STUDY DRUG: **SEL-212 (a combination of SEL-037 and SEL-110)**

STUDY NUMBER: SEL-212/201

VERSION: **7.1**

EFFECTIVE DATE: **March 19, 2018**

An Open Label Phase II Multiple Dose Safety, Pharmacokinetic and Pharmacodynamics Study of SEL-212 Followed by Open Label Administration of SEL-037 in Subjects with Symptomatic Gout and Elevated Blood Uric Acid

Sponsor: Selecta Biosciences
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Approver(s):	**Signature:**	**Date:**
Earl E. Sands MD Chief Medical Officer		19 MARCH 2018
Kei Kishimoto, Ph.D. Chief Scientific Officer		19 Mar 2018

SELECTA BIOSCIENCES CLINICAL STUDY PROTOCOL

An Open Label Phase II Multiple Dose Safety, Pharmacokinetic and Pharmacodynamics Study of SEL-212 Followed by Open Label Administration of SEL-037 in Subjects with Symptomatic Gout and Elevated Blood Uric Acid

STUDY NUMBER: SEL-212/201

CONTACT INFORMATION

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INVESTIGATOR'S AGREEMENT

I agree:

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

Hence I:

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

_____

Printed Name of Investigator

_____

Signature of Investigator Date

1. SYNOPSIS

Name of Investigational Products:

SEL-212 (a combination of SEL-037 and SEL-110)

SEL-110 and SEL-037

Name of Active Ingredient:

SEL-037 (pegsiticase, Recombinant Pegylated Candida Urate Oxidase)

SEL-110 (a nanoparticle composed of PLA (poly(D,L-lactide)) and PLA-PEG (poly(D,L—lactide)-block-poly (ethylene-glycol)) encapsulating rapamycin)

Title of Study: An Open Label Phase II Multiple Dose Safety, Pharmacokinetic and Pharmacodynamics Study of SEL-212 Followed by Open Label Administration of SEL-037 in Subjects with Symptomatic Gout and Elevated Blood Uric Acid

Study center(s): 12-18

Principal Investigator: TBD

Study period:	**Phase of development:** 2
Estimated date first patient enrolled: October, 2016 Estimated date last patient completed: September, 2018	

Objectives:

Primary:

- To assess the safety and tolerability of multiple intravenous infusions of SEL-212

Secondary:

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

Exploratory:

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

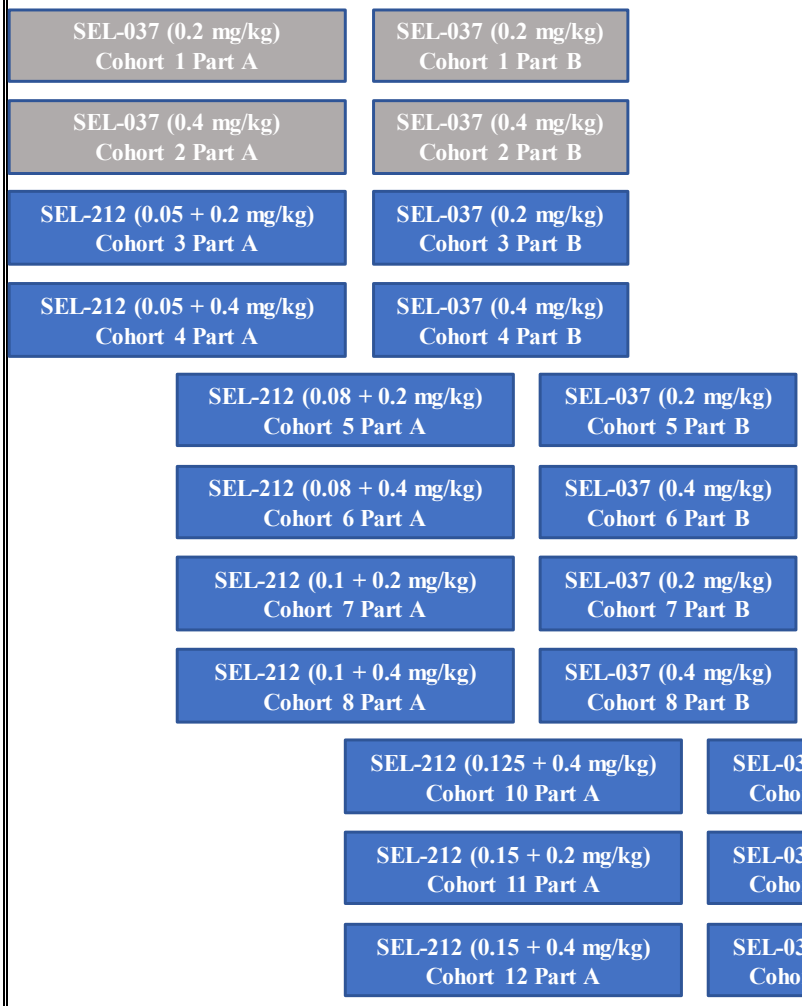
Methodology: (Part A) Open label multiple dose study of a combination drug (SEL-212) combined with an open label multiple dose study of a single drug (SEL-037) followed by (Part B) an open label administration of a single drug (SEL-037). Part C will involve patients naïve to SEL-212 who are treated with multiple doses of the combination drug (SEL-212).

Number of patients (planned): In Part A and Part B, approximately 100 subjects will be divided into 11 dosing cohorts, each consisting of 6-20 subjects. Cohorts 1-10 are closed to enrollment but are permitted to be re-opened to increase the enrollment to the maximum total number of subjects permitted. Cohorts 11 and 12 will continue enrolling up to 20 subjects per cohort. 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), 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: 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.)

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: 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.)

Subjects who withdraw early or have significant protocol deviations or compliance issues may be replaced at the discretion of the Sponsor to complete the objectives of the clinical study and maintain the integrity of the data set.

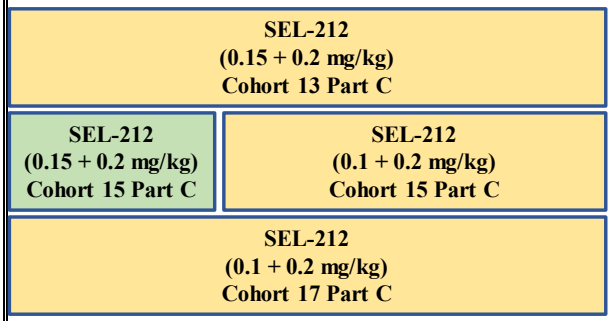
Overall scheme of trial (Part A and Part B)



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.

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.

Diagnosis and main criteria for inclusion/exclusion:

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.

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.

Investigational product, dosage and mode of administration:

SEL-037 is supplied as a lyophilized powder in a 2 ml stoppered vial with 6 mg SEL-037 per vial. SEL-037 is reconstituted with 1.1 mL of sterile water for injection, USP. A sufficient volume of reconstituted SEL-037 at 0.2 mg/kg or 0.4 mg/kg will be diluted in 100 mL of 0.9% sodium chloride for injection, USP and dosed as a single intravenous infusion with an infusion pump 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. If a subject is assigned to Cohorts 1 or 2 then the subject 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 by the infusion delivered by infusion pump of SEL-037 (0.2 mg/kg for Cohort 1 or 0.4 mg/kg for Cohort 2) 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.

SEL-110 will be supplied frozen in 10 ml glass vials. After thawing at room temperature for 2 hours, the appropriate amount of SEL-110 on a mg/kg basis will be drawn into a syringe or syringes and administered as an IV infusion with a syringe infusion pump. If a subject is part of Cohorts 3-8, 10, 11, or 12, then SEL-110 is to be administered prior to SEL-037. 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 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. For all cohorts receiving SEL-110, the infusion of SEL-037 (0.2 mg/kg for Cohorts 3, 5, 7, and 11; 0.4 mg/kg for Cohorts 4, 6, 8, 10, and 12), as described above, will be started at the 60 minute mark.

For Cohorts 13, 15, and 17, SEL-110 will be administered prior to SEL-037. 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. The infusion of 0.2 mg/kg SEL-037 will delivered by infusion pump 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.

Distribution of Subjects

All enrolled subjects will be randomized initially to Cohorts 1, 2, 3 and 4 such that upon reaching 12 subjects total 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 treatment 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 have been 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.

Premedication for Study Drug Treatments

All subjects will receive 180 mg fexofenadine orally the night before receiving study drug (12 h ± 2h) and again 2 ± 1 hours before receiving study drug (ie. prior to SEL-037 for Cohorts 1 and 2 or SEL-110 for Cohorts 3-8, 10, 11, and 12). In addition, they will also receive methylprednisolone 40 mg (or equivalent drug, for example prednisone 50 mg IV or dexamethasone 8 mg IV) intravenously 1 ± 0.5 hour before receiving study drug (ie. prior SEL-037 for Cohorts 1 and 2 or SEL-110 for Cohorts 3-8, 10, 11, 12, 13, 15, and 17). This will occur for every dose of study drug in Treatment Periods 1-5. These medications will be supplied by the clinic.

Premedication for Gout Flare

All subjects that meet all inclusion and exclusion criteria will be given premedication for gout flare prevention. The regimen will begin 1 week prior to the first dosing of study drug and continue for as long as the subject is enrolled in the clinical study. Subjects will be given colchicine 1.2 mg as a single loading dose. Then they will continue with colchicine 0.6 mg QD for the remainder of their participation in the trial. If there is a contraindication to colchicine, the subject will receive ibuprofen 600 mg TID or equivalent dose of a NSAID. If there is a contraindication to colchicine and to NSAIDs the subject will receive no premedication for gout flare. The gout flare prevention medication should continue as long as the subject is enrolled in the clinical study. Subjects who began receiving a NSAID as gout flare prevention medication due to a contraindication to colchicine or under a previous version of this protocol should continue to receive the NSAID as long as the subject is enrolled in the study. These medications will be supplied by the clinic.

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 their premedication of fexofenadine 180 mg orally. The day of initial dosing of study drug will be designated Day 0. On the morning (Day 0) subjects will report to the clinic for 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 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: 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.

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-110, subjects will receive methylprednisolone 40 mg (or equivalent drug) intravenously. Eligible subjects who have been assigned to Cohorts 3-8, 10, 11, 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 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 SEL-037 (0.2 mg/kg for Cohorts 3, 5, 7, and 11; 0.4 mg/kg for Cohorts 4, 6, 8, 10, and 12) 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.

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-110, subjects will receive methylprednisolone 40 mg (or equivalent drug) intravenously. Eligible subjects who have been assigned to Cohorts 3-8, 10, 11, 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 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 SEL-037 (0.2 mg/kg for Cohorts 3, 5, 7, and 11; 0.4 mg/kg for Cohorts 4, 6, 8, 10, and 12) 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 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-110, subjects will receive methylprednisolone 40 mg intravenously (or equivalent drug). Eligible subjects who have been assigned to Cohorts 3-8, 10, 11, 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 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 SEL-037 (0.2 mg/kg for Cohorts 3, 5, 7, and 11; 0.4 mg/kg for Cohorts 4, 6, 8, 10, and 12) 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 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-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 SEL-037 (0.2 mg/kg for Cohorts 3, 5, 7, and 11; 0.4 mg/kg for Cohorts 4, 6, 8, 10, and 12) diluted into 100 mL of normal saline over 60 minutes (+/- 2 minutes) by infusion pump. 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-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-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 SEL-037 (0.2 mg/kg for Cohorts 3, 5, 7, and 11; 0.4 mg/kg for Cohorts 4, 6, 8, 10, and 12) diluted into 100 mL of normal saline over 60 minutes (+/- 2 minutes) by infusion pump. 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-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.

