Sponsor Name:	Selecta Biosciences
Protocol Number and Title:	**SEL-212/201: A 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**
Protocol Version and Date:	**Version: 7.1 (March 19, 2018)**
Syneos Health Project Code:	**1008142**
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SAP Version:	Final 2.0
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Syneos Health

Statistical Analysis Plan

Version: _Final 1.0_____ **Version Date:** _25JUL2018_____
_Final 2.0_____ **Version Date:** _12FEB2019_____

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

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
ADA	Anti-drug antibody
AE	Adverse event
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUCinf	Serum concentration-time curve from time 0 to infinity
AUClast	Serum concentration-time curve from time 0 to the time of last quantifiable concentration
CBC	Complete blood count
CL	Serum clearance of drug
Cmax	Maximum observed serum concentration
CRF	Case report form
CRO	Contract research organization
D	Day, Study day
dL	Deciliter
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
FAAN	Food Allergy & Anaphylaxis Network
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
H	Hour
HED	Human equivalent dose
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
Kel	Terminal elimination rate constant
kg	Kilograms
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
ml	Milliliters
MTD	Maximum tolerated dose
NIAID	National Institute of Allergy and Infectious Diseases
PD	Pharmacodynamic
PEG	Polyethylene glycol

Statistical Analysis Plan

Abbreviation	Description
PK	Pharmacokinetic
PTT	Partial thromboplastin time
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SEM	Standard error of the mean
t1/2	Terminal half-life
TEAE	Treatment-emergent adverse events
Tmax	Time at which Cmax occurred
ULN	Upper limit of normal
USP	United States Pharmacopeia
V	Visit
Vss	Apparent volume of distribution at equilibrium
Vd	terminal volume of distribution
C_{max}/C_{min}	Maximum/minimal observed serum concentration
T_{max}/T_{min}	Time of maximum/minimal observed serum concentration
CFB_{max}, CFB_{min}	Maximum/minimum observed change from baseline in serum concentration
T_{CFBmax}, T_{CFBmin}	Time of maximum/minimal observed change from baseline in serum concentration
$AUE_{CFBlast}$	Area under the change from baseline in effect-time curve from time zero to the time of the last quantifiable concentration (effect – uric concentration)
$TA\_AUE_{CFBlast}$	Time adjusted area under the effect-time curve from time zero to the time of last quantifiable concentration (effect – uric concentration)
T_{onset}	Time of onset of effect – time of reduction uric acid concentration >10% of baseline
$T_{resolve}$	Time of resolution of effect – time of return of uric acid concentration to baseline defined as <10% difference from pre-dose baseline
$T_{duration}$	Time of duration of effect, calculated as $T_{resolution} - T_{onset}$

Statistical Analysis Plan

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. TIMING OF ANALYSES

The analyses of safety, efficacy and pharmacokinetics (PK) is planned after all subjects complete the final study visit or terminate early from the study.

Statistical Analysis Plan

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

To assess the safety and tolerability of multiple intravenous (IV) infusions of SEL-212.

3.2. SECONDARY OBJECTIVES

To assess the PK, pharmacodynamics (PD) (ability to reduce circulating uric acid) and immunogenicity (anti-uricase, anti-PEG and anti-pegsiticase antibodies) of SEL-037 after multiple IV infusions of SEL-037 with or without multiple doses of SEL-110.

To assess the PK of rapamycin after multiple IV infusions of SEL-110 with multiple IV infusions of SEL-037.

3.3. EXPLORATORY OBJECTIVE

To assess the effect on uric acid deposits and/or total body uric acid deposited of multiple doses of SEL-037 alone or multiple doses of SEL-212 plus additional doses of SEL-037, as measured by Dual Energy Computed Tomography scan.

3.4. BRIEF DESCRIPTION

This is a Phase 2 (Part A) open-label multiple-dose clinical study of a combination drug (SEL-212) combined with an open-label multiple-dose clinical study of one drug (SEL-037) followed by (Part B) an open-label study of a single drug (SEL-037) to assess the safety, tolerability, PK, and PD of SEL-212 (the combination of SEL-110 [Rapamycin] and SEL-037 [pegsiticase]). Part C will involve patients naïve to SEL-212 who are treated with multiple doses of the combination drug (SEL-212).

The safety, tolerability, PK and PD of multiple doses of SEL-037 will be assessed. Additionally, the ability of SEL-212 to reduce serum uric acid and prevent anti-drug antibodies to uricase and pegsiticase will be assessed.

All enrolled subjects will be randomized initially to Cohorts 1, 2, 3, and 4 such that once 12 subjects total is reached for all 4 cohorts; each cohort will contain 3 subjects. The experience of these 12 subjects will guide the further conduct of the study. Adverse events, safety labs and the rate of infusion reactions in individual cohorts will dictate the continuance of a specific cohort. After the completion of at least one cycle, the subject experience will be evaluated before enrollment is opened to all cohorts. The future enrollment will be randomized between all open cohorts. At this time

Cohorts 1-10 are closed to enrollment. Randomization into the remaining open cohorts will continue until the cohorts are closed due to enrollment reaching 6-20 subjects per cohort or due to the stopping rules for individual cohorts. Cohorts that have closed due to enrollment levels may be re-opened to increase the enrollment to the maximum total number of subjects permitted.

3.5. SUBJECT SELECTION

3.5.1. Inclusion Criteria

1. Has provided written informed consent prior to the conduct of any study specific procedures and continues to provide consent;

2. Understands and is willing and able to comply with study requirements, including the schedule of follow-up visits, and has demonstrated compliance with study requirements during Screening;

3. At the Screening Visit male age 21 - 75, inclusive or female age 21-75 of non-child bearing potential;

4. Has at the Screening Visit a serum uric acid ≥ 6 mg/dL, with established or symptomatic gout which is defined as having at least ONE of any of the 3 following factors:

    a. ≥ 1 tophus

    b. 1 gout flare within the last 6 months

    c. Chronic gouty arthropathy

5. The use of allopurinol, febuxostat (Uloric®), or probenecid as uric acid-lowering therapy is permissible if dosing has been stable for at least the month prior to the Screening Visit and remains stable during the Screening Phase (i.e., no initiation, change in dose or discontinuation 1 month prior to screening and during screening).

6. Is negative for anti-PEG antibodies at the Screening Visit;

7. Has not participated in a clinical trial within 30 days of the Screening Visit and agrees to not participate in a clinical trial for the duration of the study;

8. Negative serology for HIV-1/-2 and negative antibodies to hepatitis C;

9. Has adequate venous access and able to receive IV therapy;

10. If applicable, has fully recovered from any prior surgery;

11. Is not presently receiving any vaccination scheme or have received a live virus vaccine in the previous 6 months.

3.5.2. Exclusion Criteria

1. History of anaphylaxis or severe allergic reactions;

2. History of any allergy to pegylated products, including peginterferon alfa-2a (Pegasys®), peginterferon alfa-2b (PegIntron®), pegfilgrastim (Neulasta®), pegaptanib (Macugen®), pegaspargase (Oncaspar®), pegademase (Adagen®), peg-epoetin beta (Mircera®), pegvisomant (Somavert®) certolizumab pegol (Cimzia®), naloxegol (Movantik®), peginesatide (Omontys®), pegaptanib (Macugen®) and doxorubicin liposome (Doxil®);

3. Medications which are known CYP3A4 inhibitors or inducers **MAY** be exclusionary. Patients taking medications that are known CYP3A4 inhibitors or inducers including natural products such as St. John's Wort or grapefruit juice may be included **ONLY** if they discontinue the medication 14 days before dosing and are able to remain off the medication for the duration of the study.

4. 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.

5. Women of child bearing potential, Defined as:

    - <6 weeks after surgical bilateral salpingooperhectony with or without hysterectomy

    - Pre or perimenopausal (< less than 24 months of natural amenorrhea)

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 one month the patient may be considered for the study if she continues to meet all other inclusion and exclusion criteria

7. Uncontrolled diabetes with baseline HbA1c ≥8%;
8. Fasting screening glucose greater than 240 mg/dL
9. Fasting triglyceride greater than 300 mg/dl;
10. Fasting LDL cholesterol greater than 200 mg/dl;
11. Glucose-6-phosphate dehydrogenase deficiency;
12. Uncontrolled hypertension: Blood pressure >170/100 at screening and 1 week prior to dosing
13. Individual laboratory values which may be exclusionary
    - White blood cell count less than 3.5 $x10^9$ /L
    - Serum aspartate aminotransferase (AST) or alanine amino transferase greater than 3x upper limit of normal (ULN) in the absence of known active liver disease
    - Glomerular filtration rate less than 40 ml/min/1.73 m^2
    - Hemoglobin less than 9 gm/dL
    - Serum phosphate less than 2.0 mg/dL
14. Ongoing treatment for arrhythmia, including placement of an implantable defibrillator;
15. History of coronary artery disease, including myocardial infarction;
16. Congestive heart failure, New York Heart Association Class III or IV;
17. 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;

18. History of hematological or autoimmune disorders, is immunosuppressed or immunocompromised;

19. Subject is currently taking dabigatran (Pradaxa®), rivaroxaban (Xarelto®), edoxaban (Savaysa®), warfarin (Coumadin®) and apixaban (Eliquis®).

20. Prior exposure to any experimental or marketed uricase (e.g., rasburicase (Elitek, Fasturtec), pegloticase (Krystexxa®), pegsiticase (SEL-037)

21. History of malignancy within the last 5 years other than basal skin cancer;

22. Subjects who, in the opinion of the investigator, present with a condition that would compromise their safety or that would make study completion unlikely.

3.6. DETERMINATION OF SAMPLE SIZE

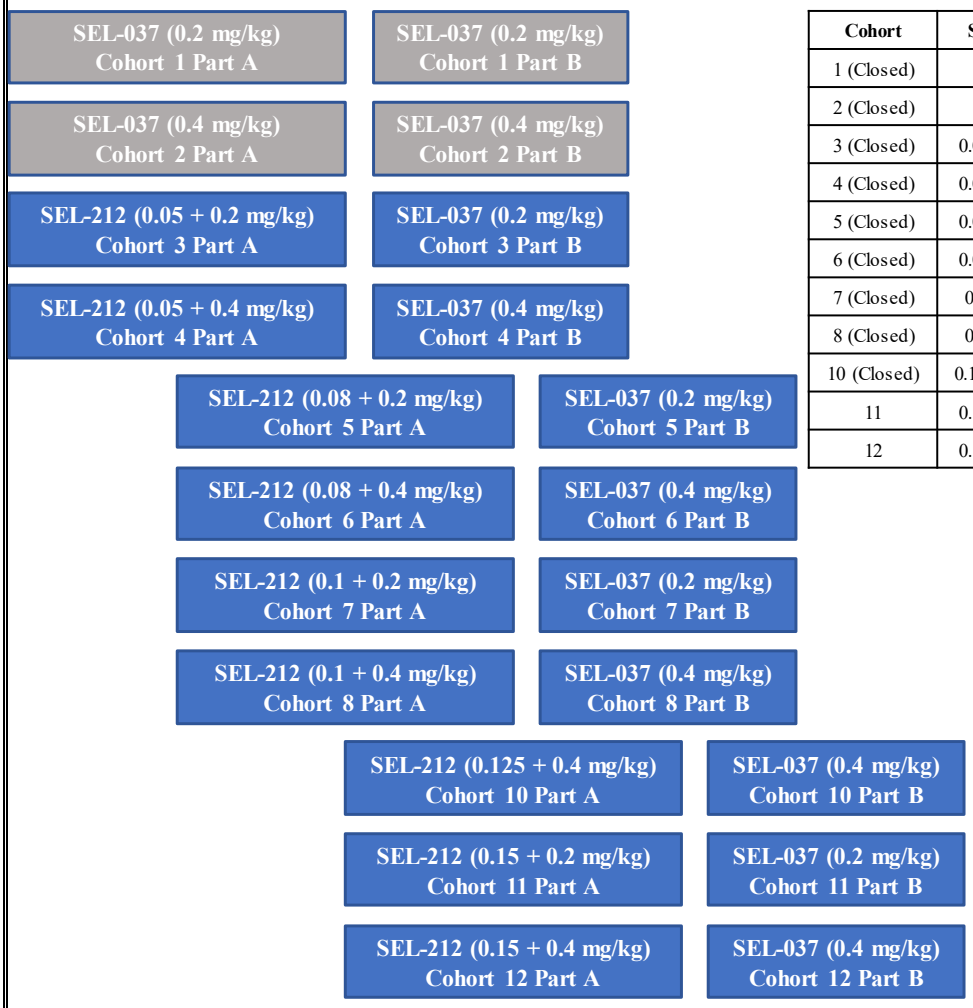
The sample size is designed to have a sufficient number of subjects per cohort to meet the objectives of the study, which are to evaluate the safety, tolerability, PK, and PD of a multiple IV infusions of SEL-212 and the safety, tolerability, PK, and PD of SEL-037 after multiple infusions.

3.7. TREATMENT ASSIGNMENT

Treatment and events are by the cohort to which each subject is assigned as following:

Statistical Analysis Plan

Overall scheme of trial (Part A and Part B)

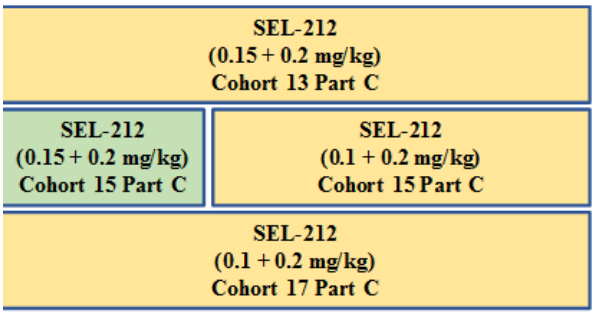


Cohort	SEL-110	SEL-037
1 (Closed)	NA	0.2 mg/kg
2 (Closed)	NA	0.4 mg/kg
3 (Closed)	0.05 mg/kg	0.2 mg/kg
4 (Closed)	0.05 mg/kg	0.4 mg/kg
5 (Closed)	0.08 mg/kg	0.2 mg/kg
6 (Closed)	0.08 mg/kg	0.4 mg/kg
7 (Closed)	0.1 mg/kg	0.2 mg/kg
8 (Closed)	0.1 mg/kg	0.4 mg/kg
10 (Closed)	0.125 mg/kg	0.4 mg/kg
11	0.15 mg/kg	0.2 mg/kg
12	0.15 mg/kg	0.4 mg/kg

Note: Cohort 9 is intentionally omitted from this protocol in order to maintain the cohort numbering convention of associating even numbered cohorts with the 0.4 mg/kg SEL-037 dose.

