.
- A sensitivity analysis which limited the analysis to results processed in the central laboratory to determine if this resulted in different conclusions to those found from the full analysis to determine consistency in laboratory testing between central and local laboratories.
- Kaplan-Meier analysis of withdrawal from study by treatment arm and presence of tophus to determine if subjects withdraw from the study in different proportions and at different rates within the treatment groups and depending on the presence of tophus.
- Kaplan-Meier analysis of withdrawal from study due to an adverse event by treatment arm and presence of tophus to determine if subjects experience adverse events in different proportions and at different rates within the treatment groups and depending on the presence of tophus.
- Poisson regression with number of gout flares experienced during treatment periods 1-6 as the dependent variable, treatment and the presence of tophus as independent variables and length of follow up as a covariate. The ITT population would be used to conduct this analysis. Similar analysis is done for periods 4-6.

# 8. Safety

The population used for safety analyses will be the Safety Set (SS). Safety will be assessed on the basis of adverse event (AE), clinical laboratory data, ECG parameters, physical examinations, and vital signs.

## 8.1. 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.

Number and percentage of patients who met stopping rules will be summarized by treatment group and treatment period. The percentage will be plotted versus treatment period by treatment. The comparison between the treatment groups will be tested using CMH-test stratified by tophus presence (Yes/No).

## 8.2. Treatment Compliance

Treatment compliance is defined as patients receiving study drug as planned.

Compliance = 100% x (total volume infused) \ (total volume planned)

For patient who has received SEL-202, compliance will be calculated for SEL-110.36 and SEL-037.

For patient who has received KRYSTEXXA®, compliance will be calculated for KRYSTEXXA®.

Total duration of infusion as well as total time duration between start of infusion and stop of infusion will be descriptively summarized by study drug and dosing time point.

The date and time of the start and stop of drug administration, total infusion duration and volume infused will be listed.

## 8.3. 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 treatment, SOC and PT. 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).

An overall summary will be provided of the number and percentage of patients reporting TEAEs, serious TEAEs, treatment-related (possibly related and related) TEAEs, Adverse events of special interest (AESIs), TEAEs leading to study drug withdrawal, and TEAEs leading to death. AESIs will be defined by medical monitor prior to database lock.

The number and percentage of patients with TEAEs / serious TEAEs / TEAEs leading to study drug 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.

## 8.4. Laboratory Evaluations

Laboratory data will be summarized by the type of laboratory test and will be presented for each scheduled visit 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®).

### 8.5. 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®).

### 8.6. ECG

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

### 8.7. 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).

### 8.8. Physical Examination

A full physical examination will be performed at Screening, end of treatment period 6 or early termination visit and directed physical examinations will be collected at the beginning of each treatment period cycle.

Physical examination results will be presented in data listings.

# 9. DSMC and Interim Analyses

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

As discussed in section 2.2, An interim analysis will be conducted when 100% of patients are scheduled to have completed 3 months of study treatment (ie scheduled to have completed Treatment Period 4 Day 0 visit).

# 10. Reference List

Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992 Jun;30(6):473-83.

# 11. Programming Considerations

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

## 11.1. General Considerations

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

## 11.2. Table, Listing, and Figure Format

### 11.2.1. General

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

### 11.2.2. Headers

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

  SELECTA Biosciences
  Protocol SEL – 212/202
  Draft/Final Run *<date>*

- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

- The date output was generated should appear along with the program name as a footer on each page.

### 11.2.3. Display Titles

- Each TFL is identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but sponsor preferences are obtained before final determination A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the

- Column headers. There will be 1 blank line between the last title and the solid line.

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

### 11.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters

- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.

- For numeric variables, include “unit” in column or row heading when appropriate.

- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of patients in the analysis set.

- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

### 11.2.5. Body of the Data Display

#### 11.2.5.1. *General Conventions*

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

- Alphanumeric values are left-justified;

- Whole numbers (e.g., counts) are right-justified; and

- Numbers containing fractional portions are decimal aligned.

#### 11.2.5.2. *Table Conventions*

- Units will be included where available

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

| Severity Rating | N |
|---|---|
| severe | 0 |
| moderate | 8 |
| mild | 3 |

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

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 patient represented in 1 or more groups are included.

- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more patients.

- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

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

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Everyp-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999

- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within

the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated are reported as "-".

- The percentage of patients is normally calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of patients exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of patients) where a patient can be included in more than one category, describe in a footnote or programming note if the patient are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

#### 11.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, patient number, visit/collection day, and visit/collection time.

- Missing data are represented on patient listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on patient listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the patient are output as "N/A", unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

- Units will be included where available

#### 11.2.5.4. *Figure Conventions*

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

### 11.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.

- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.

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

# 12. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health SOP Developing Statistical Programs (3907) .

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.