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: 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.

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.

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.

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.

Stopping Rules in an Individual Subject or in a Cohort

For this clinical trial a treatment period is defined as the period of time from the beginning of dosing of saline placebo which is followed by SEL-037 (as in the case of Cohorts 1 and 2) or SEL-212 (as in the case of Cohorts 3-8, 10, 11, and 12) to the beginning of the next scheduled dose of study drug.

For Part C (Cohorts 13, 15, and 17), a treatment period is defined as the period of time from the beginning of dosing of SEL-212 to the beginning of the next scheduled dose of study drug.

Individual

For subjects in Cohorts 1 and 2, any subject who has a weekly serum uric acid value ≥6 mg/dl or >50% of their baseline (where baseline value refers to the pre-dose serum uric acid level from visit 4, Day 0, treatment period 1) at Day 21 of their current treatment cycle will not be eligible for the next dosing of SEL-037. The subject will be followed for 30 days post the last dose of study drug at which time they will have an End of Study assessment and their participation in the study will be terminated.

In Cohorts 3-8, 10-13, 15, and 17 only subjects whose ambient blood samples indicate a serum uric acid (sUA) value less than or equal to 1.0 mg/dL at any of the Day 21 visits will be eligible for the next dosing of SEL-212 (or SEL-037). All other subjects will be followed for 30 ± 2 days post the last dose of study drug at which time all of the End of Study assessments will be completed and their participation in the study will be terminated.

Cohort

If 5 subjects in any of Cohorts 1-5 or 7, or if 10 subjects in any of Cohorts 6, 8, 10, 11, or 12 have met the requirements for individual stopping of their participation in the trial as described above or have been stopped based on Section 6.4 then that cohort will no longer have any additional subjects enrolled in it. Those subjects who have been enrolled will continue until they fulfill the requirements for individual stopping or complete the clinical trial treatment periods. If they continue to meet the requirements for continued participation they may continue in the Part B of the clinical trial.

In Part C, if 10 subjects in any of Cohorts 13, 15, or 17 have met the requirements for individual stopping of their participation in the trial as described above or have been stopped based on Section 6.4 then the cohort will no longer have any additional subjects enrolled in it. Those subjects who have been enrolled will continue until they fulfill the requirements for individual stopping or complete the clinical trial treatment periods. If they continue to meet the requirements for continued participation they may continue in the clinical trial.

Criteria for evaluation:

Pharmacokinetics:

Blood samples for measuring serum SEL-037 levels and serum uricase activity levels and whole blood levels of rapamycin (API in SEL-110) in their respective cohorts will be collected as shown in the Schedule of Events, with time zero being the start of the SEL-110 or saline IV infusion: Pharmacokinetic (PK) parameters will be calculated including the maximum observed serum concentration (C_{max}), the time at which C_{max} occurred (T_{max}), area under the serum concentration-time curve from time 0 to the time of last quantifiable concentration (AUC_{last}), area under the serum concentration-time curve from time 0 to infinity (AUC_{inf}), the terminal elimination rate constant (K_{el}), terminal half-life ($t_{1/2}$), serum clearance of drug (CL), and apparent volume of distribution at equilibrium (V_{ss}).

Pharmacodynamics:

Blood samples will be collected as indicated in the schedule of events for evaluation of circulating serum uric acid levels. The blood samples will be processed for a determination of serum uric acid levels according to the procedures in the study laboratory manual.

Blood samples will be collected as indicated in the schedule of events for evaluation of antibodies to pegsiticase, uricase, and PEG. Procedures for processing samples will be included in the study laboratory manual.

Safety (Part A and Part B):

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.

- Physical exam at the Screening Visit and Treatment Period 5, Day 30/early termination.
- Part A - Treatment period 1 - Cohort 1 (0.2 mg/kg SEL-037 alone) and Cohort 2 (0.4 mg/kg SEL-037 alone)
  - Vitals at the Screening Visit, (Day 0) predose (T-0), intradose after the start of study drug IV syringe infusion (saline placebo) at 30, 60, 90, 120, and 180 minutes, then at 6, 9 hours; and then at Day 1, 7, 14, 21 and early termination. Vitals will be assessed at the designated times ± 2.5 minutes for all treatment periods and cohorts.
  - ECG exam at the Screening Visit, (Day 0) predose, 6 hours after completion of dosing, and early termination.
- Part A - Treatment period 1 - 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)

  - Vitals at the Screening Visit, (Day 0) predose (T-0), intradose (after the start of study drug IV syringe infusion SEL-110) 15, 30, 45, 60, 90, 120 and 180 minutes, then at 6, 9 hours; and then at Day 1, 7, 14, 21 and early termination.
  - ECG exam at the Screening Visit, (Day 0) predose, 6 hours after completion of dosing and early termination.

- Part A - Treatment period 2 - Cohort 1 (0.2 mg/kg SEL-037 alone) and Cohort 2 (0.4 mg/kg SEL-037 alone)
  - Vitals at (Treatment Period 2, Day 0) predose (T-0), intradose after the start of study drug IV syringe infusion (saline placebo) at 30, 60, 90, 120 and 180 minutes, then at 6, 9 hours; and then at Treatment Period 2, Day 1, 7, 14, 21 and early termination.
  - ECG exam at (Treatment Period 2, Day 0) predose and early termination.
- Part A - Treatment period 2 - 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)
  - Vitals at (Treatment Period 2, Day 0) predose (T-0), intradose after the start of study drug IV syringe infusion (SEL-110) at 15, 30, 45, 60, 90, 120, 180 minutes, then at 6, 9 hours; and then at Treatment Period 2, Day 1, 7, 14, 21 and early termination.
  - ECG exam at (Treatment Period 2, Day 0) predose and early termination.
- Part A - Treatment period 3 - Cohort 1 (0.2 mg/kg SEL-037 alone) and Cohort 2 (0.4 mg/kg SEL-037 alone)
  - Vitals at (Treatment Period 3, Day 0) predose (T-0), intradose after the start of study drug IV syringe infusion (saline placebo) at 30, 60, 90, 120, 180 minutes, then at 6, 9 hours; and then at Treatment Period 3, Day 1, 7, 14, 21 and early termination.
  - ECG exam at (Treatment Period 3, Day 0) predose and early termination.
- Part A - Treatment period 3 - 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)

- Vitals at (Treatment Period 3, Day 0) predose (T-0), intradose after the start of study drug IV syringe infusion (SEL-110) at 15, 30, 45, 60, 90, 120, 180 minutes, then at 6, 9 hours; and then at Treatment Period 3, Day 1, 7, 14, 21 and early termination.
- ECG exam at (Treatment Period 3, Day 0) predose and early termination.

- Part B - Treatment period 4 - Cohort 1 (0.2 mg/kg SEL-037 alone) and Cohort 2 (0.4 mg/kg SEL-037 alone)
  - Vitals at (Treatment Period 4, Day 0) predose (T-0), intradose after the start of study drug IV infusion (SEL-037) at 15, 30, 45, 60, 90, 120, and 180 minutes, then at 6 hours; and then at Treatment Period 4, Day 1, 7, 14, 21 and early termination
  - ECG exam at (Treatment Period 4, Day 0) predose and early termination.
- Part B - Treatment period 4 - 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)
  - Vitals at (Treatment Period 4, Day 0) predose (T-0), intradose after the start of study drug IV infusion (SEL-037) at 15, 30, 45, 60, 90, 120, and 180 minutes, then at 6 hours; and then at Treatment Period 4, Day 1, 7, 14, 21 and early termination.
  - ECG exam at (Treatment Period 4, Day 0) predose and early termination.
- Part B - Treatment period 5 - Cohort 1 (0.2 mg/kg SEL-037 alone) and Cohort 2 (0.4 mg/kg SEL-037 alone)
  - Vitals at (Treatment Period 5, Day 0) predose (T-0), intradose after the start of study drug IV infusion (SEL-037) at 15, 30, 45, 60, 90, 120, and 180 minutes, then at 6 hours; and then at Treatment Period 5, Day 1, 7, 14, 21 and 30 or early termination
  - ECG exam at (Treatment Period 5, Day 0) predose and End of Study Treatment Period 5, Day 30 or early termination.
- Part B - Treatment period 5 - 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)

  - Vitals at (Treatment Period 5, Day 0) predose (T-0), intradose after the start of study drug IV infusion (SEL-037) at 15, 30, 45, 60, 90, 120 and 180 minutes, then at 6 hours; and then at Day 1, 7, 14, 21 and 30 or early termination.
  - ECG exam at (Treatment Period 5, Day 0) predose and End of Study Treatment Period 5, Day 30 or early termination.

- Adverse events (AE) and serious adverse events (SAE) starting at dosing. AEs will be graded according to Rheumatology Common Toxicity Criteria, version 2.0. If a severe infusion reaction occurs, a determination of anaphylaxis (Grade 4 reaction) will be based on the National Institute of Allergy and Infectious Diseases (NIAID)/ Food Allergy & Anaphylaxis Network (FAAN) Anaphylaxis Criteria.
- Concomitant medication usage will be recorded throughout the trial.
- Clinical laboratory tests (blood chemistry, hematology including clotting parameters, and urinalysis) per the Time and Events Schedule.
- Immunogenicity samples for anti-PEG antibodies at the Screening Visit and for anti-pegsiticase, anti-uricase, and anti-PEG antibodies at baseline (predose for Treatment Periods 1, 2, 3, 4 and 5), Day 7, 14, and 21 post each treatment for Treatment Periods 1, 2, 3, 4, and 5, and EOS / early termination (Treatment Period 5, Day 30).

<u>Safety (Part C, Cohorts 13, 15, and 17)</u>:

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.

- Physical exam at the Screening Visit and Treatment Period 5, Day 30/early termination.
- Part C - Treatment Period 1 – 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), and Cohort 17 (0.10 mg/kg SEL-110 + 0.2 mg/kg SEL 037)
  - Vitals at the Screening Visit, (Day 0) predose (T-0), intradose (after the start of study drug IV syringe infusion SEL-110) 15, 30, 45, 60, 90, 120 and 180 minutes, then at 6, 9 hours; and then at Day 1, 7, 14, 21 and early termination.
  - ECG exam at the Screening Visit, (Day 0) predose, 6 hours after completion of dosing and early termination.
- Part C - Treatment Period 2 – Cohort 13 (0.15 mg/kg SEL-110 + 0.2 mg/kg SEL-037), Cohort 15 (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)
  - Vitals at (Treatment Period 2, Day 0) predose (T-0), intradose after the start of study drug IV syringe infusion (SEL-110) at 15, 30, 45, 60, 90, 120, 180 minutes, then at 6, 9 hours; and then at Treatment Period 2, Day 1, 7, 14, 21 and early termination.
  - ECG exam at (Treatment Period 2, Day 0) predose and early termination.