Statistical Analysis Plan

Overall scheme of trial (Part C)



Cohort	SEL-110	SEL-037
13	0.15 mg/kg	0.2 mg/kg
15 (first/induction dose)	0.15 mg/kg	0.2 mg/kg
15 (4 subsequent doses)	0.1 mg/kg	0.2 mg/kg
17	0.1 mg/kg	0.2 mg/kg

Note: Cohorts 14 and 16 are intentionally omitted from this protocol in order to maintain the cohort numbering convention of associating odd numbered cohorts with the 0.2 mg/kg SEL-037 dose.

In Part A and Part B, approximately 100 subjects will be divided into 11 dosing cohorts, each consisting of 6-20 subjects. Cohort 1 will receive SEL-037 (pegsiticase alone, 0.2 mg/kg). Cohort 2 will receive SEL-037 (pegsiticase alone, 0.4 mg/kg), Cohort 3 will receive SEL-212 (with 0.05 mg/kg of SEL-110 + 0.2 mg/kg pegsiticase), Cohort 4 will receive SEL-212 (with 0.05 mg/kg of SEL-110 + 0.4 mg/kg pegsiticase), Cohort 5 will receive SEL-212 (with 0.08 mg/kg of SEL-110 + 0.2 mg/kg pegsiticase), Cohort 6 will receive SEL-212 (with 0.08 mg/kg of SEL-110 + 0.4 mg/kg pegsiticase), Cohort 7 will receive SEL-212 (with 0.1 mg/kg of SEL-110 + 0.2 mg/kg pegsiticase) and Cohort 8 will receive SEL-212 (with 0.1 mg/kg of SEL-110 + 0.4 mg/kg pegsiticase), Cohort 10 will receive SEL-212 (with 0.125 mg/kg of SEL-110 + 0.4 mg/kg pegsiticase), Cohort 11 will receive SEL-212 (with 0.15 mg/kg of SEL-110 + 0.2 mg/kg pegsiticase), and Cohort 12 will receive SEL-212 (with 0.15 mg/kg of SEL-110 + 0.4 mg/kg pegsiticase). Note that Cohorts 9 is intentionally omitted in order to maintain the cohort numbering convention of associating even numbered cohorts with the 0.4 mg/kg SEL-037 dose.

In Part C, up to 40 patients naïve to SEL-212 will be enrolled. Patients enrolled in Cohort 13 will receive SEL-212 (0.15 mg/kg SEL-110 + 0.2 mg/kg SEL-037). Patients enrolled in Cohort 15 will receive an initial induction dose of SEL-212 (0.15 mg/kg SEL-110 + 0.2 mg/kg SEL-037) and, then, four subsequent doses of SEL-212 (0.10 mg/kg SEL-110 + 0.2 mg/kg SEL-037). Patients enrolled in Cohort 17 will receive SEL-212 (0.10 mg/kg SEL-110 + 0.2 mg/kg SEL-037). (Note: Cohort 14 and 16 are intentionally omitted in order to maintain the cohort numbering convention of associating odd numbered cohorts with the 0.2 mg/kg SEL-037 dose.) Subjects who withdraw early, or have significant protocol violations or compliance issues may be replaced at the discretion of the Sponsor to assure completion of the objectives of the clinical study and to maintain the integrity of the data set.

3.8. ADMINISTRATION OF STUDY MEDICATION

Duration of Treatment for Cohort 1 (0.2 mg/kg SEL-037 alone) and Cohort 2 (0.4 mg/kg SEL-037 alone) – BOTH COHORTS 1 and 2 CLOSED.

Part A - Treatment Period 1

Subjects will be screened within 45 days of dosing. Once they meet inclusion/exclusion criteria and all assessments are considered acceptable they will be instructed on when to start their premedication (date and medication, Day -7) for the prevention of gout flares. On the evening of Day -1 the subject will self-administer fexofenadine 180 mg as oral premedication. The day of initial dosing of study drug will be designated Day 0. In the morning (Day 0) subjects will report to the clinic for dosing of study drug. Two hours prior to the dosing of study drug SEL-037, subjects will receive fexofenadine 180 mg orally and 1 hour prior to the dosing of study drug SEL-037, subjects will receive methylprednisolone 40 (or equivalent drug) mg intravenously. Eligible subjects who have been assigned to Cohort 1 or 2 will receive a single IV infusion of normal saline (20 mL) with a syringe infusion pump over a period of 55 minutes starting concurrently with a 60 minute infusion of 125 mL of normal saline. This will be followed (± 1 minute) by an infusion delivered by infusion pump of SEL-037 (0.2 mg/kg for Cohort 1 or 0.4 mg/kg for Cohort 2) diluted into 100 mL of normal saline delivered over 60 minutes. Subjects will remain in the clinic for 9 hours after the start of the saline infusion for safety evaluations and PK blood draws (see Schedule of Events below). Subjects will return to the clinic for PK and PD blood draws on Treatment Period 1, Days 1, 7, 14 and 21 and Antibody blood draws on Treatment Period 1, Days 7, 14 and 21 and safety blood draws on Treatment Period 1, Day 14.

Part A - Treatment Period 2

On the evening of Treatment Period 2, Day -1 (27 ± 1 days from prior dosing) subjects will self-administer fexofenadine 180 mg orally. On the morning of Treatment Period 2, Day 0, subjects will report to the clinic for the dosing of study drug. 2 hours prior to the dosing of study drug SEL-037, subjects will receive fexofenadine 180 mg orally and 1 hour prior to the dosing of study drug SEL-037, subjects will receive methylprednisolone 40 mg (or equivalent drug) intravenously. Subjects will receive a single IV infusion of normal saline (20 mL) with a syringe infusion pump over a period of 55 minutes starting concurrently with a 60 minute infusion of 125 mL of normal saline. This will be followed (± 1 minute) by an infusion delivered by infusion pump of SEL-037 (0.2 mg/kg for Cohort 1 or 0.4 mg/kg for Cohort 2) diluted into 100 mL of normal saline delivered over 60 minutes. Subjects will remain in the clinic for 9 hours after the start of the saline infusion for safety evaluations and PK blood draws (see Schedule of Events below). Subjects will return to the clinic for PK and PD blood draws on Treatment Period 2, Days

1, 7, 14 and 21 and Antibody blood draws on Treatment Period 2, Days 7, 14 and 21 and safety blood draws on Treatment Period 2, Day 14.

Part A - Treatment Period 3

On the evening of Treatment Period 3, Day -1 (27 ± 1 days from prior dosing) subjects will self-administer fexofenadine 180 mg orally. On the morning of Treatment Period 3, Day 0, subjects will report to the clinic for the dosing of study drug. 2 hours prior to the dosing of study drug SEL-037, subjects will receive fexofenadine 180 mg orally 1 hour prior to the dosing of study drug SEL-037, subjects will receive methylprednisolone 40 mg (or equivalent drug) intravenously. Subjects will receive a single IV infusion of normal saline (20 mL) with a syringe infusion pump over a period of 55 minutes starting concurrently with a 60 minute infusion of 125 mL of normal saline. This will be followed (± 1 minute) by an infusion delivered by infusion pump of SEL-037 (0.2 mg/kg for Cohort 1 or 0.4 mg/kg for Cohort 2) diluted into 100 mL of normal saline delivered over 60 minutes. Subjects will remain in the clinic for 9 hours after the start of the saline infusion for safety evaluations and PK blood draws (see Schedule of Events below). Subjects will return to the clinic for PK and PD blood draws on Treatment Period 3, Days 1, 7, 14 and 21 and Antibody blood draws on Treatment Period 3, Days 7, 14 and 21 and safety blood draws on Treatment Period 3, Day 14.

Part B - Treatment Period 4

On the evening of Treatment Period 4, Day -1 (27 ± 1 days from prior dosing) subjects will self-administer fexofenadine 180 mg orally. On the morning of Treatment Period 4, Day 0 subjects will report to the clinic for the dosing of study drug. 2 hours prior to the dosing of study drug SEL-037, subjects will receive fexofenadine 180 mg orally 1 hour prior to the dosing of study drug SEL-037, subjects will receive methylprednisolone 40 mg (or equivalent drug) intravenously. Eligible subjects will receive a single IV infusion of SEL-037 (0.2 mg/kg for Cohort 1 or 0.4 mg/kg for Cohort 2) diluted into 100 mL of normal saline over 60 minutes by infusion pump. Subjects will remain in the clinic for 9 hours after the start of the saline infusion for safety evaluations and PK blood draws (see Schedule of Events below). Subjects will return to the clinic for PK and PD blood draws on Treatment Period 4, Days 1, 7, 14 and 21 and Antibody blood draws on Treatment Period 4, Days 7, 14 and 21 and safety blood draws on Treatment Period 4, Day 14.

Part B - Treatment Period 5

On the evening of Treatment Period 5, Day -1 (27 ± 1 days from prior dosing) subjects will self-administer fexofenadine 180 mg orally. On the morning of Treatment Period 5, Day 0 subjects will report to the clinic for the dosing of study drug. 2 hours prior to the dosing of study drug SEL-037, subjects will receive fexofenadine 180 mg orally and 1

hour prior to the dosing of study drug SEL-037, subjects will receive methylprednisolone 40 mg (or equivalent drug) intravenously. Eligible subjects will receive a single IV infusion of SEL-037 (0.2 mg/kg for Cohort 1 or 0.4 mg/kg for Cohort 2) diluted into 100 mL of normal saline over 60 minutes by infusion pump. Subjects will remain in the clinic for 9 hours after the start of the saline infusion for safety evaluations and PK blood draws (see Schedule of Events below). Subjects will return to the clinic for PK and PD blood draws on Treatment Period 5, Days 1, 7, 14 and 21 and Antibody blood draws on Treatment Period 5, Days 7, 14 and 21 and safety blood draws on Treatment Period 5, Day 14.

An End of Study visit will be performed on Treatment Period 5, Day 30 ± 1 day. Subjects who terminate participation early should have an End of Study visit assessments completed.

Duration of Treatment for Cohort 3 (0.05 mg/kg SEL-110 + 0.2 mg/kg SEL-037), Cohort 4 (0.05 mg/kg SEL-110 + 0.4 mg/kg SEL-037), Cohort 5 (0.08 mg/kg SEL-110 + 0.2 mg/kg SEL-037), Cohort 6 (0.08 mg/kg SEL-110 + 0.4 mg/kg SEL-037), Cohort 7 (0.1 mg/kg SEL-110 + 0.2 mg/kg SEL-037), Cohort 8 (0.1 mg/kg SEL-110 + 0.4 mg/kg SEL-037), Cohort 10 (0.125 mg/kg SEL-110 + 0.4 mg/kg SEL-037), Cohort 11 (0.15 mg/kg SEL-110 + 0.2 mg/kg SEL-037), and Cohort 12 (0.15 mg/kg SEL-110 + 0.4 mg/kg SEL-037)

Note: Cohorts 9 is intentionally omitted from this protocol in order to maintain the cohort numbering convention of associating even numbered cohorts with the 0.4 mg/kg SEL-037 dose.

Part A - Treatment Period 1

Subjects will be screened within 45 days of dosing. Once they meet inclusion/exclusion criteria and all assessments are considered acceptable they will be instructed on when to start their premedication (date and medication, Day -7) for the prevention of gout flares. On the evening of Day -1 the subject will take their premedication of fexofenadine 180 mg orally. The day of initial dosing of study drug will be designated Day 0. On the morning of Day 0 subjects will report to the clinic for the dosing of study drug. 2 hours prior to the dosing of study drug SEL-110, the subject will receive fexofenadine 180 mg orally and 1 hour prior to the dosing of study drug SEL-037, subjects will receive methylprednisolone 40 mg (or equivalent drug) intravenously. Eligible subjects who have been assigned to Cohorts 3- 8, 10, and 12 will receive a single IV infusion of SEL-110 (dose based on a mg/kg basis administered with a syringe infusion pump. In cohorts receiving SEL-110 doses<0.10 mg/kg, SEL-110 will be infused at a single steady rate sufficient to deliver the dose volume over a period of 55 minutes concurrently with a 60 minute infusion of 125 mL of normal saline. In cohorts receiving SEL-110 >0.10 mg/kg, the rate of SEL-110 infusion will be 5.5 mL/hour for the first 30

minutes. and, then, will be increased to a steady rate sufficient to deliver the remainder of the dose volume for the additional 25 minutes, concurrently with a 60 minute infusion of 125 mL of normal saline. This will be followed (± 3 minute) by an infusion delivered by infusion pump of SEL-037 (0.2 mg/kg for Cohorts 3 , 5 and 7; 0.4 mg/kg for Cohorts 4, 6, 8, 10 and 12) diluted into 100mL of normal saline delivered over 60 minutes (+/- 2 minutes). If necessary the infusion time may be extended in order to ensure the infusion of the study medication in entirety. Subjects will remain in the clinic for 9 hours after the start of the infusion of SEL-110 for safety evaluations and PK blood draws (see Schedule of Events below). Subjects will return for PK and PD blood draws on Treatment Period 1, Days 1, 7, 14, 21 and safety and Antibody blood draws on Treatment Period 1, Days 7, 14, 21.

Part A - Treatment Period 2

On the evening of Treatment Period 2, Day -1 (27 ± 1 days from prior dosing) subjects will self-administer fexofenadine 180 mg orally. On the morning of Treatment Period 2, Day 0, subjects will report to the clinic for the dosing of study drug. 2 hours prior to the dosing of study drug SEL-110, the subject will receive fexofenadine 180 mg orally and 1 hour prior to the dosing of study drug SEL-037, subjects will receive methylprednisolone 40 mg (or equivalent drug) intravenously. Eligible subjects who have been assigned to Cohorts 3- 8, 10, and 12 will receive a single IV infusion of SEL-110 (dose based on a mg/kg basis) administered with a syringe infusion pump. In cohorts receiving SEL-110 doses ≤0.10 mg/kg, SEL-110 will be infused at a single steady rate sufficient to deliver the dose volume over a period of 55 minutes concurrently with a 60 minute infusionof 125 mL of normal saline In cohorts receiving SEL-110 >0.10 mg/kg, the rate of SEL-110 infusion will be 5.5 mL/hour for the first 30 minutes. and, then, will be increased to a steady rate sufficient to deliver the remainder of the dose volume for the additional 25 minutes, concurrently with a 60 minute infusion of 125 mL of normal saline. This will be followed (± 3 minute) by an infusion delivered by infusion pump of SEL-037 (0.2 mg/kg for Cohorts 3, 5 and 7; 0.4 mg/kg for Cohorts 4, 6, 8, 10, and 12) diluted to 100 mL of normal saline delivered over 60 minutes. Subjects will remain in the clinic for 9 hours after the start of the infusion of SEL-110 for safety evaluations and PK blood draws (see Schedule of Events below). Subjects will return for PK and PD on Treatment Period 2, Days 1, 7, 14 and 21 and safety and Antibody blood draws on Treatment Period 2, Days 7, 14 and 21.