- Part C - Treatment Period 3 – Cohort 13 (0.15 mg/kg SEL-110 + 0.2 mg/kg SEL-037), Cohort 15 (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)
  - Vitals at (Treatment Period 3, Day 0) predose (T-0), intradose after the start of study drug IV syringe infusion (SEL-110) at 15, 30, 45, 60, 90, 120, 180 minutes, then at 6, 9 hours; and then at Treatment Period 3, Day 1, 7, 14, 21 and early termination.
  - ECG exam at (Treatment Period 3, Day 0) predose and early termination.
- Part C - Treatment Period 4 – Cohort 13 (0.15 mg/kg SEL-110 + 0.2 mg/kg SEL-037), Cohort 15 (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)
  - Vitals at (Treatment Period 4, Day 0) predose (T-0), intradose after the start of study drug IV infusion (SEL-037) at 15, 30, 45, 60, 90, 120, and 180 minutes, then at 6 hours; and then at Treatment Period 4, Day 1, 7, 14, 21 and early termination.
  - ECG exam at (Treatment Period 4, Day 0) predose and early termination.
- Part C - Treatment Period 5 – Cohort 13 (0.15 mg/kg SEL-110 + 0.2 mg/kg SEL-037), Cohort 15 (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)
  - Vitals at (Treatment Period 5, Day 0) predose (T-0), intradose after the start of study drug IV infusion (SEL-037) at 15, 30, 45, 60, 90, 120 and 180 minutes, then at 6 hours; and then at Day 1, 7, 14, 21 and 30 or early termination.
  - ECG exam at (Treatment Period 5, Day 0) predose and End of Study Treatment Period 5, Day 30 or early termination.

Statistical methods:

Data will be listed and summarized as appropriate. Descriptive statistics at each dose level (number of subjects, arithmetic mean, standard deviation, geometric mean, coefficient of variation, median, minimum and maximum, as appropriate) will be used to summarize the PK and safety results by dose groups. The PK and PD relationship will be explored.

1.1. Schedule of Events

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[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																	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
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
Uricase Activity				X						X	X	X	X	X	X	X	X	X
Uric Acid	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-087									
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 ONLY for Treatment Period 1 (Visit 4) only
13 - T-Cell recall sample ONLY for Treatment Period 3 (Visit 18) only

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																X	X
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-Pegsiticase		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

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	X
Immunogenicity																			
Anti-Pegsitacase				X											X	X	X	X	X
Anti-Uricase				X											X	X	X	X	X
Anti-PEG	X			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]					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]			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: 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.

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-Pegsiticase		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: 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.

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[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
Treatment Period #4; Visit (V); Day (D); Period (P)		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 Period #5; Visit (V); Day (D); Period (P)		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[8,15,16]

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[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[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]			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, 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. concurrentlv 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 this protocol in order to maintain the cohort numbering convention of associating odd numbered cohorts with the 0.2 mg/kg SEL-037 dose.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 6: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC_{inf}	Serum concentration-time curve from time 0 to infinity
AUC_{last}	Serum concentration-time curve from time 0 to the time of last quantifiable concentration
CBC	Complete blood count
CL	Serum clearance of drug
C_{max}	Maximum observed serum concentration
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
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

Abbreviation or Specialist Term	Explanation
K_{el}	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
PK	Pharmacokinetic
PTT	Partial thromboplastin time
SAE	Serious adverse event
SEM	Standard error of the mean
$t_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse events
T_{max}	Time at which C_{max} occurred
ULN	Upper limit of normal
USP	United States Pharmacopeia
V	Visit
V_{ss}	Apparent volume of distribution at equilibrium

4. INTRODUCTION

4.1. Investigational product

SEL-212 is a combination product containing SEL-037 (pegsiticase, Recombinant Pegylated Candida Urate Oxidase) and SEL-110 a drug product consisting of a biodegradable polymeric nanoparticle consisting of PLA (poly(D,L-lactide)) and PLA-PEG (poly(D,L-lactide)-block-poly-(thylene-glycol)) encapsulating rapamycin.

SEL-037 (pegsiticase; Recombinant Pegylated Candida Urate Oxidase) is a lyophilized recombinant uricase (urate oxidase) conjugated to multiple 20 kDa molecular weight polyethylene glycol (PEG) molecules. The uricase component of SEL-037 is cloned from the yeast *Candida utilis* (Koyama, 1996) and expressed in *Escherichia coli* for production (Bomalaski, 2002). The uricase component catalyzes the conversion of uric acid to the more soluble compound allantoin that is then readily excreted and is being developed to reduce hyperuricemia in chronic gout patients refractory to conventional therapy. SEL-037 has been given to humans in a single ascending dose escalation Phase 1 clinical study SEL-037/101 and was given in a single fixed dose of 0.4 mg/kg with or without SEL-110 in a Phase 1b clinical study SEL-212/101.

SEL-110, (PLA, PLA-PEG nanoparticle encapsulating rapamycin) is designed to inhibit the formation of anti-drug antibodies (ADAs) when concomitantly administered with a biologic drug during the first few doses of the biologic. When SEL-110 is dosed in this manner it induces durable, antigen-specific immune tolerance to the biologic therapeutic in animal models. SEL-110 has demonstrated the ability to induce antigen specific immune tolerance to pegylated uricase (SEL-037) in wild type mice, uricase deficient (knock-out) mice, rats and cynomolgus monkeys. SEL-110 was tested in man for the first time in a single ascending dose clinical study SEL-212/101. All of the proposed SEL-110 alone doses (0.03 mg/kg, 0.1mg/kg, 0.3mg/kg and 0.5mg/kg) have been completed. We believe we have identified a MTD in this clinical study for SEL-110 of 0.3 mg/kg as discussed further in Section 4.3.2.2.

SEL-212 is the combination (i.e. sequentially administered) of SEL-110 and SEL-037 in order to prevent the formation of anti-drug antibodies (ADAs) and induce immune tolerance to SEL-037 such that subsequent doses of SEL-037 will remain effective at lowering uric acid levels in patients. SEL-212 was evaluated in a single dose clinical study (SEL-212/101). The highest dose cohort of SEL-212 proposed was not enrolled as the SEL-110 component dose exceeded what we believe was the MTD for SEL-110.

The current multiple dose study of SEL-212 evaluates the safety, pharmacokinetics, immunogenicity, and the ability of SEL-212 to reduce blood uric acid levels, reduce/prevent the development of anti-uricase and anti-pegsiticase antibodies in patients with symptomatic gout and elevated uric acid levels.

4.2. Background

4.2.1. Hyperuricemia

Uric acid is a poorly soluble end product of purine nucleotide metabolism. Humans do not have uricases to metabolize uric acid and renal clearance is the sole method of elimination of uric acid (Wu, 1989; Wu, 1992; Oda, 2002). Hyperuricemia can occur when excess circulating uric acid overwhelms renal excretion capacity or when renal clearance is impaired. As uric acid concentrations rise and reach saturation or super-saturation levels, urate crystals can precipitate in tissues. This can lead to gout, a painful joint inflammation, due to the precipitation of urate crystals in joints. This can also lead to tophus formation, destructive arthritis and renal calculi. The American College of Rheumatology guidelines recommend lowering uric acid levels to at least below 6 mg/dL (Khanna, 2012a; Khanna, 2012b).

There are 5 lines of therapy for the reduction of uric acid levels and gout treatment: 1) nonpharmacological therapy through diet, lifestyle and comorbidity management, 2) symptomatic treatment with NSAIDS, colchicine, or corticosteroids, 3) xanthine oxidase inhibitors that inhibit uric acid production like allopurinol, 4) uricosuric agents that improve uric acid renal clearance such as probenecid and febuxostat, and 5) uricase therapy with pegloticase (Krystexxa®) in patients with severe gout who are refractory to other treatments.

4.2.2. Use of Uricases to Treat Hyperuricemia and Gout

Uricases metabolize uric acid to allantoin, which is readily soluble and excreted. Uricase therapies infused into humans have been shown to reduce blood uric acid levels and improve gout symptoms. Rasburicase (Elitek®), an unpegylated recombinant uricase cloned from *Aspergillus flavus* (Oldfield, 2006; Cammalleri, 2007), is approved for management of uric acid levels in patients with tumor lysis syndrome (Elitek®). Krystexxa® (pegloticase) is a recombinant uricase (primarily porcine with a carboxyl-terminus sequence from baboon) bound by multiple 10 kDa PEG molecules approved for the treatment of refractory gout (Biggers, 2008; Sherman, 2008). The conjugation of uricase with PEG is thought to decrease the immunogenicity and increase the half-life of the uricase molecules (Zalipsky, 1992; Mehvar, 2000; Fishburn, 2008; Veronese, 2008). The clinical experience with Krystexxa® has shown that a significant number of patients will develop anti-drug antibodies which limit the long term efficacy of the drug (Lipsky, 2014).

4.2.3. Other Pegylated Proteins

Pegylated proteins are also approved for use in other indications such as pegylated E. coli asparginase (Oncaspar) as a component of chemotherapy for the treatment of acute lymphoblastic leukemia and bovine pegademase (pegylated adenosine deaminase) as a replacement therapy for adenosine deaminase deficiency in infants and children.

4.3. Summary of Previous Findings of SEL-037 and SEL-110

4.3.1. Nonclinical Animal Studies

4.3.1.1. SEL-037

SEL-037 in rodent models reduces serum uric acid concentrations in a dose related manner at doses tested up to 1.2 mg/kg.

Nonclinical drug metabolism and pharmacokinetic studies of SEL-037 showed dose-dependent increases in exposure in both the rat and monkey, though terminal half-life was considerably longer in the monkey. The distribution study in rat indicated accumulation in the lungs, kidneys and bladder at all time points relative to the concentration found in plasma and other tissues. Renal excretion is the primary route of elimination of SEL-037 in rats.

The nonclinical toxicology program consists of single intravenous dose toxicity studies conducted in rats and monkeys at doses up to 58.2 mg/kg and 28 day general toxicity studies in rats and monkeys in doses up to 10 mg/kg and 5 mg/kg, respectively, a reproductive and early embryonic developmental toxicology study conducted in rats up to a dose of 10 mg/kg, an immunotoxicology study conducted in guinea pigs, an immunogenicity study conducted in monkeys, an in-vitro hemolysis test conducted in blood obtain from New Zealand White rabbits, and a 28-day injection site evaluation study conducted in monkeys.

SEL-037 was well tolerated and there were no clinically significant findings observed in any of the above studies with the exception of immunotoxicity noted in the guinea pig and a decrease in complement in the monkey. Following sensitization in the guinea pig, a strong anaphylactic reaction leading to death in all dosing groups was observed. In monkeys, following weekly intravenous administration, SEL-037 produced a low titer of non-neutralizing antibodies to SEL-037 and uricase at all dosing levels. Antibodies were noted within 14 days of the initiation of dosing. In general, antibodies to PEG were not observed. A decrease in complement was also noted in monkeys at 5 mg/kg which appears to return to near normal values following a 4 week recovery period. These changes noted in complement may be secondary to consumption of formed immune complexes.

In addition, SEL-037 was further evaluated in multidose intravenous toxicity studies of five monthly repeated doses of SEL-037 with a one month recovery in rats and cynomolgus monkeys.