Part A - Treatment Period 3

On the evening of Treatment Period 3, Day -1 (27 ± 1 days from prior dosing) subjects will self-administer fexofenadine 180 mg orally the night before dosing. On the morning of Treatment Period 3, Day 0 subjects will report to the clinic for the dosing of study drug. 2 hours prior to the dosing of study drug SEL-110, subjects will receive

fexofenadine 180 mg orally and 1 hour prior to the dosing of study drug SEL-037, subjects will receive methylprednisolone 40 mg (or equivalent drug) intravenously. Eligible subjects who have been assigned to Cohorts 3- 8, 10, and 12 will receive a single IV infusion of SEL-110 (dose based on a mg/kg basis) administered with a syringe infusion pump at a single steady rate sufficient to deliver the dose volume over a period of 55 minutes concurrently with a 60 minute infusion of 125 mL of normal saline. In cohorts receiving SEL-110 >0.10 mg/kg, the rate of SEL-110 infusion will be 5.5 mL/hour for the first 30 minutes and, then, will be increased to a steady rate sufficient to deliver the remainder of the dose volume for the additional 25 minutes, concurrently with a 60 minute infusion of 125 mL of normal saline. This will be followed (± 3 minute) by an infusion delivered by infusion pump of SEL-037 (0.2 mg/kg for Cohorts 3, 5 and 7; 0.4 mg/kg for Cohorts 4, 6, 8, 10, and 12) diluted into 100mL normal saline delivered over 60 minutes. Subjects will remain in the clinic for 9 hours after the start of the infusion of SEL-110 for safety evaluations and PK blood draws (see Schedule of Events below). Subjects will return for PK and PD blood draws on Treatment Period 3, Days 1, 7, 14 and 21 and safety and Antibody blood draws on Treatment Period 3, Days 7, 14 and 21.

Part B - Treatment Period 4

On the evening of Treatment Period 4, Day -1 (27 ± 1 days from prior dosing) subjects will self-administer fexofenadine 180 mg. On the morning of Treatment Period 4, Day 0 subjects will report to the clinic for the dosing of study drug. 2 hours prior to the dosing of study drug SEL-110, subjects will receive fexofenadine 180 mg orally and 1 hour prior to the dosing of study drug SEL-037, subjects will receive methylprednisolone 40 mg (or equivalent drug) intravenously. Subjects will receive a single IV infusion of SEL-037 (0.2 mg/kg for Cohorts 3, 5 and 7; 0.4 mg/kg for Cohorts 4, 6 , 8, 10, and 12) diluted into 100 mL of normal saline over 60 minutes by infusion pump. Subjects will remain in the clinic for 9 hours after the start of the infusion of SEL-037 for safety evaluations and PK blood draws (see Schedule of Events below). Subjects will return for PK and PD blood draws on Treatment Period 4, Days 1, 7, 14 and 21 and safety and Antibody blood draws on Treatment Period 4, Days 7, 14 and 21.

Part B - Treatment Period 5

On the evening of Treatment Period 5, Day -1 (27 ± 1 days from prior dosing) subjects will self-administer fexofenadine 180 mg orally. On the morning of Treatment Period 5, Day 0 subjects will report to the clinic for the dosing of study drug. 2 hours prior to the dosing of study drug SEL-110, subjects will receive fexofenadine 180 mg orally and 1 hour prior to the dosing of study drug SEL-037, subjects will receive methylprednisolone 40 mg (or equivalent drug) intravenously. Subjects will receive a single IV infusion of SEL-037 (0.2 mg/kg for Cohorts 3, 5 and 7; 0.4 mg/kg for Cohorts 4, 6 , 8, 10, and 12) diluted into 100 mL of normal saline over 60 minutes by infusion pump. Subjects will

remain in the clinic for 9 hours after the start of the infusion of SEL-037 for safety evaluations and PK blood draws (see Schedule of Events below). Subjects will return for PK and PD blood draws on Treatment Period 5, Days 1, 7, 14 and 21 and safety and Antibody blood draws on Treatment Period 5, Days 7, 14 and 21.

An End of Study visit will be performed on Treatment Period 5, Day 30 ± 1 days. Subjects who terminate participation early should have an End of Study visit assessments completed.

Duration of treatment for Cohort 13 (0.15 mg/kg SEL-110 + 0.2 mg/kg SEL-037) , Cohort 15 (induction dose of 0.15 mg/kg SEL-110 + 0.2 mg/kg SEL-037 THEN 0.1 mg/kg SEL-110 + 0.2 mg/kg SEL-037),), and Cohort 17 (0.10 mg/kg SEL-110 + 0.2 mg/kg SEL 037)

Note: Cohort 14 and 16 are intentionally omitted from this protocol in order to maintain the cohort numbering convention of associating odd numbered cohorts with the 0.2 mg/kg SEL-037 dose.

Part C – Treatment period 1

Subjects will be screened within 45 days of dosing. Once they meet inclusion/exclusion criteria and all assessments are considered acceptable they will be instructed on when to start their premedication (date and medication, Day -7) for the prevention of gout flares. On the evening of Day -1 the subject will take their premedication of fexofenadine 180 mg orally.

The day of initial dosing of study drug will be designated Day 0. On the morning of Day 0 subjects will report to the clinic for the dosing of study drug. 2 hours prior to the dosing of study drug SEL-110, the subject will receive fexofenadine 180 mg orally and 1 hour prior to the dosing of study drug SEL-110, subjects will receive methylprednisolone 40 mg (or equivalent drug) intravenously. Eligible subjects assigned to Cohort 13, 15 and 17 will receive a single IV infusion of SEL-110 (dose based on a mg/kg basis) administered with a syringe infusion pump. The rate of SEL-110 infusion will be 5.5 mL/hour for the first 30 minutes and, then, will be changed to a steady rate sufficient to deliver the remainder of the dose volume for the additional 25 minutes, concurrently with a 60 minute infusion of 125 mL of normal saline. This will be followed (± 3 minutes) by an infusion delivered by infusion pump of 0.2 mg/kg SEL-037 diluted into 100 mL of normal saline delivered over 60 minutes (+/- 2 minutes). If necessary the infusion time may be extended in order to ensure the infusion of the study medication in entirety. Subjects will remain in the clinic for 9 hours after the start of the infusion of SEL-110 for safety evaluations and PK blood draws (see Schedule of Events below). Subjects will return for PK and PD blood draws on Treatment Period 1, Days 1, 7, 14, 21 and safety and Antibody blood draws on Treatment Period 1, Days 7, 14, 21.

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Part C – Treatment periods 2, 3, 4, and 5

On the evening of each of Treatment Periods 2-5, Day -1 (27 ± 1 days from prior dosing) subjects will self-administer fexofenadine 180 mg orally. On the morning of Treatment Period 2, Day 0, subjects will report to the clinic for the dosing of study drug. 2 hours prior to the dosing of study drug SEL-110, the subject will receive fexofenadine 180 mg orally and 1 hour prior to the dosing of study drug SEL-110, subjects will receive methylprednisolone 40 mg (or equivalent drug) intravenously. Eligible subjects who have been assigned to Cohorts 13, 15 and 17 will receive a single IV infusion of SEL-110 (dose based on a mg/kg basis) administered with a syringe infusion pump. The rate of SEL-110 infusion will be 5.5 mL/hour for the first 30 minutes and, then, will be changed to a steady rate sufficient to deliver the remainder of the dose volume for the additional 25 minutes, concurrently with a 60 minute infusion of 125 mL of normal saline. This will be followed (± 3 minutes) by an infusion delivered by infusion pump of 0.2 mg/kg SEL-037 diluted into 100 mL of normal saline delivered over 60 minutes (+/- 2 minutes). If necessary the infusion time may be extended in order to ensure the infusion of the study medication in entirety. Subjects will remain in the clinic for 9 hours after the start of the infusion of SEL-110 for safety evaluations and PK blood draws (see Schedule of Events below). Subjects will return for PK and PD on Days 1, 7, 14 and 21 of each treatment period and will return for safety and Antibody blood draws on Days 7, 14 and 21 of each treatment period.

Statistical Analysis Plan

3.9. STUDY PROCEDURES AND FLOWCHART

Table 1: Schedule of Events, Cohorts 1 & 2, Part A – Treatment Periods 1-3

Cohorts 1 & 2 Phases:	Screen	Outpatient visits		In Clinic										Outpatient Follow-up Visits				
Treatment Period #1; Visit (V); Day (D); Period (P)	V1 D-45 to -1	V2[11] P1 D-7	V3 P1 D-1	V4 P1 D0										V5 P1 D1	V6 P1 D7	V7 P1 D14	V8 P1 D21	Early Term
Treatment Period #2; Visit (V); Day (D); Period (P)			V9 P2 D-1	V10 P2 D0[5] (28 days after P1 D0)										V11 P2 D1	V12 P2 D7	V13 P2 D14	V14 P2 D21	Early Term
Treatment Period #3; Visit (V); Day (D); Period (P)			V15 P3 D-1	V16 P3 D0[5] (28 days after P2 D0)										V17 P3 D1	V18 P3 D7	V19 P3 D14	V20 P3 D21	Early Term
Hour (h)				Pre-dose	Infusion (time after dosing started) 0h	0.25h	0.5h	0.75h	1h	1.5h	Post-infusion (time after dosing started) 2h	3h	6h	9h	PK at 12h from D0 0h[9]	PK blood draws should occur at same time each visit ± 8 h from D0 0 hour[9]			
Informed Consent	X																	
Dual Energy CT Scan	X																	X
Inflammatory Markers	X																	X
T-Cell Recall				X[12]											X[13]			
Demographics	X																	
Inclusion/exclusion	X			X														
Medical History[1]	X			X														
Safety Examinations				Predose	0h	0.25h	0.5h	0.75h	1h	1.5	2h	3h	6h	9h					
Physical Examination	X																	X
Concomitant medications	← continuous →																	
Vital signs[2]	X			X			X		X	X	X	X	X	X	X	X	X	X	X
ECG[3]	X			X									X[10]						X
Adverse Events - Rheumatology CTC					← continuous →														
Safety Labs				Predose	0h	0.25h	0.5h	0.75h	1h	1.5h	2h	3h	6h	9h					
Safety Labs - As indicated in individual schedules[4]	X			X													X		X
Immunogenicity																			
Anti-Pegsitica se				X												X	X	X	X
Anti-Uricase				X												X	X	X	X
Anti-PEG	X			X												X	X	X	X
PK/PD Assessments																			
SEL-110 PK																			
SEL-037 PK				X											X	X	X	X	X
Uricase Activity				X						X	X	X	X	X	X	X	X	X	X
Uric Acid	X			X						X	X	X	X	X	X	X	X	X	X
Study Treatment				Predose	0h	0.25h	0.5h	0.75h	1h	1.5h	2h	3h	6h	9h					
Study drug IV (Saline) : 0-55min					IV Saline														
Study drug IV (SEL-037) : 60-120 min									IV SEL-037										
Premedicate against Gout Flare[5]		X																	
Premedicate against infusion reaction[6]			X(-12h)	X (-2h)															
Premedicate against infusion reaction[7]				X (-1h)															

1 - Confirm no active vaccinations
2 - Blood pressure after sitting 5 minutes, heart rate, oral temperature, respiratory rate
3 - If a conflict occurs due to multiple assessments occurring at the same time point, the ECG may be performed +/- 30 minutes from the designated time
4 - All Safety Labs indicated in individual schedule by cohort
5 - Premedicate with colchicine 0.6 mg QD beginning at D-7 for duration of study
6 - Premedicate with fexofenadine at -12h ± 2h and -2h ± 1h prior to dose
7 - Additionally premedicate with IV methylprednisolone at -1h ± 0.5 h
8 - Window for visit is +/- 1 day
9 - Blood work as subset of listed points per schedules in Appendices by cohort
10 - ECG at 6 hr ONLY for Treatment Period 1, not for Treatment Periods 2 nor 3
11 - Gout flare premedication can be started during screening interval and does not require an on-site visit
12 - T-Cell recall sample ONLY for Treatment Period 1 (Visit 4) only
13 - T-Cell recall sample ONLY for Treatment Period 3 (Visit 18) only

Statistical Analysis Plan

Table 2: Schedule of Events, Cohorts 1 & 2, Part B – Treatment Periods 4-5

Cohorts 1 & 2 Phases:	Out patient	In Clinic											Outpatient Follow-up Visits					
Treatment Period #4; Visit (V); Day (D); Period (P)	V21	V22											V23	V24	V25	V26		Early Term
	P4 D-1	P4 D0[8] (28 days after P3 D0)											P4 D1	P4 D7	P4 D14	P4 D21		
Treatment Period #5; Visit (V); Day (D); Period (P)	V27	V28											V29	V30	V31	V32	P5 D21 to D30	Early Term / EOS P5 D30[8,10]
	P5 D-1	P5 D0[8] (28 days after P4 D0)											P5 D1	P5 D7	P5 D14	P5 D21		
Hour (h)		Pre-dose	Infusion (time after dosing started) 0h	0.25h	0.5h	0.75h	Post-infusion (time after dosing started) 1h	1.5h	2h	3h	6h	9h	PK at ±2h from D0 0h[9]	PK blood draws should occur at same time each visit ± 8 h from D0 0 hour[9]				
Informed Consent																		
Dual Energy CT Scan																	X	X
Inflammatory Markers																	X	X
T-Cell Recall														X[11]				
Demographics																		
Inclusion/exclusion		X																
Medical History[1]		X																
Safety Examinations		Predose	0h	0.25h	0.5h	0.75h	1h	1.5	2h	3h	6h	9h						
Physical Examination																		X
Concomitant medications		← continuous →																
Vital signs[2]		X		X	X	X	X	X	X	X	X		X	X	X	X		X
ECG[3]		X																X
Adverse Events - Rheumatology CTC			← continuous →															
Safety Labs		Predose	0h	0.25h	0.5h	0.75h	1h	1.5h	2h	3h	6h	9h						
Safety Labs - As indicated in individual schedules[4]		X													X			X
Immunogenicity																		
Anti-Pegsitacase		X												X	X	X		X
Anti-Uricase		X												X	X	X		X
Anti-PEG		X												X	X	X		X
PK/PD Assessments																		
SEL-110 PK																		
SEL-037 PK		X											X	X	X	X		X
Uricase Activity		X			X		X	X	X	X	X		X	X	X	X		X
Uric Acid		X			X		X	X	X	X	X		X	X	X	X		X
Study Treatment		Predose	0h	0.25h	0.5h	0.75h	1h	1.5h	2h	3h	6h	9h						
Study drug IV (SEL-037) : 0-60min			IV SEL-037															
Premedicate against Gout Flare[5]																		
Premedicate against infusion reaction[6]	X(-12h)	X (-2h)																
Premedicate against infusion reaction[7]		X (-1h)																