In the GLP repeated dose study of SEL-037 in rats (Study 1933-008), reversible test article-related clinical pathology findings included mild transient prolongation in APTT and mild to moderate transient decreases in absolute reticulocyte counts that resolved despite continued dosing. Test article-related slight increased incidence of minimal to mild mononuclear cell infiltration and/or fibrosis of the heart in both males and females remaining slightly increased over that of controls following the recovery phase. Based on the reversibility and/or minimal severity of the findings, 8.0 mg/kg/dose, the highest dose level tested, was identified as the NOAEL for repeated doses of SEL-037 in rats.

In the GLP repeated dose study of SEL-037 in cynomolgus monkeys (Study 1933-009), there were no adverse findings noted. Test article-related effects were limited to watery feces which were observed in males in all treated groups periodically throughout the treatment phase, but not observed during the recovery period and were not considered to be adverse due to the sporadic and minimal nature of the finding. Based on these data, the NOAEL for this study was 4.0 mg/kg SEL-037, the highest dose level tested.

4.3.1.2. SEL-110

Consistent with ICH guidance, SEL-110 has been evaluated in nonclinical studies to support clinical study in humans, including safety pharmacology studies in rats and monkeys, as well as single and multiple dose toxicology studies in rats and monkeys. Immunotoxicology and local injection site reactions also were evaluated as a component of a repeat dose study in monkeys (Study 1933-004). Initial nonGLP dose finding studies of SEL-110 toxicity were completed in Sprague Dawley rats (Study 14-04312-N1) and cynomolgus monkeys (Study 14-04311-N1) in 8-week studies (given biweekly five times by IV bolus).

In the GLP repeated dose study of SEL-110 in rats (Study 1933-005), 1, 3 and 6 mg/kg were given as an intravenous slow bolus 3 times separated by 28 days. SEL-110 produced dose-dependent decreases in body weight and food consumption over the course of the study, primarily in the male animals that persisted for both sexes in the 6 mg/kg dose group through the end of the recovery period. Observation of reduced sizes of reproductive organs including testes and ovaries, as well as microscopic correlates, were observed at the 3 and 6 mg/kg dose levels. These changes are consistent with the known effect of rapamycin on the gonadotropin axis (Roa, 2009). Microscopic changes were observed in the heart (mild cardiomyopathy) in males at the high dose 6.0 mg/kg group. At recovery, bilateral incipient cataracts were present in all male animals in the 6.0 mg/kg/dose group. Cataracts are a known toxicity of rapamycin in male rats, which is thought to be related to the development of hyperglycemia (Rapamune NDA 21-083). Based on the adverse findings observed at 3 and 6 mg/kg/dose including effects on the male reproductive system, 1 mg/kg/dose was identified as the No-Observed-Adverse-Effect-Level (NOAEL) for SEL-110 (rapamycin containing nanoparticle) when administered as a bolus intravenous injection on three occasions (Days 1, 29, and 57) in rats.

While adverse effects of rapamycin in the male rat reproductive system are not unexpected (e.g., Chen et al., 2013), they have been shown to be reversible (Rovira et al., 2012). Because the major impact of SEL-110 was on the seminiferous epithelium, which produces the spermatozoa, it is important for the recovery period to span at least one spermatogenic cycle. In rats, spermatogenesis is approximately 53 days (Gray et al., 2004) and is followed by approximately 8-10 days during which the sperm enter and mature in the epididymis. Because there were findings of nearly empty epididymal lumens (which account for the reduced epididymal weights), it is important to allow the recovery period to span at least 63 days before looking for signs of potential recovery. In the completed toxicology studies the recovery period was 30 days.

In response to the findings involving the reproductive organs of rats in Study 1933-005, the Sponsor conducted Study 1933-013, an 8-week toxicity study in rats with a recovery period of up

to 36 weeks. This study examined the effects produced when both male and female rats were treated with the high dose of SEL-110 (6 mg/kg) administered as IV bolus injections on study days 1, 29, and 57. A total of 195 animals (75 males and 120 females) were randomly assigned by weight to control or treatment groups for the dosing period of the study. Animals were euthanized at 61 days (4 days after the last administration) and at times during the recovery period correlating with successive spermatogenic cycles in male rats. Histopathologic examination of the organs in the reproductive systems of both males and females was performed. In males, recovery appeared to begin as soon as Day 124, when active degeneration of germ cells was no longer identified and early spermatocytes were regularly observed suggesting that spermatogonial mitotic activity continued and spermatogenesis was starting to resume. Absence of spermatids and pachytene spermatocytes was likely the result of degeneration of those cell types at Day 61 and depletion may have contributed to the lower mean testis weight at this time point. By Day 187, 20% of animals showed testes within normal limits and in many animals, tubules displayed normal spermatogenesis. By Day 250, the amount of sperm present in all animals was within normal limits, suggesting full recovery. The testes of 40% of animals were within normal limits. At Days 187, 250, and 313, varying degrees of tubular atrophy were present in over half of the animals. Most cases were minimal to mild and the majority of the tubules displayed normal spermatogenesis. In females, differences in follicular cyst formation and decreased corpora lutea were observed between rats at the 6.0 mg/kg dose and in controls at Days 61 and 89. However, differences were minor and may have represented a spectrum of normal age-related changes. Notably, at Day 118 there were no microscopic differences between control animals and those at 6.0 mg/kg/dose. In females, the partial reversibility of ovarian findings seen previously in the rat was shown to be completely reversible during extended recovery. The return of spermatogenesis and normal levels of sperm in many male rats suggest recovery from the original testicular effects. In some rats the presence of atrophic tubules at the end of the recovery period may represent partial recovery or may have been related to normal senescence. In either case, in both male and female rats, there was nonetheless strong evidence of reversibility of the toxic effects of high dose (6 mg/kg) SEL-110 on reproductive organs in both female and male rats.

In the multi-dose study of SEL-110 in cynomolgus monkeys (Study 1933-006), 0.3, 1.0 and 3.0 mg/kg were given as an intravenous slow bolus 3 times separated by 28 days. SEL-110 was well tolerated at all doses, although there were observations of inappetence, vomitus and watery feces in males and females at the 1.0 and 3.0 mg/kg doses. It should be noted that reproductive organ toxicity was not observed in Cynomolgus monkeys and no adverse findings were observed in the reproductive tracts of either sex at any time or at any dose level. Additionally, consistent with the immunosuppressive action of rapamycin, test article related microscopic findings of minimal follicular lymphoid depletion in the spleen in males and females at all dose levels and lymph nodes (mandibular and mesenteric) in males and females at 1.0 and 3.0 mg/kg were observed, but were not severe enough to be considered adverse. The no-observed-adverse-effect level (NOAEL) for this study was 3.0 mg/kg for males and females, the highest dose level tested.

In order to provide more comprehensive PK data, the Sponsor also undertook an additional GLP rat PK study (1933-014) that examined dose levels of 0.5, 1.5, and 3 mg/kg of SEL-110. In this study whole blood samples containing SEL-110/rapamycin were analyzed using a new validated

GLP assay. At the 0.5 mg/kg dose level of SEL-110 reported in study 1933-014, AUC_{0-720} was determined to be 43,300 ng*hr/mL for SEL-110 administered alone and 57,700 ng*hr/mL for SEL-110 administered in combination with 0.4 mg/kg of SEL-037. At the 1.5 mg/kg dose level of SEL-110, AUC_{0-720} was 289,000 ng*hr/mL for SEL-110 administered alone and 243,000 ng*hr/mL for SEL-110 administered in combination with 0.4 mg/kg of SEL-037. These exposures are significantly higher than the AUC_{0-672} of 5,100 ng*hr/mL previously reported in the 1933-005 study, which used a non-validated bioanalytical method. This difference was due to using a validated assay in the 1933-014 study that overcame the extraction limitations experienced previously when attempting to measure high concentrations of SEL-110/rapamycin in rat whole blood at the early PK time points for study 1933-005. Based on these results, the AUC corresponding to the 1 mg/kg NOAEL (study 1933-005) is conservatively estimated to be 86,600 ng*hr/mL and therefore, using the recommended $AUC_{NOAELrat}/2$, the data support clinical doses with 4-week AUC values of 43,400 ng*hr/mL.

4.3.1.3. SEL-212

Consistent with ICH guidance, SEL-212 has been evaluated in nonclinical studies to support clinical study in humans, including safety pharmacology studies in monkeys, as well as a single dose toxicology study in rats, a two dose toxicology study in Cynomolgus monkeys and a repeated dose toxicology study in Cynomolgus monkeys.

Consistent with the 3 R's principle, a modified acute toxicology study of SEL-212 in Cynomolgus monkeys was conducted (Study 1933-011). Animals received a slow bolus intravenous injection on Day 1 and Day 14 with animals sacrificed 24 hours after the second injection. The groups were SEL-110 alone at 0.3, 1 and 3 mg/kg, SEL-037 at 2.0 mg/kg with SEL-110 at 0.3, 1.0, and 3.0 mg/kg, SEL-037 at 5.0 mg/kg with SEL-110 at 0.3, 1.0 and 3.0 mg/kg as well as 3 control groups of saline, empty nanoparticle (same composition of SEL-110 but without the rapamycin) and SEL-037 at 5.0 mg/kg. SEL-110 (alone or in combination with SEL-037) administered by intravenous injection 14 days apart for a total of 2 doses did not result in adverse findings. Evidence of an inflammatory effect was noted in groups receiving 1.0 or 3.0 mg/kg SEL-110 (rapamycin) as indicated by minimal to mild increases in fibrinogen and microscopic changes consisting of granulomatous inflammation, decreased hematopoietic cellularity, and abscess of the femoral bone marrow. There were no adverse effects of SEL-037 or SEL-110 given alone or in combination and no evidence of exacerbation of effects of either component on the other one. Based on all of the data, the NOAEL for the combination (SEL-212) was 3.0 mg/kg SEL-110 and 5.0 mg/kg SEL-037.

In rats, a single dose, slow bolus intravenous study of SEL-212 was conducted with the main group sacrificed 24 hours after dosing and the recovery group sacrificed 14 days after dosing (Study 1933-010). The groups included SEL-110 alone at 1, 3 and 6 mg/kg, SEL-037 at 4.0 mg/kg with SEL-110 at 1, 3, and 6 mg/kg, SEL-037 at 10 mg/kg with SEL-110 at 1, 3 and 6 mg/kg as well as 3 control groups of saline, empty nanoparticle (same composition of SEL-110 but without the rapamycin) and SEL-037 at 10 mg/kg. A single intravenous dose of SEL-110 (alone or in combination with SEL-037) administered to rats resulted in adverse mean body weight decreases compared to control in males (at 3 and 6 mg/kg) and microscopic findings (at

1, 3, and 6 mg/kg) that were noted in the heart and correlated to hematology findings consistent with inflammation (increased circulating neutrophils and/or monocytes and increased fibrinogen). The microscopic finding in the heart was considered to be adverse due to the trend towards increased incidence and severity over the course of the recovery phase.

In the multi-dose study of SEL-212 in Cynomolgus monkeys (study 1933-007), the toxicity of repeated doses of SEL-037 alone, SEL-110 alone, and the combination product SEL-212 was assessed over 16 weeks with a one month recovery. Once monthly IV administration of SEL-110 for a total of 3 doses (alone or in combination with SEL-037) plus two additional doses of SEL-037 alone did not result in adverse findings. Microscopic findings related to SEL-110 consisted of follicular lymphoid depletion in the spleen and lymph nodes (mandibular and mesenteric). Microscopic finding related to SEL-037 consisted of minimal follicular lymphoid hyperplasia in the spleen and/or lymph nodes (mesenteric, mandibular) of some animals. SEL-110-related clinical pathology changes consisted of infrequent minor increases in lymphocytes, monocytes, fibrinogen and/or eosinophils. Clinical signs related to SEL-110 consisted of watery feces and periocular erythema and/or swelling in individual males and females. Based on these data, the NOAEL for the study was 3.0 mg/kg SEL-110 when administered alone or in combination with SEL-037 and was 4.0 mg/kg SEL-037 when administered alone or in combination with SEL-110.

Local irritation was evaluated in a nonGLP repeated dose study of SEL-212 in Cynomolgus monkeys to assess anti-drug antibodies (Study 1933-004). There was no evidence of dermal irritation with repeated dosing of SEL-212.

4.3.2. Previous Human Experience SEL-212, SEL-037 alone and SEL-110 alone

4.3.2.1. SEL-037

To date there has been one completed clinical study (Phase I Study SEL-037/101) in humans for SEL-037 under IND 126034. Doses of 0.1, 0.2, 0.4, 0.8 and 1.2 mg/kg SEL-037 administered as single IV infusions to otherwise healthy patients with screening serum uric acid > 6 mg/dL demonstrated no evidence of safety signals as no SAEs or clinically significant treatment-emergent adverse events (TEAEs). SEL-037 demonstrated potent dose-dependent reductions in serum uric acid levels that were below quantification limits from Study Day 2 for all subjects (N=22). The duration of the PD effect was durable to Day 7 for all except 1 subject and to Day 30 in 1 subject. Duration appeared to be subject-dependent, not dose-dependent. The presence of ADA generally correlated with enhanced clearance of SEL-037 and diminished pharmacodynamic activity of SEL-037 at Study Day 14 in 3 subjects (0.1 mg/kg), 2 subjects (0.2 mg/kg), 3 subjects (0.4 mg/kg), and 2 subjects (0.8 mg/kg). At Study Day 30, two subjects with very low anti-uricase antibodies had serum uric acid concentrations below 1 mg/kg. The clinical study report was submitted to IND 126034.

A second Phase I clinical study (SEL-212/101) in humans for SEL-212 (the combination of SEL-110 and SEL-037) under IND 124184 is complete. SEL-212 in this clinical study was tested as a single dose where increasing amounts of SEL-110 were combined with SEL-037 at a fixed dose

level. In this study there were 4 cohorts of SEL-110 alone, 6 cohorts of the combination SEL-212 (SEL-110 with SEL-037), and one cohort of SEL-037 alone. In the cohort of subjects who received SEL-037 alone (0.4 mg/kg), one serious adverse event (SAE) of non-study drug-related atrial fibrillation was reported. In addition, among the 5 subjects who received 0.4 mg/kg SEL-037, the pharmacodynamic activity of SEL-037 was demonstrated by rapid reduction in serum uric acid levels (Figure 1). Data for this clinical study has been submitted to the FDA under IND 124184.

Additionally a similar product, designated Uricase-PEG 20 and manufactured by EnzymeRx (Paramus, NJ) was evaluated in two Phase 1 clinical studies under IND 009800. The first study (NCT01038947) examined the safety, pharmacokinetics and pharmacodynamics of Uricase-PEG 20 after intramuscular administration and the second study (NCT1021241) examined the safety, pharmacokinetics and pharmacodynamics of Uricase-PEG 20 after intravenous administration. In both studies, Uricase-PEG 20 was found to be well tolerated and effective in reducing serum uric acid levels.

4.3.2.2. SEL-110

SEL-110 was investigated in the completed Phase I study (SEL-212/101) in a total of 28 subjects with elevated uric acid levels (excluding the potential need for replacement subjects) who were dosed in four cohorts in a stepwise ascending manner. Within each cohort, five subjects received active drug substance and two subjects received placebo (saline). The doses of SEL-110 evaluated were 0.03, 0.1, 0.3, and 0.5 mg/kg. In that study, overall, SEL-110 was well tolerated, at doses < 0.5 mg/kg, and the majority of TEAEs were mild or moderate in severity. Treatment-emergent AEs (all causality) that occurred in ≥ 2 subjects who received SEL-110 alone (N=20) were headache (7 subjects, 35%), infusion related reaction (4 subjects, 20%), dizziness (2 subjects, 10%), paresthesia (2 subjects, 10%), rash maculopapular (2 subjects, 10%), and stomatitis (2 subjects, 10%). Two subjects each experienced SAEs of stomatitis at the highest dose of SEL-110 (0.5 mg/kg). The events were assessed as severe and related to study drug, and the subjects recovered from the events. As a result of these events, the Sponsor did not investigate planned doses of the combination drug (SEL-212) that had the 0.5 mg/kg SEL-110 dose level as a component. Stomatitis is a known adverse event associated with rapamycin, the active ingredient in SEL-110. Data for this trial has been submitted to IND 124184.

Additionally, the components of SEL-110 have been in previous clinical trials. The nanoparticles primarily consist of the class of biodegradable lactide polymers, part of the family of poly(lactide-*co*-glycolide) (PLGA) biodegradable polymers such as those found in the Food and Drug Administration (FDA) approved absorbable sutures Vicryl® and Dexon® and FDA approved products Zoladex®, Risperdal® Consta®, and Vivitrol®. Rapamycin (sirolimus) is the active ingredient in Rapamune, an FDA approved product for the prevention of organ rejection in kidney transplant patients.

SEL-110 at any of the dose levels tested alone has not demonstrated any effect on serum uric acid levels.

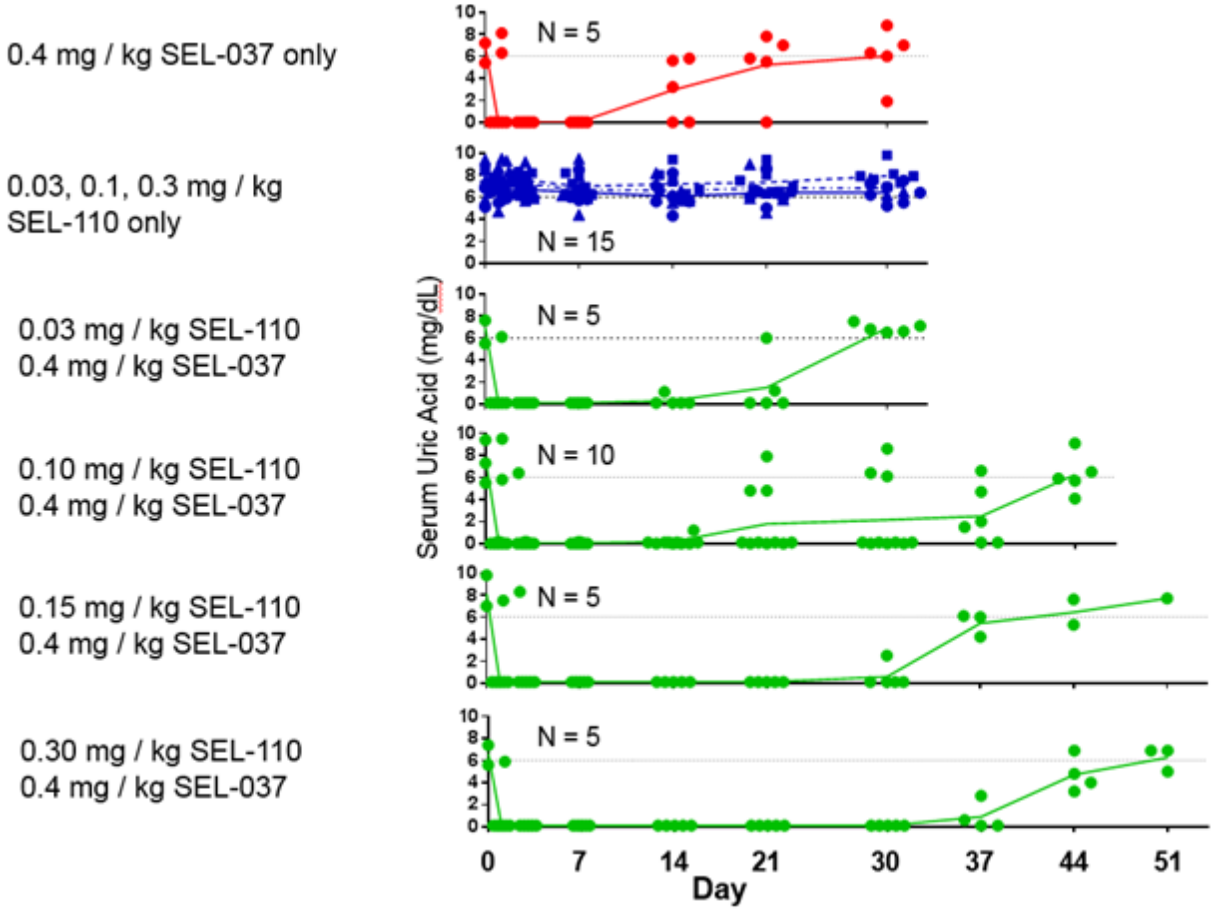
4.3.2.3. SEL-212

In the completed Phase I study of SEL-212, six cohorts received a combination of SEL-037 at a dose of 0.4 mg/kg and increasing doses of SEL-110 (0.03, 0.1, 0.15, and 0.3 mg/kg). Adult male and female subjects (N= 36) were enrolled on a dose level (cohort) basis with 5 subjects per cohort, with each cohort administered study drug in an ascending, stepwise manner. In addition, the order of administration was reversed and the time of administration between the components of SEL-212 was separated by 48 hours rather than sequentially and immediately. Safety and tolerability, pharmacodynamic activity, and pharmacokinetics of SEL-212 were assessed.

Overall, SEL-212 was well tolerated, and the majority of TEAEs were mild or moderate in severity. Treatment-emergent AEs that occurred in ≥ 2 subjects who received SEL-212 (N=31) were headache (4 subjects, 13%), rash (4 subjects, 13%), dizziness (3 subjects, 9.7%), dyspnea (3 subjects, 9.7%), nausea (3 subjects, 9.7%), aphthous ulcer (2 subjects, 6.5%), arthralgia (2 subjects, 6.5%), flushing (2 subjects, 6.5%), gout (2 subjects, 6.5%), pneumonia (2 subjects, 6.5%), and rash pruritic (2 subjects, 6.5%). Two subjects who received SEL-212 (0.1 mg/kg SEL-110 + 0.4 mg/kg SEL-037) were reported with SAEs that were moderate in intensity and assessed by the investigator as related to study drug. One subject experienced drug hypersensitivity, and the other subject experienced acute kidney injury and pneumonia (assessed by the Sponsor as not likely related to study drug). Both subjects recovered from the events. A third subject who received SEL-212 (0.15 mg/kg SEL-110 + 0.4 mg/kg SEL-037) had SAEs of upper gastrointestinal hemorrhage, small bowel obstruction, and intestinal mass that were assessed as not related to study drug. The subject recovered from these events.