1 - Confirm no active vaccinations
2 - Blood pressure after sitting 5 minutes, heart rate, oral temperature, respiratory rate
3 - If a conflict occurs due to multiple assessments occurring at the same time point, the ECG may be performed +/- 30 minutes from the designated time
4 - All Safety Labs indicated in individual schedule by cohort
5 - Premedicate with colchicine 0.6 mg QD beginning at D-7 for duration of study
6 - Premedicate with fexofenadine at -12h ± 2h and -2h ± 1h prior to dose
7 - Additionally premedicate with IV methylprednisolone at -1h ± 0.5h
8 - Window for visit is +/- 1 day
9 - Blood work as subset of listed points per schedules in Appendices by cohort
10 - DECT and inflammatory markers at EOS unless done at previous P5 visit
11 - T-Cell recall sample ONLY for Treatment Period 5 (Visit 30) only

Statistical Analysis Plan

Table 3: Schedule of Events, Cohorts 3-8, 10, 11, and 12, Part A – Treatment Periods 1-3

Cohorts 3 - 8, 10, 11, & 12 Phases:	Screen	Outpatient Visits		In Clinic										Outpatient Follow-up Visits				
Treatment Period #1; Visit (V); Day (D); Period (P)	V1 D-45 to -1	V2[11] P1 D-7	V3 P1 D-1	V4 P1 D0										V5 P1 D1	V6 P1 D7	V7 P1 D14	V8 P1 D21	Early Term
Treatment Period #2; Visit (V); Day (D); Period (P)			V9 P2 D-1	V10 P2 D0[8] (28 days after P1 D0)										V11 P2 D1	V12 P2 D7	V13 P2 D14	V14 P2 D21	Early Term
Treatment Period #3; Visit (V); Day (D); Period (P)			V15 P3 D-1	V16 P3 D0[8] (28 days after P2 D0)										V17 P3 D1	V18 P3 D7	V19 P3 D14	V20 P3 D21	Early Term
Hour (h)				Pre-dose	Infusion (time after dosing started) 0h	0.25h	0.5h	0.75h	1h	1.5h	Post-infusion (time after dosing started) 2h	3h	6h	9h	PK at ±2h from D0 0h[9]	PK blood draws should occur at same time each visit ± 8 h from D0 0 hour[9]			
Informed Consent	X																	
Dual Energy CT Scan	X																X[15]	X
Inflammatory Markers				X[12]														X
T-Cell Recall				X[12]												X[13]		X
Demographics	X																	
Inclusion/exclusion	X			X														
Medical History[1]	X			X														
Safety Examinations				Predose	0h	0.25h	0.5h	0.75h	1h	1.5	2h	3h	6h	9h					
Physical Examination	X																	X
Concomitant medications	← continuous →																	
Vital signs[2]	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X																X	
ECG[3]	X			X									X[10]					X
Adverse Events - Rheumatology CTC				← continuous →														
Safety Labs				Predose	0h	0.25h	0.5h	0.75h	1h	1.5h	2h	3h	6h	9h					
Safety Labs - As indicated in individual schedules[4]	X			X												X	X	X	X
Immunogenicity																			
Anti-Pegsitacase				X												X	X	X	X
Anti-Uricase				X												X	X	X	X
Anti-PEG	X			X												X	X	X	X
PK/PD Assessments																			
SEL-110 PK				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
SEL-037 PK				X											X	X	X	X	X
Uricase Activity				X					X	X	X	X	X	X	X	X	X	X	X
Uric Acid	X			X					X	X	X	X	X	X	X	X	X	X	X
Study Treatment				Predose	0h	0.25h	0.5h	0.75h	1h	1.5h	2h	3h	6h	9h					
Study drug IV (SEL-110) : 0-55min[14]					IVSEL-110														
Study drug IV (SEL-037) : 60-120 min									IVSEL-037										
Premedicate against Gout Flare[5]		X																	
Premedicate against infusion reaction[6]			X(-12h)	X (-2h)															
Premedicate against infusion reaction[7]				X (-1h)															

1 - Confirm no active vaccinations
2 - Blood pressure after sitting 5 minutes, heart rate, oral temperature, respiratory rate
3 - If a conflict occurs due to multiple assessments occurring at the same time point, the ECG may be performed +/- 30 minutes from the designated time
4 - All Safety Labs indicated in individual schedule by cohort
5 - Premedicate with colchicine 0.6 mg QD beginning at D-7 for duration of study
6 - Premedicate with fexofenadine at -12h ± 2h and -2h ±1h prior to dose
7 - Additionally premedicate with IV methylprednisolone at -1h ± 0.5h
8 - Window for visit is +/- 1 day
9 - Blood work as subset of listed points per schedules in Appendices by cohort
10 - ECG at 6 hr ONLY for Treatment Period 1, not for Treatment Periods 2 nor 3
11 - Gout flare premedication can be started during screening interval and does not require an on-site visit
12 - T-Cell recall sample and Inflammatory marker sample ONLY for Treatment Period 1 (Visit 4) only
13 - T-Cell recall sample ONLY for Treatment Period 3 (Visit 18) only
14 - In cohorts receiving SEL-110 doses <0.10 mg/kg, SEL-110 will be infused at a single steady rate sufficient to deliver the dose volume over a period of 55 minutes concurrently with a 60 minute infusion of 125 mL of normal saline. In cohorts receiving ≥0.10 mg/kg SEL-110, the rate of SEL-110 infusion will be 5.5 mL/hour for the first 30 minutes and, then, will be changed to a steady rate sufficient to deliver the remainder of the dose volume for the additional 25 minutes, concurrently with a 60 minute infusion of 125 mL of normal saline.
15 - DECT is permitted to be performed at any time between Days 21-28 (inclusive) of Treatment Period 3.

Note: Cohorts 9 is intentionally omitted from the protocol in order to maintain the cohort numbering convention of associating even numbered cohorts with the 0.4 mg/kg SEL-037 dose.

Statistical Analysis Plan

Table 4: Schedule of Events, Cohorts 3-8, 10, 11, and 12, Part B - Treatment Periods 4-5

Cohorts 3 - 8, 10, 11, & 12 Phases:	Out patient	In Clinic										Outpatient Follow-up Visits					
Treatment #4; Visit (V); Day (D)	V21 P4 D-1	V22 P4 D0[8] (28 days after P3 D0)										V23 P4 D1	V24 P4 D7	V25 P4 D14	V26 P4 D21		Early Term
Treatment #5; Visit (V); Day (D)	V27 P5 D-1	V28 P5 D0[8] (28 days after P4 D0)										V29 P5 D1	V30 P5 D7	V31 P5 D14	V32 P5 D21	P5 D21 to D30	Early Term / EOS P5 D30[8,10,13]
Hour (h)		Pre-dose	Infusion (time after dosing started) 0h	0.25h	0.5h	0.75h	Post-Infusion (time after dosing started) 1h	1.5h	2h	3h	6h	9h	PK at ±2h from D0 0h[9]	PK blood draws should occur at same time each visit ± 8 h from D0 0 hour[9]				
Informed Consent																	
T-Cell Recall													X[12]				X
Dual Energy CT Scan																X	X
Inflammatory Markers																X	X
Demographics																	
Inclusion/exclusion	X																
Medical History[1]	X																
Safety Examinations		Predose	0h	0.25h	0.5h	0.75h	1h	1.5	2h	3h	6h	9h						
Physical Examination																	X
Concomitant medications	← continuous →																
Vital signs[2]		X		X	X	X	X	X	X	X	X		X	X	X	X		X
Weight																X		
ECG[3]		X																X
Adverse Events - Rheumatology CTC	← continuous →																	
Safety Labs		Predose	0h	0.25h	0.5h	0.75h	1h	1.5h	2h	3h	6h	9h						
Safety Labs - As indicated in individual schedules[4]		X												X	X	X		X
Immunogenicity																		
Anti-Pegsitacase		X												X	X	X		X
Anti-Uricase		X												X	X	X		X
Anti-PEG		X												X	X	X		X
PK/PD Assessments																		
SEL-110 PK		X[11]																X
SEL-037 PK		X											X	X	X	X		X
Uricase Activity		X			X		X	X	X	X	X		X	X	X	X		X
Uric Acid		X			X		X	X	X	X	X		X	X	X	X		X
Study Treatment		Predose	0h	0.25h	0.5h	0.75h	1h	1.5h	2h	3h	6h	9h						
Study drug IV (SEL-037) : 0-60min			IV SEL-037															
Premedicate against Gout Flare[5]																		
Premedicate against infusion reaction[6]	X(-12h)	X (-2h)																
Premedicate against infusion reaction[7]		X (-1h)																

1 - Confirm no active vaccinations
2 - Blood pressure after sitting 5 minutes, heart rate, oral temperature, respiratory rate
3 - If a conflict occurs due to multiple assessments occurring at the same time point, the ECG may be performed +/- 30 minutes from the designated time
4 - All Safety Labs indicated in individual schedule by cohort
5 - Premedicate with colchicine 0.6 mg QD beginning at D-7 for duration of study
6 - Premedicate with fexofenadine at -12h ± 2h and -2h ± 1h prior to dose
7 - Additionally premedicate with IV methylprednisolone at -1h ± 0.5h
8 - Window for visit is +/- 1 day
9 - Blood work as subset of listed points per schedules in Appendices by cohort
10 - DECT and inflammatory markers at EOS unless done at previous P5 visit
11 - Predose sample collected on Treatment Period 4 only
12 - T-Cell recall sample ONLY for Treatment Period 5 (Visit 30) only
13 - Additional observational visit at Treatment Period 5, Day 60 may be required as per section 10.1.1

Note: Cohorts 9 is intentionally omitted from the protocol in order to maintain the cohort numbering convention of associating even numbered cohorts with the 0.4 mg/kg SEL-037 dose.

Statistical Analysis Plan

Table 5: Schedule of Events, Cohorts 13, 15, and 17 Part C - Treatment Periods 1-5

Cohorts 13, 15, & 17 Phases:	Screen	Outpatient Visits		In Clinic											Outpatient Follow-up Visits					
Treatment Period #1; Visit (V); Day (D); Period (P)	V1 D-45 to -1	V2[11] P1 D-7	V3 P1 D-1	V4 P1 D0											V5 P1 D1	V6 P1 D7	V7 P1 D14	V8 P1 D21		Early Term
Treatment Period #2; Visit (V); Day (D); Period (P)			V9 P2 D-1	V10 P2 D0[2] (28 days after P1 D0)											V11 P2 D1	V12 P2 D7	V13 P2 D14	V14 P2 D21		Early Term
Treatment Period #3; Visit (V); Day (D); Period (P)			V15 P3 D-1	V16 P3 D0[2] (28 days after P2 D0)											V17 P3 D1	V18 P3 D7	V19 P3 D14	V20 P3 D21		Early Term
Treatment Period #4; Visit (V); Day (D); Period (P)			V21 P4 D-1	V22 P4 D0[2] (28 days after P3 D0)											V23 P4 D1	V24 P4 D7	V25 P4 D14	V26 P4 D21		Early Term
Treatment Period #5; Visit (V); Day (D); Period (P)			V27 P5 D-1	V28 P5 D0[2] (28 days after P4 D0)											V29 P5 D1	V30 P5 D7	V31 P5 D14	V32 P5 D21	P5 D21 to D30	Early Term / EOS P5 D30[8,15,16]
Hour (h)				Pre-dose	Infusion (time after dosing started) 0h	0.25h	0.5h	0.75h	1h	1.5h	Post-infusion (time after dosing started) 2h	3h	6h	9h	PK at ≥2h from D0 0h[9]	PK blood draws should occur at same time each visit ± 8 h from D0 0 hour[9]				
Informed Consent	X																			
T-Cell Recall	X			X[12]												X[13]				X
Dual Energy CT Scan	X																	X[14]	X	X
Inflammatory Markers				X												X			X	X
Demographics	X																			
Inclusion/exclusion	X			X																
Medical History[7]	X			X																
Safety Examinations				Predose	0h	0.25h	0.5h	0.75h	1h	1.5	2h	3h	6h	9h						
Physical Examination	X																			X
Concomitant medications	← continuous →																			
Vital signs[3]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Weight	X																	X		
ECG[3]	X			X									X[10]							X
Adverse Events - Rheumatology CTC				← continuous →																
Safety Labs				Predose	0h	0.25h	0.5h	0.75h	1h	1.5h	2h	3h	6h	9h						
Safety Labs - As indicated in individual schedules[4]	X			X												X	X	X		X
Immunogenicity																				
Anti-Pegsitcase				X												X	X	X		X
Anti-Uricase				X												X	X	X		X
Anti-PEG	X			X												X	X	X		X
PK/PD Assessments																				
SEL-110 PK				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
SEL-037 PK				X											X	X	X	X		X
Uricase Activity				X					X	X	X	X	X	X	X	X	X	X		X
Uric Acid[18]	X			X					X	X	X	X	X	X	X	X	X	X		X
Study Treatment				Predose	0h	0.25h	0.5h	0.75h	1h	1.5h	2h	3h	6h	9h						
Study drug IV (SEL-110) : 0-55min[14]					IV SEL-110															
Study drug IV (SEL-037) : 60-120 min									IV SEL-037											
Premedicate against Gout Flare[5]		X																		
Premedicate against infusion reaction[6]			XI(-12h)	X (-2h)																

1 - Confirm no active vaccinations
2 - Blood pressure after sitting 5 minutes, heart rate, oral temperature, respiratory rate
3 - If a conflict occurs due to multiple assessments occurring at the same time point, the ECG may be performed +/- 30 minutes from the designated time
4 - All Safety Labs indicated in individual schedule by cohort
5 - Premedicate with colchicine 0.6 mg QD beginning at D-7 for duration of study
6 - Premedicate with fexofenadine at -12h ± 2h and -2h ± 1h prior to dose
7 - Additionally premedicate with IV methylprednisolone at -1 h ± 0.5h
8 - Window for visit is +/- 1 day
9 - Blood work as subset of listed points per schedules in Appendices by cohort
10 - ECG at 6 hr ONLY for Treatment Period 1, not for Treatment Periods 2, 3, 4 nor 5
11 - Gout flare premedication can be started during screening interval and does not require an on-site visit
12 - T-Cell recall sample ONLY for Treatment Period 1 (Visit 4) only
13 - T-Cell recall sample ONLY for for Treatment Period 3 (Visit 18) and Treatment Period 5 (Visit 30) only
14 - DECT ONLY for Treatment Period 3 and is permitted to be performed at any time between Days 21-28 (inclusive) of Treatment Period 3.
15 - Only 1 Inflammatory marker and 1 DECT sample to be collected for the end of Treatment Period 5 - may be done at V32, between V32 and EOS or at EOS Visit or at ET Visit
16 - Additional observational visit at Treatment Period 5, Day 60 may be required as per section 10.1.1
17 - In cohorts receiving ≥0.10 mg/kg SEL-110, the rate of SEL-110 infusion will be 5.5 mL/hour for the first 30 minutes and, then, will be changed to a steady rate sufficient to deliver the remainder of the dose volume for the additional 25 minutes. concurrently with a 60 minute infusion of 125 mL of normal saline.
18 - Collect 2 blood samples at each timepoint for sUA measurement. Store and ship 1 sample at ambient temperature and 1 sample under frozen conditions. Refer to the Laboratory Manual for details about sample handling.