SEL-212 demonstrated pharmacodynamic activity in reducing serum uric acid levels rapidly at the SEL-037 dose tested (0.4 mg/kg) and reducing or preventing the formation of anti-uricase antibodies in a dose dependent fashion. The uric acid level of all subjects treated with SEL-212 dropped to below 0.1 mg/dL within 24 hours after infusion. SEL-110 appeared to inhibit the formation of anti-uricase antibodies in a dose-dependent manner correlating with more sustained control of uric acid levels (Figure 1). Evaluation of anti-uricase, anti-PEG, and anti-pegsiticase antibodies showed that anti-uricase antibodies were the most sensitive measure of ADAs in the Phase 1 study, corresponding with decreased pharmacodynamic activity of SEL-037 as evidenced by increased serum uric acid levels.

Figure 1: Pharmacodynamic Activity of SEL-212 and Components (SEL-037 and SEL-110)



Pharmacokinetic assessments of concentrations of SEL-110 in whole blood were performed on samples collected from cohorts who received SEL-110 alone and in combination with SEL-037. Results are summarized in Table 7 for cohorts of patients who received SEL-110 doses above ≥0.1 mg/kg (ie, suggested minimum therapeutic dose) and showed dose-dependent responses to SEL-110 with potential influence by co-administration with SEL-037. Importantly, the mean and median values for systemic exposure (AUC) of SEL-110 at doses of 0.1 mg/kg and 0.3 mg/kg (Table 7) examined in conjunction with the results of analyses depicted in Figure 2 and Figure 3 suggest that a dose of 0.15 mg/kg SEL-110 will result in systemic exposure substantially below the exposure determined by the recent nonclinical analyses for the NOAEL in rats (Section 4.3.1.2).

Table 7. Summary of SEL-110 Whole Blood PK Parameters

Parameter	Statistic	Cohort 3 0.1 mg/kg SEL-110 (alone)	Cohort 4 0.1 mg/kg SEL-110 + 0.4 mg/kg SEL-037	Cohort 5 0.3 mg/kg SEL-110 (alone)	Cohort 6 0.3 mg/kg SEL-110 + 0.4 mg/kg SEL-037	Cohort 7 0.5 mg/kg SEL-110 (alone)
C_{max}	N	4	5	5	5	4
(ng/mL)	Mean (SD)	558.5 (181.92)	631.0 (177.87)	1173.8 (326.81)	2434.4 (428.80)	2464.3 (463.91)
	Median	621.5	582.3	1076.4	2319.6	2292.8
	Min, Max	291, 700	495, 942	854, 1640	1942, 3096	2142, 3130
T_{max}	N	4	5	5	5	4
(h)	Median	1.0	1.0	1.0	1.0	1.0
	Min, Max	1, 2	1, 1	1, 1	1, 2	1, 1
$AUC_{0\text{-last}}$	N	4	5	5	5	4
(h*ng/mL)	Mean (SD)	6671.4 (2006.87)	10332.1 (4912.06)	18043.4 (7908.47)	37015.0 (7920.00)	37537.9 (4543.67)
	Median	6811.0	8177.8	19620.0	36847.8	39221.7
	Min, Max	4187, 8877	6223, 18548	7056, 28308	25217, 46916	30827, 40881
$AUC_{0\text{-inf}}$	N	3	3	4	5	4
(h*ng/mL)	Mean (SD)	6596.2 (1747.06)	7817.6 (901.59)	23241.2 (6277.67)	37950.3 (7590.15)	39812.8 (5077.75)
	Median	6565.9	8126.3	22759.2	37635.8	41569.2
	Min, Max	4865, 8358	6802, 8524	16065, 31381	26629, 47451	32363, 43749
$t_{½z}$	N	3	3	5	5	4
(h)	Mean (SD)	280.2 (18.36)	299.7 (60.73)	214.7 (131.67)	284.4 (54.46)	207.6 (23.68)
	Median	287.7	322.4	290.6	278.5	212.1
	Min, Max	259, 294	231, 346	25, 333	235, 375	177, 229
CL	N	3	3	4	5	4
(L/h)	Mean (SD)	1.415 (0.16299)	1.139 (0.14129)	1.159 (0.22069)	0.9555 (0.36861)	1.217 (0.15249)
	Median	1.372	1.219	1.144	0.9661	1.161
	Min, Max	1.28, 1.6	0.976, 1.22	0.905, 1.44	0.569, 1.46	1.1, 1.44
V_d	N	3	3	4	5	4
(L)	Mean (SD)	574.4 (99.00)	489.8 (105.15)	433.6 (159.46)	380.1 (114.56)	360.9 (18.04)
	Median	569.5	407	454.8	396.5	362.8
	Min, Max	478, 676	453.9, 608	220, 604	204, 495	338, 380

Abbreviations: $AUC_{0\text{-inf}}$ = area under the plasma concentration-time curve from time 0 to infinity; $AUC_{0\text{-last}}$ = area under the plasma concentration-time curve from time 0 to the time t of the last quantifiable concentration; CL = total plasma clearance; C_{max} = maximum observed plasma concentration; max = maximum; min = minimum; NA = not applicable; PK = pharmacokinetics; SD = standard deviation; $t_{½z}$ = apparent terminal elimination half-life; T_{max} = time of maximum observed plasma concentration; V_d = distribution volume in the terminal elimination phase; n = number of actual reliable observations, may be lower for elimination parameters due to exclusion of unreliable PK parameters based on PK acceptance criteria as described in SAP.

The relationship between SEL-110 exposure (C_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$) and dose level was explored using two statistical approaches. The first approach applied the Hummel power analysis performed using Linear Mixed Effects model to determine the slope of the linear regression between log-transformed PK parameters. The second approach applied ANOVA comparisons of PK parameters for cohorts at the same dose level. Under both approaches, cohorts that received SEL-110 alone and co-administered with SEL-037 were analyzed.

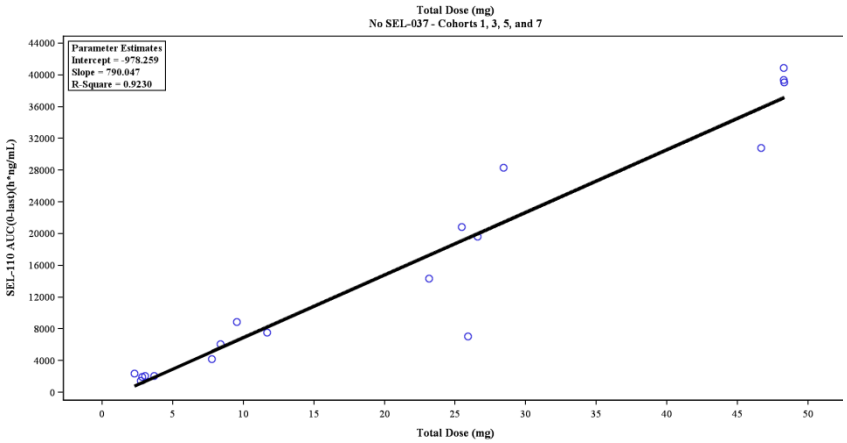
Dose proportionality was confirmed for SEL-110 administered alone (slope of approximately 1) and SEL-110 co-administered with SEL-037 (slope of approximately 1.2) (Figure 2). Further, ANOVA confirmed that SEL-037 increased systemic exposure of SEL-110 (Figure 3).

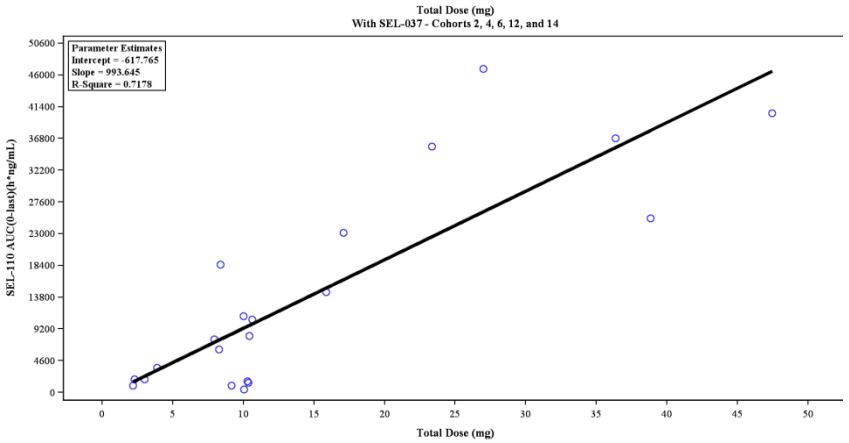
Figure 2. Dose Proportionality of SEL-110 AUC

Cohorts 1, 3, 5, 7 – (SEL-110 administered alone)

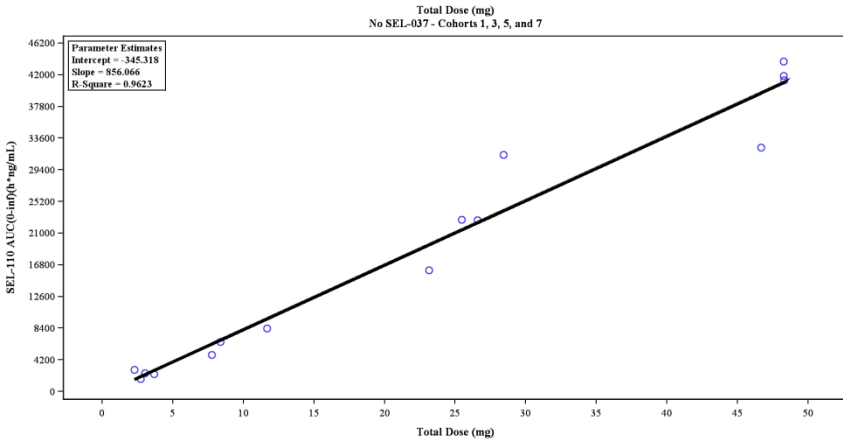
Cohorts 2, 4, 6, 12, 14 (SEL-212)