Note: Cohorts 14 and 16 are intentionally omitted from the protocol in order to maintain the cohort numbering convention of associating odd numbered cohorts with the 0.2 mg/kg SEL-037 dose.

4. ENDPOINTS

4.1. PHARMACOKINETIC ENDPOINTS

The following PK parameters will be calculated on SEL-037 and SEL-110 (rapamycin) PK concentration as well as uricase activity separately for each analyte and type of PK assessment using noncompartmental intravascular infusion log-linear model for each Cohort and Treatment Period where possible and summarized statistically:

C_{max}	Maximum observed PK concentration or activity
T_{max}	Time of maximum observed PK concentration or activity
C_{last}	Last observed PK concentration or activity
T_{llast}	Time of last observed PK concentration or activity
$AUC_{0\text{-}last}$	Area under the serum concentration-time curve from time zero to the time of the last quantifiable PK concentration or activity
$AUC_{0\text{-}inf}$	Area under the PK concentration or activity-time curve from time zero extrapolated to infinity
$t_{1/2}$	Terminal elimination half-life
λ_z	Terminal elimination rate constant
CL	Clearance of drug
V_d	Terminal volume of distribution

Additional PK parameters may be calculated as needed. Change from baseline in uricase activity may be used for derivation of PK parameters in addition to actual measured activity.

Multiple dose parameters will be also derived where possible:

C_{min}	Min observed trough PK concentration or activity
T_{min}	Time of min observed PK concentration or activity
C_{ave}	Average observed PK concentration or activity
AUC_{tau}	Area under the PK concentration or activity from time 0 to the end of dosing interval
% Fluctuation	Difference between C_{max} and C_{min} normalized by average concentration
R_{AUCtau}	Accumulation ratio based on comparison of AUC_{tau} between last and first dose
R_{Cmax}	Accumulation ratio based on comparison of C_{max} between last and first dose
R_{Cmin}	Accumulation ratio based on comparison of C_{min} between last and first dose
CL_{ss}	Steady state clearance (if steady state is achieved)

4.2. PHARMACODYNAMIC ENDPOINTS

The following PD parameters will be calculated on PD uric acid for each Cohort and Treatment period and Overall where possible. The parameters will be derived for actual measurements of uric acid as well as for % change from baseline:

C_{min}	Minimal observed serum concentration
T_{min}	Time of minimal observed serum concentration
CFB_{min}	Minimum observed change from baseline in serum concentration
$AUE_{CFBlast}$	Absolute value for Area under the change from baseline in effect-time curve from time zero to the time of the last quantifiable concentration (effect – uric concentration)
$TA\_AUE_{CFBlast}$	Time adjusted area under the absolute value for effect-time curve from time zero to the time of last quantifiable concentration (effect – uric concentration)
T_{onset}	Time of onset of effect – first time point of reduction uric acid concentration >10% of baseline
$T_{resolve}$	Time of resolution of effect – first time point of return of uric acid concentration to baseline defined as <10% difference from pre-dose baseline
$T_{duration}$	Time of duration of effect, calculated as $T_{resolve}$ - T_{onset}

4.3. SAFETY ENDPOINTS

The primary objective of this study is to assess the safety and tolerability of multiple IV infusions of SEL-212. Safety assessments will be based on medical review of adverse event (AE) reports and the results of vital sign measurements, electrocardiograms (ECGs), physical examinations, and clinical laboratory tests. These endpoints will be measured at the time points specified in the protocol in Section 1.1, Schedules of Events. The primary endpoints are frequencies of AEs, serious AEs (SAEs), AEs leading to discontinuation, and ECG and laboratory abnormalities occurring up to 30 days after the last dose of study medication.

4.4. IMMUNOGENICITY ENDPOINTS

Immunogenicity endpoints include occurrence of anti-PEG, anti-pegsiticase, and anti-uricase specific antibodies based on screening assay; and the titer for the anti-pegsiticase antibodies, where the confirmation assay is also available. Frequency of occurrence of antibodies by study day and overall by cohort, time of onset immunogenicity, and time of resolution of immunogenicity will be calculated and summarized by treatment in summary tables. Time of onset is defined as the first time point with positive ADA (anti-drug antibodies) result; time of resolution is defined as the

first time point when a previously observed positive ADA result returns to baseline. Titers of antibodies against PEG, uricase and pegsiticase will be listed.

5. ANALYSIS SET

5.1. SCREENED/RANDOMIZED SUBJECTS

- Screened subjects are defined as all subjects who signed an informed consent; Screen Failure Subjects are defined as all subjects who were screened but not dosed.

- Randomized subjects are defined as all subjects who are assigned a randomization number.

5.2. SAFETY ANALYSIS SET

The safety analysis set will include all subjects who are randomized and have drug exposure. The safety analysis set will be used for all analyses of safety endpoints.

5.3. PHARMACOKINETIC ANALYSIS SET

The PK analysis set will include all subjects who are randomized, dosed with any amount of study drug, and for whom PK data are available with no significant protocol violations or deviations that would significantly affect the PK evaluation of the drug.

Factors that may influence serum SEL-037 concentrations and/or the whole blood rapamycin concentrations (e.g., interruptions in the infusion or changes in the infusion rate) will be reviewed. If an influencing factor is present, a decision will be made by the responsible pharmacokineticist, whether to include or exclude the specific sample or subject. If a whole blood rapamycin concentration sample or a serum SEL-037 concentration sample is the subject of an ongoing investigation at the time of databased lock, the corresponding tables, figures and listings involving that sample may be calculated additionally with the exclusion of the sample in question. All subjects and samples excluded from the analysis will be clearly documented in the study report.

5.4. PHARMACODYNAMIC ANALYSIS SET

The PD analysis set will include will include all subjects who are randomized, receive any amount of study drug, and have at least one post-baseline assessment of sUA is available. Uric acid concentrations will be listed for all subjects in PD analysis set.

All available PD data will be included in the listings; the PD data will be evaluated for protocol violations or deviations that would significantly affect the PD evaluation of the drug. Profiles or individual time points with such violations or deviations will be flagged and may be excluded from summary statistics and the derivation of PD parameters. Examples to treat as the deviations will be but not limited to:

1) Dose interruptions in their SEL-037 dose such that only partial doses were delivered – PD profiles may be excluded from summaries and may be used in analyses with actual dose of SEL-037 used if possible

2) Dose interruptions in their SEL-110 dose such that only a partial dose of SEL-110 and/or NO DOSE of SEL-037 was administered (since only SEL-037 will cause sUA to be reduced) – the profiles for the treatment period with deviation will be excluded from summaries and may be used for additional analyses without SEL-037 if needed; the data for prior periods will be included

3) Subjects who have a dose interruption during SEL-110 administration in the 1st treatment period and so do not ever receive SEL-037 but do have measured sUA values – as above, may be used for additional analyses without SEL-037 if needed post-hoc.

5.5. PROTOCOL DEVIATIONS

All protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management, dosing, and sampling procedures or subject assessment will be listed. The list of protocol deviations will be reviewed by the Sponsor, the medical director at Syneos Health , the study statistician and the study pharmacokineticist and finalized before database lock.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

SAS® version 9.3 will be used for all statistical analyses and tabulations.

In general, summaries will present data by treatment/cohort 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 windows, 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. The data for the EOS visit at day 140 will be separated from the Early Termination visit data and will be summarized for all the subjects within the defined population who reached this visit. An additional observational visit for subjects with <6 mg/dL uric acid concentration on day 140 (approx. 30 days after last dose) were scheduled at approx. 170 days from 1st dose. The data for the observational visit will be reported and summarized for all subjects participating in this visit. Data for Early Termination visits will be listed with actual day from dose included and will not be summarized. The last result for repeat test at screening visit will be considered as final and will be included in summaries. Previous results will be listed but not summarized.

Adverse events and medical history will be coded according to the most recent Medical Dictionary for Regulatory Activities (MedDRA) version. Prior and concomitant medications will be coded using the most recent WHO Drug Dictionary version.

Derivation of PK parameters will be performed using Phoenix WinNonLin 6.4 or higher on a Windows 7 platform or higher.

6.2. KEY DEFINITIONS

The last non-missing value prior to the start of infusion of any study drug in Period 1 will be used as baseline.

6.3. MISSING DATA

The handling of missing PK data is detailed in SAP section 8.2.1.

The handling of missing PD data is detailed in SAP section 9.3.1.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

Subject disposition will be listed. Summary tables reflecting the number of subjects for the following will be presented:

- Screened subjects
- Randomized subjects
- Safety analysis set
- PK analysis set
- PD analysis set
- Subjects who complete the study
- Subjects who early terminate the study and reasons for early termination

Screen Failure subjects will be listed.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic characteristics such as sex, age, race, and ethnicity will be summarized for Safety Analysis Set, by treatment and overall. Demographic characteristics will be also listed for Safety Analysis Set.

7.3. MEDICAL HISTORY AND CONCOMITANT DISEASES

Medical history will be listed by treatment and subject. Summaries will be provided. Medical history will be coded by using the most recent (MedDRA®) version.

7.4. MEDICATION

Concomitant therapy includes any medication (eg, prescription drugs, over-the-counter drugs, vaccines, topical medications, herbal or homeopathic remedies, nutritional supplements) used by a subject from 3 months prior to screening to the last study visit. All such medications should be reported to the investigator and 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 subject's eligibility to participate or continue to participate in the study.

Statistical Analysis Plan

The original verbatim terms collected in the eCRF for concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD September 2015 version) into drug class (Anatomical Therapeutic Classification [ATC] level 4) and preferred term.

Concomitant medication will be listed and summarized.

8. ANALYSIS OF PHARMACOKINETICS

The PK analysis set will be used to calculate PK parameters, graphical displays of individual data, and the listings of PK concentrations and parameters, and for all PK summaries. Subjects with missing PK parameters due to unreliable or missing data will be flagged and excluded from summarization.

Concentrations of pegsiticase and uricase activity in serum at different time points will be used as measures of the PK of SEL-037. Concentrations of rapamycin in whole blood will be used to characterize the PK of SEL-110.

The Parts A/B (Treatment periods 1-3 and 4-5 for cohorts 1-8, 10-12 respectively) will be presented together, Part C (cohorts 13 and 15) will be presented separately unless necessary for comparative analysis.

Statistical Analysis Plan

8.1. COLLECTION SCHEDULE

Cohorts 1-2

Period	Day	Time from start of dose for saline, h	Time from start of dose for SEL-037, h	
			SEL-037 PK concentration	Uricase activity
1-3	0	0	-1 (0)	-1 (0)
		1.5		0.5
		2		1
		3		2
		6		5
		9		8
	1	24	23	23
	7	168	167	167
	14	336	335	335
	21	504	503	503
	28*	672	671	671
4-5	0		0	0
			0.5	0.5
			1	1
			1.5	1.5
			2	2
			3	3
			6	6
	1		24	24
	7		168	168
	14		336	336
	21		504	504
	28**		672	672
	30***		720	720

* - pre-dose for next Treatment period
** - PK point for Treatment period 4 as pre-dose for Treatment period 5
*** - last point for Treatment period 5 only

Repeat the same for other periods

Statistical Analysis Plan

Cohorts 3-8, 10, 11, 12

Period	Day	Time from start of dose for SEL-110, h	Time from start of dose for SEL-037, h	
		SEL-110 concentration	SEL-037 PK concentration	Uricase activity
1-3	0	0	-1 (0)	-1 (0)
		0.25		
		0.5		
		0.75		
		1.5	0.5	
		2	1	
		3	2	
		6	5	
		9	8	
	1	24	23	23
	7	168	167	167
	14	336	335	335
	21	504	503	503
	28*	672	671	671
4-5	0		0	
			0.5	
			1	
			1.5	
			2	
			3	
			6	
	1		24	24
	7		168	168
	14		336	336
	21		504	504
	28**		672	672
	30***		720	720

* - pre-dose for next Treatment period
** - PK point for Treatment period 4 as pre-dose for Treatment period 5
*** - last point for Treatment period 5 only

Cohorts 13, 15, 17

Period	Day	Time from start of dose for SEL-110, h	Time from start of dose for SEL-037, h	
		SEL-110 concentration	SEL-037 PK concentration	Uricase activity
1-5	0	0	-1 (0)	-1 (0)
		0.25		
		0.5		
		0.75		
		1.5	0.5	
		2	1	
		3	2	
		6	5	
		9	8	
	1	24	23	23
	7	168	167	167
	14	336	335	335
	21	504	503	503
	28*	672	671	671
	30**		720	720

* - pre-dose for next Treatment period
** - last point for Treatment period 5 only

8.2. PHARMACOKINETIC PARAMETERS

The following PK parameters will be calculated on SEL-037 and SEL-110 (rapamycin) PK concentration as well as uricase activity using noncompartmental intravascular infusion log-linear model for each Cohort and Treatment Period where possible and summarized statistically:

C_{max}	Maximum observed PK concentration or activity
T_{max}	Time of maximum observed PK concentration or activity
C_{last}	Last observed PK concentration or activity
T_{last}	Time of last observed PK concentration or activity
$AUC_{0\text{-}last}$	Area under the serum concentration-time curve from time zero to the time of the last quantifiable PK concentration or activity
$AUC_{0\text{-}inf}$	Area under the PK concentration or activity-time curve from time zero extrapolated to infinity
$t_{1/2}$	Terminal elimination half-life
λ_z	Terminal elimination rate constant
CL	Clearance of drug
V_d	Terminal volume of distribution

Statistical Analysis Plan

Additional PK parameters may be calculated as needed.