$AUC_{0\text{-last}}$ – total dose





$AUC_{0\text{-inf}}$ – total dose



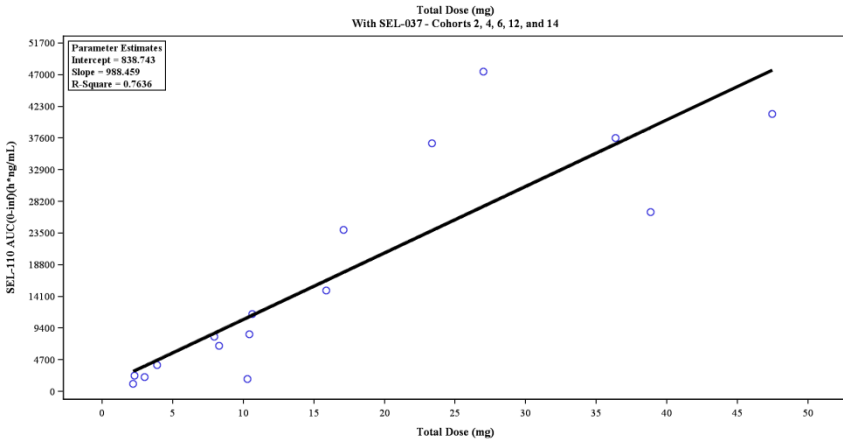
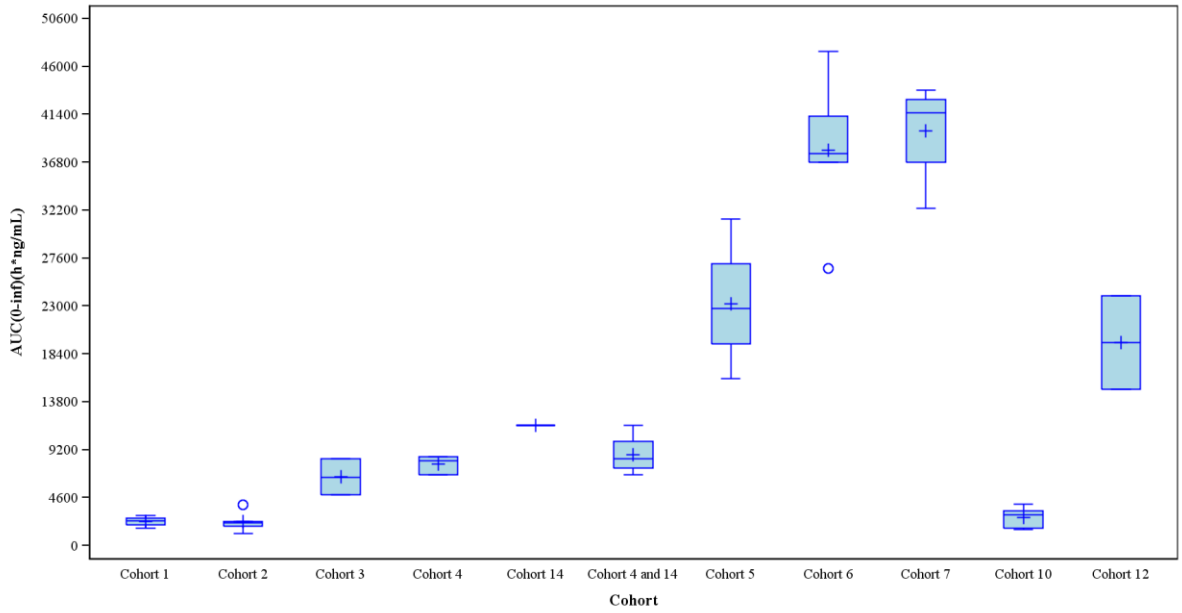


Figure 3. Effect of SEL-037 on SEL-110 Systemic Exposure ($AUC_{0\text{-}inf}$) (ANOVA)



Note: The horizontal solid line inside the box represents arithmetic mean value, dashed line – median value, box represents 1st and 3rd quartile (25th and 75th percentile), whisker bars represent fences of 1.5x IQR (interquartile range) or min/max range if smaller than 1.5xIQR , markers represent outlier points (outside fences).

Data for this clinical study has been submitted to the FDA under IND 124184.

4.4. Potential Risks and Benefits

4.4.1. SEL-037

Some subjects may have uric acid levels lowered for a brief or a longer period depending upon the subject's response to multiple doses of pegisiticase alone.

Potential risks include those that have been identified in preclinical studies and clinical studies of SEL-037 and SEL-212 as well as similar marketed products. These include 1) infusion reactions including anaphylaxis, 2) gout flares and 3) methemoglobinemia and hemolysis.

The use of biological therapeutics utilizing a protein of non-human origin is associated with the risk of immunogenicity that could result in infusion reactions including anaphylaxis. The formation of antibodies to SEL-037 was found in the animal toxicology studies. Previous human use of pegylated and unpegylated uricases have been associated with infusion reactions and anaphylaxis (Sundy, 2007; Cortes, 2010; Sundy, 2011). These adverse events would appear to be more prevalent in multiple dosing regimens but have been reported associated with the first dose presumably due to cross-reactivity or preexisting immunogenicity to the various components of the drug product or non-IgE related reactions. The current study excludes subjects with previous exposure to uricases and with preexisting immunoreactivity to PEG.

Gout flares are a potential risk in subjects with gout as therapies that reduce uric acid concentrations can produce flares. Premedication for flare will be given to subjects.

One of the byproducts of the degradation of uric acid by SEL-037 is hydrogen peroxide. Excessive oxidative stress can be detrimental to red blood cells. Serious hemolytic reactions and methemoglobinemia were reported in less than 1% of the oncology patients with tumor lysis syndrome in clinical studies with Elitek®. Similar events of severe hemolytic reactions have been reported with Krystexxa®. Subjects that are catalase or glucose-6-phosphate dehydrogenase deficient have a reduced ability to deal with oxidative stress and these subjects will be excluded.

4.4.2. SEL-110

Some subjects who receive SEL-110 as part of a SEL-212 arm may have uric acid levels lowered for a brief or a longer period depending upon the subject's anti-drug antibody response and the effect of SEL-212 to mitigate the formation of anti-drug antibodies over multiple doses and may have the development of antibodies to both uricase and pegsiticase prevented.

Potential risks include those that have been identified in preclinical and clinical studies of SEL-110 and SEL-212 as well as similar marketed products. These include 1) infusion reactions including anaphylaxis, 2) leukopenia and opportunistic infection, 3) metabolic disturbances (hyperglycemia, hypertriglyceridemia and hypercholesterolemia), 4) hypophosphatemia, 5) stomatitis, 6) oligo/azoospermia and 7) potential fetal development effects as seen in preclinical studies.

Rare cases of anaphylaxis were reported in the Phase 3 trials of Sirolimus (Rapamune®) during its development. Identification of the reason for these reactions has not been made whether it be the rapamycin or other ingredients in the oral formulation. Subjects with a history of anaphylaxis, angioedema or previous infusion reactions will be excluded from the trial. Additionally only sites with immediate capability to handle a reaction of this severity will be allowed to participate in the trial to reduce the risk to any subject.

Leukopenia has been reported in patients taking oral rapamycin. Whether the cause of the leukopenia is a direct relation to the rapamycin exposure, precedes or is due to the development of an opportunistic infection is unknown. Resolution of the leukopenia occurred in cases without subsequent infection with the stoppage of Sirolimus (Rapamycin) exposure. The current study will exclude subjects with any evidence of infection or developing infection by evaluating their WBC count and differential. Additionally all subjects will told to avoid anyone who has an active infection either bacterial or viral. Subjects will also have a WBC performed on day 7, 14, 21 and 28 post exposure of each treatment cycle. In our single clinical study SEL-212/101 we have not seen this effect. (Data on file)

Metabolic disruptions (hyperglycemia, insulin resistance, hypertriglyceridemia and hypercholesterolemia) have been reported in post-transplant patients who have been exposed to rapamycin (Johnston, 2008; Ghisdal, 2012). The occurrence of post-transplant diabetes mellitus (PTDM) has been recognized for many years as a consequence of solid organ transplant

immunosuppression (Shivaswamy, 2013). Dyslipidemia is a well-recognized side effect of rapamycin therapy (Hakeam, 2008). In our single ascending dose clinical study SEL-212/101 we have not seen this effect. (Data on file)

The exact mechanisms of rapamycin induced hyperglycemia, insulin resistance and its lipid effects are unclear at this time. It has been shown that rapamycin can diminish β-cell proliferation in hyperglycemic states thereby inhibiting the natural cellular response of neogenesis, proliferation, hypertrophy and a reduction in aptosis (Barlow, 2013). Additionally, rapamycin has been shown to inhibit phosphorylation of IRS-1 and IRS-2 in human adipocytes mimicking changes seen in type 2 diabetes and in human peripheral blood monocytes associated with insulin resistance (Pereira, 2012). Rapamycin has also been shown to increase basal lipolysis and reduce lipid storage (Pereira, 2012). Due to these, subjects who participate will have these specific laboratories (fasting glucose, triglyceride and cholesterol levels) monitored closely for significant changes during their participation. Subjects will be monitored on days 7, 14, 21 and 28 of each treatment cycle as is directed in the schedule of events.

The mechanism of hypophosphatemia is not known, but it has been seen in patients that have received mTOR inhibitors such as rapamycin (Soefje, 2011). And so subjects will be monitored on days 7, 14, 21 and 28 of each treatment cycle as is directed in the schedule of events.

The mechanism of stomatitis is not known, but it has been seen in patients that have received mTOR inhibitors such as rapamycin as early as 7 days after treatment and responds to locally applied Clobetasol cream (Soefje, 2011). And so subjects will be monitored on days 7, 14, 21 and 28 of each treatment cycle as is directed in the schedule of events.

Oligo/azoospermia has been seen in some male renal transplant patients taking an oral form of SEL-110 (rapamycin) administered chronically on a daily or three times weekly basis for the prevention of transplant rejection when treated for a period greater than six months. The mechanism for this effect is not known. In those patients where oligo/azoospermia has been seen partial to full reversibility of sperm production following cessation of treatment with the oral form of rapamycin has been demonstrated (e.g., Deutsch et al., 2007; Skrzypek, 2007; Zuber et al., 2008). Male patients should be informed that their fertility may be affected temporarily or permanently after being given SEL-110.

In preclinical animal studies performed with an oral form of the drug to be administered in this study, SEL-110 (a component of SEL-212) showed adverse effects when given to pregnant rats. These effects included fetal death, reduced fetal weights, and delays in the formation of bones. It is not known whether these effects would also occur humans, a similar risk should be considered possible until such studies are performed. Because of these potential adverse effects, all females who directly participate in this clinical study must be of no childbearing potential and all males with female partners with childbearing potential must agree to use effective contraception and agree to continue doing so for four months after study drug dosing. Childbearing potential is defined as: a) less than 6 weeks after surgical removal of ovaries, tubes with or without removal of the womb or (b) pre or perimenopausal (less than 24 months of being without a period naturally).

4.4.3. SEL-212

Some subjects may have uric acid levels lowered for a brief or a longer period depending upon the subject's anti-drug antibody response and the effect of SEL-212 to mitigate the formation of anti-drug antibodies over multiple doses and may have the development of antibodies to both uricase and pegsiticase prevented.

No additional risks have been identified at this time to the combination of SEL-037 and SEL-110 when presented as SEL-212.

4.5. Rationale for SEL-212 Doses Selected

Dosing in this Phase II study (SEL-212/201) of up to 0.15 mg/kg SEL-110 in combination with either 0.2 mg/kg or 0.4 mg/kg SEL-037 (ie, SEL-212) is supported by the nonclinical and clinical data presented in Section 4.3.1 and Section 4.3.2, respectively.

Doses of 0.2 mg/kg and 0.4 mg/kg SEL-037 were selected for the Phase II study based on preclinical evaluation in rodent, rat, and monkey (Section 4.3.1.1) and clinical evaluation in two completed Phase I studies. In the Phase I clinical study SEL-037/101 (IND 126034) doses of 0.1, 0.2, 0.4, 0.8 and 1.2 mg/kg SEL-037 demonstrated potent and dose-dependent reductions in serum uric acid levels and no evidence of safety signals as no SAEs or clinically significant treatment-emergent adverse events (TEAEs) were reported. Further clinical evidence supporting the Phase II doses of SEL-037 come from the completed Phase I Study SEL-212/101. Preliminary analyses of the study data show that one serious adverse event (SAE) of non-study drug-related atrial fibrillation was reported in 1 subject who received 0.4 mg/kg SEL-037 alone. Among the 5 subjects who received 0.4 mg/kg SEL-037, the pharmacodynamic activity of SEL-037 was demonstrated by rapid reduction in serum uric acid levels (Figure 1).