Multiple dose parameters will be also derived where possible:

C_{min}	Min observed trough PK concentration or activity
T_{min}	Time of min observed PK concentration or activity
C_{ave}	Average observed PK concentration or activity
AUC_{tau}	Area under the PK concentration or activity from time 0 to the end of dosing interval
% Fluctuation	Difference between C_{max} and C_{min} normalized by average concentration
R_{AUCtau}	Accumulation ratio based on comparison of AUC_{tau} between last and first dose
R_{Cmax}	Accumulation ratio based on comparison of C_{max} between last and first dose
R_{Cmin}	Accumulation ratio based on comparison of C_{min} between last and first dose
CL_{ss}	Steady state clearance (if steady state is achieved)

Dose dependent parameters for SEL-110 (C_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$) will be dose normalized for comparison between treatments involving different doses of SEL-037.

The PK parameters will be estimated as follows:

The apparent C_{max} and the corresponding T_{max} will be read directly from the concentration-time plot (observed data, not predicted data by the program);

AUCs will be calculated using the linear-log trapezoidal rule;

The terminal elimination rate constant (λ_z) will be determined by log linear regression obtained on at least the 3 last quantifiable concentrations and will not include C_{max}. The adjusted square of the correlation coefficient (Rsquare adjusted) for the goodness of fit of the regression line through the data points must be at least 0.8500 for the λ_z value to be considered reliable;

$t_{1/2}$ is calculated by the program as $\ln 2/\lambda_z$;

If the time interval between the lower and upper time points used for the regression spans less than the derived half-life itself then λ_z and the associated $t_{1/2}$ will be considered unreliable;

The AUC from 0 to infinity is calculated by the program as:

$AUC_{inf} = AUC_{last} + AUC_{last\text{-}inf}$ where last is the sampling time point of the last measurable concentration (t_{last}). $AUC_{last\text{-}inf}$ is calculated by the program as: C_{last}/λ_z, where C_{last} is the

observed concentration at time t_{last} and λ_z is the elimination rate constant during the apparent terminal elimination phase; AUC_{inf} will only be presented for subjects with a reliable λ_z;

The AUC extrapolation to infinity must be ≤20% of the total area for AUC_{inf} to be considered reliable;

CL is calculated by program as (dose/AUC_{inf})

V_d is calculated by the program as (dose/AUC_{inf})/ λ_z.

For subjects with unreliable λ_z (ie, Rsquare adjusted <0.8500, interval for λ_z calculation shorter than $t_{1/2}$, number of points to calculate λ_z <3), λ_z, $t_{1/2}$, AUC_{inf}, CL and V_d will be flagged in the individual data.

For subjects with unreliable AUC_{inf} (because of extrapolation >20%), AUC_{inf}, CL and V_d will be flagged in the individual data.

Flagged PK parameters will be excluded from summarization and statistical analyses.

8.2.1. Handling of Dropouts, Missing Data or Data Below the Lower Limit of Quantification

Missing concentration data for all subjects who are administered scheduled study treatments will be considered as non-informative missing and will not be imputed for each treatment period individually. The missing data will not affect analyses for the previous treatment periods where complete dose were administered and PK profiles available. No concentration estimates will be provided for missing sample values.

For the derivation of PK parameters, the following rules will apply:

Concentration values below the assay's lower limit of quantification (BLQ) in pre-dose samples and in samples taken before the time of the first quantifiable concentration will be treated as zero.

The sampling time of pre-dose samples relative to dosing will also be treated as zero.

Post-dose BLQ values after the first quantifiable time point will be set to missing.

If the actual time of sampling is missing, the planned time may be used.

Samples taken outside the sampling windows may be excluded from by-time point summary statistics. This will be determined prior start of analyses around timing for database lock.

For serum or whole blood concentration summary, individual concentration versus time curves and mean concentration versus time graphs, the following rules will apply:

- Serum or whole blood concentrations BLQ in pre-dose samples and in samples taken before the time of the first quantifiable value will be set to zero
- The serum or whole blood concentrations BLQ after quantifiable concentration will be set to zero

No further imputation will be applied to any missing values.

8.3. DATA SUMMARIZATION

PK parameters and serum (SEL-037) or whole blood (SEL-110) concentration data will be summarized by treatment using the following descriptive statistics:

Variable	Summarized with:
Serum or whole blood concentration at each nominal time point	n, number and % BLQ, arithmetic mean, SD, coefficient of variance (CV) %, minimum, median and maximum
AUC, C_{max}, CL and V_d	n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV%
$t_{1/2}$, and λ_Z	n, arithmetic mean, SD, CV%, minimum, median, maximum
T_{max} (actual time)	n, minimum,Q1, median, Q3 and maximum

Note: CV% = SD/mean in %.
%BLQ = 100 * (total number of subjects who have BLQ values/total number of subjects within each cohort at each time point)

Mean concentrations will not be presented if 30% or more of the actual values for PK analysis set at any one time point in the terminal phase are BLQ or missing.

Samples taken outside the allowed time windows may be excluded from summarization. This will be determined prior to database lock.

The following conventions will be used for the presentation of the descriptive statistics of PK parameters and of serum or whole blood concentrations:

PK Reporting Precision

Statistics	Degree of Precision
Minimum, Maximum	3 significant digits or as needed based on actual measured values (for example PK concentrations)
Mean (arithmetic and geometric), Median	4 significant digits or as needed based on actual measured values (for example PK concentrations)
Standard deviation	5 significant digits or as needed based on actual measured values (for example PK concentrations)
CV% and Geometric CV%	1 decimal point or as needed based on actual measured values (for example PK concentrations)

8.4. DATA PRESENTATION FOR SEL-110 AND SEL-037

The actual sampling time of PK blood sample collection will be listed for each cohort and will include the deviation in time from the protocol scheduled time, if applicable.

Individual subject serum (SEL-037) or whole blood (SEL-110) concentration data will be listed by subject, time point and treatment (in relevant concentration units) and will be summarized at each time point by cohort. Individual subject PK parameters will be listed for the PK analysis set in a table by subject and will be summarized, by treatment group/cohort. Unreliable PK parameters will be listed but flagged and excluded from the summary.

PK parameters of secondary interest, namely Rsquare adjusted, the number of data points used for estimating λ_z, the upper and lower time point used for estimation of λ_z, and the % AUC extrapolation from t_{last} to infinity will be listed by subject and dose level/cohort to enable verification of the exclusions, if any, of data from the summary statistics of the PK parameters of primary interest.

The following figures will be produced for SEL-110:

Mean ± SD whole blood concentration-time profiles will be presented, combining the curves for all treatment periods within the same figure for each cohort separately. Individual whole blood concentration-time profiles will be presented, for each cohort with all subjects in the same figure on linear and log-linear scales – 3 curves on the plot

for 3 treatment periods for Part A (cohorts 1-8, 10-12, treatment periods 1-3). For Part C of the study (cohorts 13, 15) the presentation will include 5 curves for treatment periods 1-5 on the same plot.

Additional mean ± SD whole blood concentration-time profiles will be presented, combining the curves for all dose levels of SEL-110 separately in Part A for cohorts with 0.2 mg/kg SEL-037 (cohorts 3, 5, 7, 11) and 0.4 mg/kg SEL-037 (cohorts, 4, 6, 8, 10, 12) within the same figure for each of the three treatment periods 1-3 on a separate plot – 4 and 5 curves respectively, 6 plots total for 3 treatment periods.

The following figures will be produced for SEL-037:

Mean ± SD serum concentration-time profiles will be presented on linear and log-linear scales for all Treatment periods within the same figure for each cohort separately. PK concentrations of SEL-037 and uricase activity will be also presented on the same plot with double Y axes for each Cohort and Treatment period separately.

Additionally mean ± SD serum concentration-time profiles will be presented on linear and log-linear scales for all cohorts in Parts A/B with 0.2 mg/kg SEL-037 (cohorts 1, 3, 5, 7, 11) or 0.4 mg/kg dose levels (cohorts 2, 4, 6, 8, 10, 12) within the same figure for each treatment period separately. Cohorts 13, 15 in Part C of the study will be presented separately.

Individual serum concentration-time profiles will be presented, for each Cohort and Treatment period with all subjects in the same figure on linear and log-linear scales.

Regression/scatter plots for SEL-037 PK parameters (C_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$) for dose levels 0.2 and 0.4 mg/kg separately versus dose of SEL-110 (for cohorts 1 and 2, the SEL-110 dose level will be set to 0) on the same plot for each parameter individually. The plots will be produced for all treatment periods in Part A of the study separately and can be combined for treatment periods 1-3 with Part C data cohorts 13, 15 as additional plot.

8.5. ASSESSMENT OF DOSE PROPORTIONALITY FOR SEL-110

Exploratory dose proportionality will be analyzed with the method originally described by Gough et al. (1995)[1] and modified as described by Smith et al. (2000)[2] and further adapted by Hummel et al. (2009)[3]. Hereby Analyses of Variance model (ANOVA) method will be performed on the logarithm e transformed PK parameter endpoints: C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$, C_{min} and AUC_{tau} for all treatment periods 1-3 in Part A of the study. Additional analysis may combine Part A data with the data from Part C treatment periods 1-3. The model will include log e-transformed SEL-110 dose level as independent variable. This model will be used to investigate the null hypothesis (H0:

ß=1). Dose-proportionality will be rejected if the 90% confidence interval (CI) of the estimated slope falls outside the critical interval. The linear form of the model will be as following:

$Y_{ij} = \alpha + \beta * X_i + \varepsilon_{ij}$

Where:

- Y_{ij} = logarithm of the pharmacokinetic endpoint for subject j at dose level i; where i = 1, 2, …m, j = 1, 2, …, n
- α = intercept parameter
- ß = slope parameter
- X_i = logarithm of dose i
- ε_{ij} = random error associated with subject j at dose level i (assumed to be independent and identically normally distributed).

An example SAS code will be:

```
PROC MIXED DATA=xx ALPHA = .1;
MODEL loge(PK parameter) = loge(dose of SEL-110) / CL;
RUN;
```

The critical interval will be calculated as follows: First the ratio (r) of the highest dose level to the lowest dose level will be calculated. The lower limit of the critical interval will be calculated as: Ln (0.5)/ln(r) + 1. The upper limit of the critical interval will be calculated as: Ln (2.0)/ln(r) + 1.

r value is based on the ratio between highest and lower dose levels of SEL-110 and equals to 0.15 / 0.05 mg/kg = 3

Thus critical interval to declare dose linearity will be 0.37 to 1.63 for 90% confidence interval of the slope estimate.

The effect of SEL-037 doses may be explored by including them as fixed covariate effect in the model. p-value for SEL-037 dose will be presented.

Additionally PK parameters C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$, C_{min}, AUC_{tau} with total dose and body weight adjusted dose will be investigated using Pearson correlation analysis to estimate which type of dosing has an effect on pharmacokinetics of SEL-110. The correlations for combination with 0.2 and 0.4 mg/kg SEL-037 will be explored separately and overall. The data for Parts A and C (treatment periods 1-3 only) will also be combined in the separate table.

The FISHER option in the PROC CORR statement will be used to estimate confidence limits and p-values for Pearson correlation coefficients based on Fisher's z transformation. Alpha value and a null hypothesis value will be specified for 95% two-sided confidence interval.

Dose proportionality analysis for both Hummel power analysis and Pearson correlation analysis will be also presented graphically as described in Section 8.4 of the SAP. Dose proportionality plots will be presented for SEL-110 C_{max} and $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}last}$ for Part A only and for combined data from Parts A and C treatment periods 1-3.

8.6. ASSESSMENT OF DOSE PROPORTIONALITY FOR SEL-037

Single and multiple dose PK parameters for SEL-037 PK concentrations or uricase activity C_{max}, C_{min}, $AUC_{0\text{-}last}$, AUC_{tau} normalized by dose of SEL-037 will be compared between cohorts 1, 3, 5, 7, 11 with 0.2 mg/kg and 2, 4, 6, 8, 10, 12 with 0.4 mg/kg doses of SEL-037 using ANOVA model separately for Parts A and B and each treatment period and combined data for Parts A and C (treatment periods 1-3 only).

For Part A of each cohort, the dose of SEL-110 will be included as fixed effect in this comparison.

The dose normalized PK parameters for SEL-037 will be presented on box plots for each treatment and part separately and overall for all cohorts with the same dose level for comparison for Parts A and B and separately for combined data Parts A and C (treatment periods 1-3).

8.7. ASEESSMENT OF EFFECT OF VARIOUS DOSES OF SEL-110 ON PHARMACOKINETICS OF SEL-037

Effect of co-administration of various doses of SEL-110 on pharmacokinetics of SEL-037 PK parameters for serum concentrations or uricase activity for cohorts 1, 3, 5, 7, 11 (SEL-037 dose 0.2 mg/kg) and 2, 4, 6, 8, 10, 12 (SEL-037 dose 0.4 mg/kg) separately (SEL-110 dose in cohorts 1 and 2 will be set to 0) will be performed by a linear mixed-effect model:

$$PKparam(SEL-037) = \alpha + s_i + \beta \times Dose(SEL-110) + e_i$$

α: population mean intercept

β: population mean slope

s_i: random effect of subject i on the intercept, iid N(0, σ_s^2)

e_i: residual, iid N(0, $б_e$) for subject i

Statistical Analysis Plan

the PK parameters and dose of SEL-110 will not be log-transformed to allow inclusion of 0 dose of SEL-110 into the model

P value will be calculated for slope and intercept. If the p-value of the slope is less than 0.05, a direct relationship is declared. If p value for slope will be >0.05 the result will be interpreted as lack of effect of SEL-110 on pharmacokinetics of SEL-037.

SEL-110 co-administration effect will also be explored graphically with scatter plots of C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ for SEL-037 serum concentrations or uricase activity vs dose levels of co-administered SEL-110 including 0 dose for placebo.
The example SAS code will be:

```
PROC MIXED DATA=data_set_name;
CLASS treatment;
MODEL PK Parameter = dose /DDFM=KR;
LSMEANS dose / CL;
RUN;
```

Additionally the effect of SEL-110 on PK of SEL-037 will be performed by comparison of data from Parts B vs Part C for treatment periods 4-5 using ANOVA model as described in the Section 8.6 of the SAP.

The contrasts will include:

Cohort 13 treatment period 4 vs Cohort 11 treatment period 4
Cohort 13 treatment period 5 vs Cohort 11 treatment period 5
Cohort 15 treatment period 4 vs Cohort 11 treatment period 4
Cohort 15 treatment period 5 vs Cohort 11 treatment period 5
Cohort 15 treatment period 4 vs Cohort 13 treatment period 4
Cohort 15 treatment period 5 vs Cohort 13 treatment period 5

Graphic presentation in the form of box plots will be also added to the exploratory analysis.

9. ANALYSIS OF PHARMACODYNAMICS

9.1. MEASUREMENTS

Concentration of uric acid in serum will be used as measure of PD for both drugs. The concentration-time profile of uric acid is used to determine PD parameters as described in section 9.3. PD parameters will be derived based on actual measurements and %CFB (%CFB = value of change from baseline at each time point / value of measurement at baseline * 100%) for each cohort and treatment period and overall where applicable.

The Parts A/B (Treatment periods 1-3 and 4-5 for cohorts 1-8, 10-12 respectively) will be presented together, Part C (cohorts 13 and 15) will be presented separately unless necessary for comparative analysis.

9.2. COLLECTION SCHEDULE

Venous blood samples with corresponding time post-dose for uric acid are shown in table below:

Cohorts 1-2

Period	Day	Time from start of dose for saline, h	Time from start of dose for SEL-037, h
1-3	0	0	-1 (0)
		1.5	0.5
		2	1
		3	2
		6	5
		9	8
	1	24	23
	7	168	167
	14	336	335
	21	504	503
	28*	672	671
4-5	0		0
			0.5
			1
			1.5
			2
			3
			6
	1		24
	7		168

Statistical Analysis Plan

Period	Day	Time from start of dose for saline, h	Time from start of dose for SEL-037, h
	14		336
	21		504
	28**		672
	30***		720

* - pre-dose for next Treatment period
** - PD point for Treatment periods 4 as pre-dose for Treatment period6
*** - last point for Treatment period 5 only

Cohorts 3-8, 10, 11, 12

Period	Day	Time from start of dose for saline, h	Time from start of dose for SEL-037, h
1-3	0	0	-1 (0)
		1	0
		1.5	0.5
		2	1
		3	2
		6	5
		9	8
	1	24	23
	7	168	167
	14	336	335
	21	504	503
	28*	672	671
4-5	0		0
			0.5
			1
			1.5
			2
			3
			6
	1		24
	7		168
	14		336
	21		504
	28**		672
	30***		720

* - pre-dose for next Treatment period
** - PD point for Treatment periods 4 as pre-dose for Treatment period6
*** - last point for Treatment period 5 only

Cohorts 13, 15

Period	Day	Time from start of dose for saline, h	Time from start of dose for SEL-037, h
1-5	0	0	-1 (0)
		1	0
		1.5	0.5
		2	1
		3	2
		6	5
		9	8
	1	24	23
	7	168	167
	14	336	335
	21	504	503
	28*	672	671
	30**		720

* - pre-dose for next Treatment period
** - last point for Treatment period 5 only

9.3. PHARMACODYNAMICS PARAMETERS

The following PD parameters will be calculated based on actual measurements of PD uric acid for each Cohort and Treatment period and Overall where possible:

C_{min}	Minimal observed serum concentration
T_{min}	Time of minimal observed serum concentration
CFB_{min}	Minimum observed change from baseline in serum concentration
$AUE_{CFBlast}$	Absolute value for Area under the change from baseline in effect-time curve from time zero to the time of the last quantifiable concentration (effect – uric concentration)
$TA\_AUE_{CFBlast}$	Time adjusted area under the absolute value for effect-time curve from time zero to the time of last quantifiable concentration (effect – uric concentration)
T_{onset}	Time of onset of effect – first time point of reduction uric acid concentration >10% of baseline
$T_{resolve}$	Time of resolution of effect – first time point of return of uric acid concentration to baseline defined as <10% difference from pre-dose baseline
$T_{duration}$	Time of duration of effect, calculated as $T_{resolve}$ - T_{onset}

The following PD parameters will be calculated based on %CFB of PD uric acid for each Cohort and Treatment period and Overall where possible

$\%CFB_{min}$	Minimum %CFB in serum concentration
$AUE_{\%CFBlast}$	Absolute value for Area under the %CFB in effect-time curve from time zero to the time of the last quantifiable concentration (effect – uric concentration)
$TA\_AUE_{\%CFBlast}$	Time adjusted area under the %CFB for effect-time curve from time zero to the time of last quantifiable concentration (effect – uric concentration)
# and % of patients with SUA<6 in TP3	The number and % of patients maintaining sUA concentrations below 6 mg/dL at the end of treatment period 3
# and % of patients with SUA<6 in TP5	The number and % of patients maintaining sUA concentrations below 6 mg/dL at the end of treatment period 5

9.3.1. Handling of Dropouts, Missing Data or Data Below the Lower Limit of Quantification

Missing concentration data for all subjects who are administered scheduled study treatments will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

For the derivation of PD parameters, serum concentration summary, individual serum concentration versus time curves and mean concentration versus time graphs the following rules will apply:

- Concentration values below the assay's lower limit of quantification (BLQ) for all time points will be treated as zero
- The sampling time of pre-dose samples relative to dosing will also be treated as zero
- If the actual time of sampling is missing, the planned time may be used
- In case of discrepancy between the nominal time and time stamp on the sample concentration data, which affects the temporal order of PD samples and is not related to documented protocol deviations, the nominal (planned) time will be used only for the pre-dose samples before treatment period 1. All other data with such time discrepancy will be removed from PD parameter derivations and summaries. The profiles for subjects with the single PD points removed due to this type of discrepancy can still be used for derivation of PD parameters and any summaries or models for other PD time points.

Samples taken outside the sampling windows may be excluded from by-time point summary statistics. This will be determined prior to the start of analyses around database lock.

No further imputation will be applied to any missing values.

9.4. DATA SUMMARIZATION

PD parameters and serum concentration data will be summarized by Treatment period and Cohort using the following descriptive statistics:

PD Summary Statistics:

Variable	Summarized with:
Serum concentration at each nominal time point	n, number and % BLQ, arithmetic mean, SD, CV%, minimum, median and maximum
CFB_{min}, $\%CFB_{min}$, $AUE_{CFBlast}$, $AUE_{\%CFBlast}$ and $TA\_AUE_{CFBlast}$, $TA\_AUE_{\%CFBlast}$	n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV%
T_{onset}, $T_{resolve}$, $T_{duration}$, and T_{min} (actual time)	n, minimum, Q1, median, Q3 and maximum

Mean concentrations will not be presented if 50% or more of the available observations relative to total number of subjects within the treatment at any time point are missing. BLQ values for uric acid concentration will be summarized as 0 (zero) for all time points.

Samples taken outside the allowed time windows may be excluded from summarization. This will be determined prior to database lock.

The following conventions will be used for the presentation of the descriptive statistics of PD parameters and serum concentrations for uric acid:

PD Reporting Precision:

Statistics	Degree of Precision
Minimum, Maximum	3 significant digits or as needed based on actual measured values (for example PD concentrations)
Mean (arithmetic and geometric), Median	4 significant digits or as needed based on actual measured values (for example PD concentrations)
Standard deviation	5 significant digits or as needed based on actual measured values (for example PD concentrations)
CV, Geometric CV	1 decimal point or as needed based on actual measured values (for example PD concentrations)

9.5. DATA PRESENTATION FOR DUAL ENERGY COMPUTED TOMOGRAPHY (DECT) SCANS

Dual energy computed tomography (CT) scans will be performed as an exploratory measure for at least 2 subjects in Cohorts 10, 11, and 12 during the screening interval, between Days 21-28 of Treatment Period 3 (Visit 20-Visit 21), and between Days 21-30 (inclusive) of Treatment Period 5 (Visit 32) or at Early Termination to investigate changes to uric acid deposits. In addition, in any cohorts reopened for enrollment, at least 2 newly enrolled subjects per cohort will undergo DECT during the screening interval, between Days 21-28 of Treatment Period 3 (Visit 20-Visit 21), and between Days 21-30 (inclusive) of Treatment Period 5 (Visit 32) or at Early Termination to investigate changes to uric acid deposits.

In Part C, dual energy CT scans will be performed for Cohorts 13, 15, and 17 as described above.

The summary statistics at baseline, and both the changes from baseline and percent change from baseline at the specified post-baseline time points in total urate volume (mL), knee volume (mL), hand/wrist volume (mL) and foot/ankle volume (mL). In addition, line plot of individual patients for total urate volume (mL), knee volume (mL), hand/wrist volume (mL) and foot/ankle volume (mL) over post-infusion days will be provided.

9.6. DATA PRESENTATION FOR URIC ACID

The actual sampling time of uric acid blood sample collection will be listed for each cohort and will include the deviation in time from the protocol scheduled time, if applicable.

Individual subject serum concentration data and %CFB will be listed by subject, time point, and treatment group (combined placebo or dose group in relevant concentration units) and will be summarized at each time point by cohort. Baseline is defined as the last concentration of uric acid measured before dose for the 1st Treatment period and Cohort separately.

Individual subject PD parameters derived using actual measurements and %CFB will be listed for the PD analysis set in a table by subject and will be summarized, by treatment group (combined placebo or dose group) and cohort.

The table summarizing the number and % of the subjects maintaining sUA levels below 6 mg/dL at the end of treatment period 3 (week 12, visit 22) and at the end of treatment period 5 (Week 20, visit 32)will be produced.

Additionally the sUA concentrations for the week 12, visit 22 will be summarized in separate table including frequency of the subjects with sUA levels <6 mg/dL at this visit for a subset of population meeting the following eligibility criteria;

1. Patients received entire 1st doses (without drug discontinuation)
2. Patients did NOT discontinue due to a withdrawal of consent during Treatment Period 1 or TP2
3. Patients did NOT discontinue due to a protocol deviation during Treatment Period 1 or TP2
4. Patients did NOT discontinue due to NON-study drug related (OR unlikely to be study drug related) SAE during TP1 or TP2

Additionally the sUA concentrations for the week 20, visit 32 will be summarized in separate table including frequency of the subjects with sUA levels <6 mg/dL at this visit for a subset of population meeting the following eligibility criteria;

1. Patients received entire 1st doses (without drug discontinuation)
2. Patients did NOT discontinue due to a withdrawal of consent during Treatment Period 1, TP2, TP3 or TP4
3. Patients did NOT discontinue due to a protocol deviation during Treatment Period 1 or TP2
4. Patients did NOT discontinue due to NON-study drug related (OR unlikely to be study drug related) SAE during TP1 or TP2

The following figures will be produced for Uric Acid:

Mean time response profiles for uric acid concentration raw values and %CFB at each time point for each Treatment period and cohort plotted against time for each Cohort separately with curves for all Treatment periods overlaid on one plot. BLQ values for uric acid concentration will be assigned 0 values for linear scales and 1/10 of LLOQ values for all time points for the graphic representation on log-linear scales only. Actual measured concentrations will be presented on both linear and log-linear scales while %CFB profiles will be presented on linear scale only.

Box plots for each derived PD parameter based on actual measurements and %CFB: CFBmin, $AUE_{CFBlast}$, $TA\_AUE_{CFBlast}$ will also be plotted by treatment.

Individual profiles for uric acid concentration absolute values and %CFB will be plotted for each Treatment period and cohort on a separate plot.

9.7. ASSESSMENT OF THE EFFECTS OF SEL-110 (RAPAMYCIN) AND SEL-037 (PEGSITICASE) ON PD PARAMETERS OF URIC ACID

Assessments done outside the assessment windows may be excluded from summarization. This will be determined prior to database lock.

The key PD parameters based on measured values and %CFB $\%CFB_{min}$, $AUE_{\%CFBlast,}$ and $TA\_AUE_{\%CFBlast}$ as well as uric acid concentration and %CFB on day 21 of each treatment period will be analyzed using linear mixed model for the response to SEL-110 dose levels co-administered with either 0.2 or 0.4 mg/kg of SEL-037 (the dose level of SEL-110 for Cohorts 1 and 2 will be assigned as 0). Additionally contribution of SEL-110 to the PD effect of SEL-037 will be tested to compare the following (test – reference). For PD

parameters based on actual measured values baseline concentration of uric acid will be incorporated in the model as covariate.

For Parts A and B following contrasts will be tested:

Cohort 3 Part A vs Cohort 1 Part A
Cohort 5 Part A vs Cohort 1 Part A
Cohort 7 Part A vs Cohort 1 Part A
Cohort 4 Part A vs Cohort 2 Part A
Cohort 6 Part A vs Cohort 2 Part A
Cohort 8 Part A vs Cohort 2 Part A
Cohort 10 Part A vs Cohort 2 Part A
Cohort 12 Part A vs Cohort 2 Part A
Cohort 1 Part A vs Cohort 2 Part A
Cohort 3 Part A vs Part B
Cohort 5 Part A vs Part B
Cohort 7 Part A vs Part B
Cohort 4 Part A vs Part B
Cohort 6 Part A vs Part B
Cohort 8 Part A vs Part B
Cohort 10 Part A vs Part B
Cohort 12 Part A vs Part B

For Part C (cohorts 13, 15, 17) additional contrasts will be:

Cohort 13 treatment period 4 vs Cohort 11 treatment period 4
Cohort 13 treatment period 5 vs Cohort 11 treatment period 5
Cohort 15 treatment period 4 vs Cohort 11 treatment period 4
Cohort 15 treatment period 5 vs Cohort 11 treatment period 5
Cohort 15 treatment period 4 vs Cohort 13 treatment period 4
Cohort 15 treatment period 5 vs Cohort 13 treatment period 5

Cohort 17 treatment period 4 vs Cohort 11 treatment period 4
Cohort 17 treatment period 5 vs Cohort 11 treatment period 5
Cohort 17 treatment period 4 vs Cohort 13 treatment period 4
Cohort 17 treatment period 5 vs Cohort 13 treatment period 5

Cohort 17 treatment period 4 vs Cohort 15 treatment period 4
Cohort 17 treatment period 5 vs Cohort 15 treatment period 5

Statistical Analysis Plan

Unstructured variance-covariance matrix will be used. If the model cannot converge or unable to make hessian positive definite, compound symmetry or other variance-covariance matrices will be explored and used.

Example SAS code will be:

```
PROC MIXED DATA=data_set_name;
CLASS subject_id treatment;
MODEL loge(PD Parameter) = treatment /DDFM=KR;
RANDOM subject_id / TYPE=UN;
LSMEANS treatment / DIFFS CL;
RUN;
```

1. The following hypotheses will be tested:

   - H_{01}: $\mu_T/\mu_R \leq 80\%$ vs. H_{A1}: $\mu_T/\mu_R > 80\%$

     and

   - H_{02}: $\mu_T/\mu_R \geq 125\%$ vs. H_{A2}: $\mu_T/\mu_R < 125\%$

If the 90% confidence interval (CI) for the geometric mean ratio (GMR) is within (80% – 125%) for any of the contrasts for C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$, the null hypotheses, that is H_{01} and H_{02}, will be rejected and we will conclude that the Test (T) is equivalent to the Reference (R).

2. If bioequivalence cannot be established in step 1 above, the following hypothesis will be tested to explore noninferiority (1-sided test):

   - H_{01}: $\mu_T/\mu_R \leq 80\%$ vs. H_{A1}: $\mu_T/\mu_R > 80\%$

If the lower 90% CI bound for the GMR is greater than 80% for C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$, H_{01} will be rejected and we will conclude that the new therapy (T=Test) is no worse than the old therapy (R=Reference).

The formula for calculation of the estimated ratio between the test and reference and the (1-2*α)*100 % CI of the ratio is given below.

Difference = Estimate of difference between test and reference least square means

Statistical Analysis Plan

$$Ratio = 100 \times e^{Difference}$$

(1-2*α)*100% CIs for the Ratio:

$$Lower = 100 \times e^{(LowerBound\,(1\text{-}2*\alpha)\%CIs\ for\ the Difference)}$$

$$Upper = 100 \times e^{(UpperBound\,(1\text{-}2*\alpha)\%CIs\ for\ the Difference)}$$

GMR ratio outside equivalence criteria 80-125% will demonstrate (1) dose effect SEL-110; (2) synergy or additive effect of SEL-110 administration on PD by SEL-037. P-values will be generated for all contrasts. Values of $p<0.05$ will indicate statistical significance of the effect.

The results of the comparisons will be graphically illustrated using box plots for Part A/B and comparison between Part C and B separately.

Correlations between PD endpoints (C_{min}, CFB_{min}, $AUE_{CFBlast}$, and $TA\_AUE_{CFBlast}$) and PK parameters (C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$) for both SEL-110 and SEL-037 will be explored using Spearman correlation analysis. The correlations for Part C treatment periods will be presented in the separate table.

The correlation between each of these PK (C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$) and PD (C_{min}, CFB_{min}, $AUE_{CFBlast}$, and $TA\_AUE_{CFBlast}$) parameters will also be explored and presented in a scatter plot with a regression line on it using simple linear regression which will have PK parameter as dependent variable and PD parameter as independent variable. The additional plots will be created for the Part C.

Example SAS code will be:

```
PROC GLM DATA=PKPDDATA;
MODEL PD_parameter = PK_parameter;
RUN;
```

10. ANALYSIS OF IMMUNOGENICITY

Immunogenicity endpoints include screening and confirmation results for IgG antibodies to pegsiticase, uricase, and IgM anti-PEG antibody. The titer for the antipegsiticase IgG antibodies will be determined during confirmation assay. The titer for the anti-uricase IgGs will be reported for positive samples. Preliminary concentration for anti-PEG IgM will be estimated in screening assay and confirmed in confirmation assay using multiple dilutions.

The Parts A/B (Treatment periods 1-3 and 4-5 for cohorts 1-8, 10-12 respectively) will be presented together separately from Part C (cohorts 13, 15) unless necessary for comparative analysis.

10.1. COLLECTION SCHEDULE

Cohorts 1-8, 10, 11, 12

Period	Day	Time from start of dose for saline, h	Time from start of dose for SEL-037, h
1-3	0	0	-1 (0)
	7	168	167
	14	336	335
	21	504	503
	28*	672	671
4-5	0		0
	7		168
	14		336
	21		504
	28**		672
	30***		720

* - pre-dose for next Treatment period
** - immunogenicity point for Treatment period 4 as pre-dose for Treatment period 5
*** - last point for Treatment period 5 only

Cohorts 13, 15

Period	Day	Time from start of dose for saline, h	Time from start of dose for SEL-037, h
1-5	0	0	-1 (0)
	7	168	167
	14	336	335
	21	504	503
	28*	672	671
	30**		720

* - pre-dose for next Treatment period
** - last point for Treatment period 5 only

10.2. DERIVED AND IMPUTED DATA

No imputation of missing immunogenicity data will be performed.

10.3. DATA SUMMARIZATION

Tables summarizing the frequency of the occurrence of ADAs by dose and by time point with overall summary per treatment will be produced for all cohorts separately and combined. The time of onset of immunogenicity, duration and number of resolved ADA cases will be summarized.

10.4. DATA PRESENTATION FOR IMMUNOGENICITY

Immunogenicity sampling times and results will be listed for safety analysis set outlined in Section 5.2 in this SAP. Immunogenicity endpoints include occurrence of anti-PEG, anti-pegsiticase, and anti-uricase specific antibodies based on screening assay and the titer for the anti-drug antibodies as identified in the confirmation assay.
Frequency of occurrence of antibodies by study day and overall by cohort, time of onset immunogenicity and time of resolution of immunogenicity will be calculated and summarized by treatment in summary tables. Time of onset is defined as 1st time point with positive ADA result; time of resolution is defined as 1st time point when previously observed positive ADA result returns to baseline. Titer of antibodies against PEG, uricase and pegsiticase will be listed. The effect of possible antibody responses on PK and PD parameters will be evaluated descriptively.

Cumulative positive ADA result for subject will be defined for each treatment period separately as at least one positive antibody post-dose time point for each Treatment period and Overall. The ADA positive subjects will be also stratified by the titer values for anti-pegsiticase and anti-uricase. The limits for titer values for low, moderate and high range will be identified based on percentiles after review of actual data (for example ≤30 percentile - low, 31-70 percentile - moderate, 71-100 percentile – high). Cumulative negative result will be defined as negative ADA result at all time points for a subject during each Treatment period.

Following tables will be produced to evaluate effect of immunogenicity on PK:

- Descriptive statistics of the key PD parameters based on measured values and %CFB $\%CFB_{min}$, $AUE_{\%CFBlast,}$ and $TA\_AUE_{\%CFBlast}$ as well as uric acid concentration and %CFB on day 21 of each treatment period for ADA positive and negative, ADA low, moderate and high titer groups including Q1, Q3, 5, 10, 90 and 95 percentiles. The data will be presented by cohort and overall.

- Descriptive statistics of the key PK parameters based on measured values and C_{max}, Tmax, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ for ADA positive and negative, ADA low, moderate and high titer groups including Q1, Q3, 5, 10, 90 and 95 percentiles. The data will be presented by cohort and overall.

- Frequency summary of subjects for ADA positive and negative results on day 21 as well as titer groups stratified by stopping rule from the protocol – subjects who had serum uric acid (sUA) value less than or equal to 1.0 mg/dL at any of the Day 21 visits and were eligible for the next dosing of SEL-212 (or SEL-037) vs subjects who had > 1mg/dL sUA at this time point. The results for the treatment periods will be time-matched between immunogenicity testing and sUA concentration measurement. The data will be presented by cohort and overall.

- Additionally model for the evaluation of the dose effect of SEL-110 and SEL-037 on PD results described in the section 9.6 of the SAP may be repeated with additional covariate for immunogenicity (cumulative positive, negative, positive low, high and moderate titer) to evaluate if immunogenicity had an additive or individual effect on the sUA as compared to the dose effect.

Following plots will be presented for immunogenicity and PK parameters:

Box and whiskers plot for comparison of CL values for SEL-037 (pegsiticase), C_{max}, T_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ derived using both PK concentrations and uricase activity between subjects with cumulative positive and negative immunogenicity results for each antigen separately (PEG, uricase or pegsiticase) by Cohort with varying doses of SEL-110 and overall. The additional plots will be created for the Part C.

Following plots will be presented for immunogenicity and PD parameters:

Box and whiskers plot for comparison of C_{min}, CFB_{min}, $AUE_{CFBlast}$ and $TA\_AUE_{CFBlast}$, $\%CFB_{min}$, $AUE_{\%CFBlast}$ and $TA\_AUE_{\%CFBlast}$ values for uric acid between subjects with cumulative positive and negative immunogenicity results for each antigen separately (PEG, uricase or pegsiticase) by cohort and overall.

10.5. ASSESSMENT OF THE EFFECTS OF IMMUNOGENICTY OF PHARMACOKINETICS OF SEL-037(PEGSITICASE) AND ON PD PARAMETERS OF URIC ACID

The effect of possible antibody responses on PK parameters will be evaluated descriptively.

Immunogenicity results will be compared descriptively between treatments using frequency of each type of ADA as main parameter as well as the time of onset of immunogenicity.

The CL for SEL-037 (pegsiticase), C_{max}, T_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ derived using both PK concentrations and uricase activity will be compared between subjects with cumulative negative and cumulative positive ADA results by Treatment period and cohort and overall for each cohort individually in the descriptive statistics table.

Similarly, PD parameters C_{min}, CFB_{min}, $AUE_{CFBlast}$, $TA\_AUE_{CFBlast}$, $\%CFB_{min}$, $AUE_{\%CFBlast}$ and $TA\_AUE_{\%CFBlast}$ will be compared between subjects with cumulative negative and cumulative positive ADA results by Treatment period and cohort and overall for each cohort individually in the descriptive statistics table.

No statistical inferences will be done for the comparisons.

11. SAFETY

Safety analysis set will be used for safety analyses. Safety will be assessed on the basis of AE reports, clinical laboratory data, ECG parameters, physical examinations, and vital signs.

11.1. EXTENT OF EXPOSURE

Study drug administration and randomization schedule will be documented as per subject listings. Frequency counts of number of subjects who received all doses and descriptive statistics of doses and total cumulative doses by treatment group will be presented.

11.2. TREATMENT COMPLIANCE

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

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 listed.

11.3. ADVERSE EVENTS

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 SOCs and PTs.

By definition, the study only collects treatment-emergent adverse events (TEAEs) so all AEs are TEAEs. The percentage of subjects with specific TEAEs will be summarized for each cohort and part (Part A and Part B and Part C).

All AEs will be listed by treatment, subject, SOC, and PT.

TEAEs will be summarized (number of events, number and % of subjects having experienced at least one event) by treatment, SOC, and PT. TEAEs will be also be summarized by intensity and causality. SAEs will be listed and summarized by causality.

Clinical study report narratives will be prepared for deaths, other serious adverse events, and withdrawals due to adverse events.

11.4. LABORATORY EVALUATIONS

Laboratory data will be summarized by the type of laboratory test. 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. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point for each dose and treatment. Changes from baseline results will be presented descriptively as well as in pre- versus post-treatment cross tabulations (with classes for below, within, and above normal ranges). A listing of subjects with any laboratory results outside the reference ranges will be provided.

11.5. VITAL SIGNS

Pulse, temperature, respiration rate, and systolic and diastolic blood pressure will be analyzed. Data will be flagged according to the reference limits (High or Low), if applicable. Descriptive statistics on actual values and changes from baseline by dose will be computed at each scheduled time point. Plots (mean ± standard error of the mean [SEM]) on changes from baseline over time will be given as appropriate.

Vital sign data will also be listed.

11.6. ELECTROCARDIOGRAM

The ECG variables that will be analyzed are heart rate, RR interval, PR interval, QRS interval, QT interval, QTcB, and QTcF. The ECG measurements will be summarized at each time point of measurement. The change from baseline will be summarized. Descriptive statistics on actual values and changes from baseline by dose and time will be computed. Plots (mean ± SEM) on changes from baseline over time will be provided. A listing of abnormal clinically significant evaluations as well as a listing of subjects with abnormal QTcF/QTcB values (>450, >480 and >500 ms) and of subjects with abnormal QTcF/QTcB changes from baseline (≥ 30 but <60; ≥ 60) will be provided.

All important abnormalities from the ECG readings, including changes in T wave morphology and/or the occurrence of U waves versus baseline recordings, will be included in the AE listing.

11.7. PHYSICAL EXAMINATION

Physical examination will be performed at Screening and early termination.

Physical examination data will be listed.

12. INTERIM ANALYSES

No interim analysis is planned for this study.

13. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

No changes from the analysis planned in the protocol have been made.

14. REFERENCE LIST

1. Gough K, Hutchinson M, Keene O, Byrom B, Ellis S, Lacey L, McKellar J. Assessment of Dose Proportionality: Report from the Statisticians in The Pharmaceutical Industry/Pharmacokinetics UK joint working party. Drug Inf J. 1995; 29:1039-1048.

2. Smith BP, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT, Forgue ST. Confidence interval criteria for assessment of dose proportionality, Pharmaceutical Research, Volume 17, Number 10, October 2000.

3. Hummel J, McKendrick S, Brindley C and French, R. Exploratory assessment of dose proportionality: review of current approaches and proposal for a practical criterion. Pharmaceut. Statist. 2009; 8: 38-49.

4. Maganti L, Panebianco DL, Maes AL. Evaluation of Methods for Estimating Time to Steady State with Examples from Phase 1 Studies. The AAPS Journal. 2008; 10(1):141-147.

5. Kenward, M. G. and J. H. Roger Small sample inference for fixed effects from restricted maximum likelihood. Biometrics, 1997, 53(3), 983–997.

Statistical Analysis Plan

15. PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.3 (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

15.1. 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

15.2. TABLE, LISTING, AND FIGURE FORMAT

15.2.1. 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., cm2, Cmax) 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.

15.2.2. Headers

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

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SELECTA Biosciences

Protocol SEL-212/201
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- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be 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).

- All output should have date of data (Data as of DDMMMYYYY) on bottom of each page.

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

15.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be 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

Safety Set

15.2.4. Column Headers

- Column headings should be 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 subjects 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).

15.2.5. Body of the Data Display

15.2.5.1. General Conventions

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

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

15.2.5.2. 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 should be 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 any 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 subject represented in 1 or more groups should be included.

- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.

- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be 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 (SD)	XX.X (XX.XX)
Median (Min, Max)	XX.X(XX.X, XX.X)
95% CI	(XX,XX, XX,XX)

- P-values should be output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be 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 should be 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 subjects 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% should be presented as 100%, without any decimal places.

- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be 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) should be 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 should be reported as "-".

- The percentage of subjects is normally calculated as a proportion of the number of subjects 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 subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be 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.

15.2.5.3. Listing Conventions

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

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

- All observed time values must 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

15.2.5.4. 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.

15.2.6. 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.
- Subject specific footnotes should be avoided, where possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may 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’).

16. QUALITY CONTROL

SAS programs are developed to produce clinical trial output such as analysis data sets, summary tables, data listings, figures or statistical analyses. Syneos Health SOP 03.010.00 and 03.013.00 provide an overview of the development of such SAS programs.

Syneos Health SOP 03.009.00 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 proper clinical trial output by checking for their logic, efficiency and commenting and by review of the produced output.