Doses of SEL-110 in the Phase II Study of SEL-212 (SEL-212/201) are based on the nonclinical toxicological data (Section 4.3.1.2) and the dose range tested in the Phase I single ascending dose clinical trial SEL-212/101. Preliminary analyses of safety data in the Phase I study suggest that doses of SEL-110 up to 0.3 mg/kg were well-tolerated (Section 4.3.2.2). In nonclinical studies, the concern regarding the irreversibility of testis toxicity (the effect on the gonadotropin axis) in the rat was addressed by strong evidence of reversibility established in the nonclinical Study 1933-013 with an extended recovery period covering multiple spermatogenic cycles (Section 4.3.1.2). Importantly, a rat GLP PK study performed with a validated PK assay shows that the SEL-110 exposure based on AUC at the NOAEL dose of 1 mg/kg provides a greater than 4-fold safety margin at the proposed dose level of 0.15 mg/kg in humans (Section 4.3.1.2). In addition, the calculation of the clinical doses of SEL-110 are predicted based upon the NOAEL of 3 mg/kg in Cynomolgus monkeys which is an appropriate species for these estimates. Therefore, the clinical dose of 0.15 mg/kg SEL-110 represents a 6.5-fold safety factor over the 3 mg/kg NOAEL in the non-human primate study based on body surface area (Section 4.3.1.2) and a 6.5-fold safety factor over the 6 mg/kg dosed to rats in Study 1933-013 based on body surface area (Section 4.3.1.2).

Finally, doses of SEL-212 (ie, combination of SEL-037 and SEL-110) in the Phase II study are supported by the preliminary analyses of safety, pharmacodynamic, and pharmacokinetic data in the completed Phase I study (SEL-212/101). SEL-212 appears to be well-tolerated at doses of 0.03-0.3 mg/kg SEL-110 in combination with 0.4 mg/kg SEL-037. SEL-212 reduces serum uric acid levels rapidly and demonstrates dose-dependent inhibition of ADAs with increasing doses of SEL-110 (Section 4.3.2.3). Importantly, the mean and median values for systemic exposure (AUC) of SEL-110 at doses of 0.1 mg/kg and 0.3 mg/kg (Table 7) examined in conjunction with the results of analyses depicted in Figure 2 and Figure 3 suggest that a dose of 0.15 mg/kg SEL-110 will result in systemic exposure substantially below the exposure determined by the recent nonclinical analyses for the NOAEL in rats (Section 4.3.1.2).

The dose-dependent inhibition of the formation of anti-uricase antibodies correlated with more sustained control of uric acid levels and is an important consideration for higher doses of SEL-110 in light of the potential risk of infusion related reactions with repeat dosing with SEL-037. It is expected that the risk of anaphylaxis will decrease with increasing doses of SEL-110 due to inhibition of ADA formation.

4.5.1. Rationale for Dose Selected (Part C)

Dosing in the Part C of this Phase II study (SEL-212/201) of up to 0.15 mg/kg SEL-110 in combination with 0.2 mg/kg SEL-037 (ie, SEL-212) is similarly supported by the nonclinical and clinical data presented in Section 4.3.1 and Section 4.3.2, respectively. From our review of interim serum uric acid and antibody data from Part A and B cohorts, we believe that 5 doses of the combination may be allow enhanced reduction of antibodies and serum uric acid for the duration of the therapy. Similar to Parts A & B, doses of 0.2 mg/kg SEL-037 were selected for Part C based on preclinical evaluation in rodent, rat, and monkey (Section 4.3.1.1) and clinical evaluation in two completed Phase I studies. Support for 3 doses of SEL-110 in combination with SEL-037 is described above for Part A and B. We have continued to extend our toxicology program to include additional doses of SEL-110 alone and in combination with SEL-037. We will submit toxicology data that demonstrates the safety of delivering 5 doses at up to 0.15 mg/kg SEL-110 prior to any patients receiving the 4th dose of SEL-212 in Part C. Should a delay occur such that the toxicology data to support the safety of the 4th and 5th doses of the combination of SEL-212 at the proposed doses is not available at the scheduled time of the 4th dose for a subject, that subject will be converted from the planned regimen of 5 doses of SEL-212 to a receive only SEL-037 at 0.2 mg/kg at the 4th and 5th dose and hence converted to a regimen of 3 doses of SEL-212 followed by 2 doses of SEL-037. This regimen is similar to the regimen of previous cohorts in Part A and B.

To investigate dose ranging in the 5 combination dosing regimen, Cohort 17 will have 5 doses of SEL-110 at a lower dose of 0.1 mg/kg at all 5 treatment periods and Cohort 15 will have 4 doses of SEL-110 at a lower dose of 0.1 mg/kg at treatment periods 2-5. Preliminary analyses of data in the Phase I study (SEL-212/101) and cohorts in Part A and Part B suggest that the first treatment period may be a critical time period for preventing antibody development to SEL-037; thus increased doses of SEL-110 in the first treatment period may help achieve a higher rate of patients who do not develop antibodies to SEL-037. As such, the first dose of SEL-110 in

treatment period 1 will be at a higher dose of 0.15 mg/kg in Cohort 15 to allow for comparison of efficacy and safety with other regimens in Part C.

4.6. Study Population

Approximately 140 subjects with symptomatic gout and elevated uric acid levels ≥ 6 mg/dL.

4.7. Study Rationale

When blood levels of urate exceed the physiologic limit of solubility, it may crystallize in the tissues and cause gout. Gout is an intermittent inflammatory arthritis caused by the formation of urate crystals in joint fluid, which can cause an intensely painful joint inflammation. Chronic hyperuricemia can lead to further deposition of uric acid in soft tissues, resulting in destructive arthritis and formation of tophi and renal calculi (Choi, 2006; So, 2008; Wortmann, 2008).

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

Intravenous uricase therapies have been shown to reduce uric acid levels (Goldman, 2001; Cortes, 2010; Sundy, 2011). They have also been shown to lose efficacy due to the formation of anti-drug antibodies (Lipsky, 2014). SEL-212 is an intravenous uricase therapy consisting of a combination SEL-037 and of SEL-110, a synthetic biodegradable polymeric nanoparticle encapsulating rapamycin an immune modulator. This therapy differs from other uricase therapies in the source of the uricase, product formulation and the type of pegylation which may improve tolerability and efficacy, and the addition of the immune modulator to reduce/prevent anti-uricase antibody formation. The current study evaluates the safety, tolerability, pharmacokinetics, pharmacodynamics (uric acid lowering ability) and the ability to mitigate the formation of anti-drug antibodies of SEL-212 after multiple IV infusion administration in subjects with symptomatic gout and circulating uric acid levels greater than or equal to 6 mg/dL.

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Primary Objective

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

5.2. Secondary Objectives

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

5.3. Exploratory objective

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

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

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, 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).

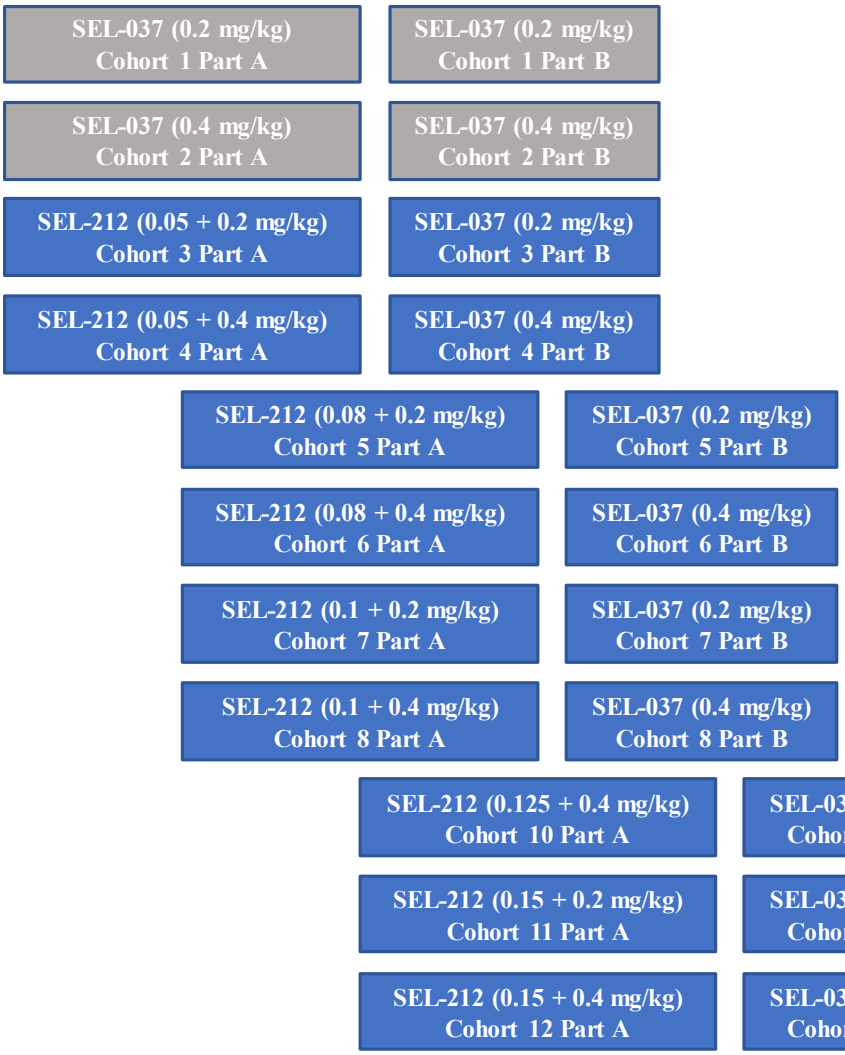
The safety, tolerability, PK and PD of multiple doses of SEL-037 will be assessed. Additionally to assess the ability of SEL-212 to reduce serum uric acid and prevent anti-drug antibodies to uricase and pegsiticase.

All enrolled subjects will be randomized initially to Cohorts 1, 2, 3 and 4 such that upon reaching 12 subjects total 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 treatment 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.

Treatment and events are by the cohort to which each subject is assigned.

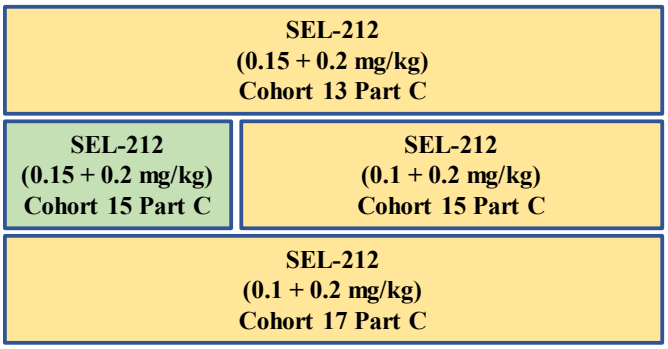
Figure 4: Overall scheme of trial (Part A and Part B)



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.

Figure 5: 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.

Screening procedures will begin after a subject voluntarily agrees to participate in the clinical trial and signs the ICF. After the informed consent process, subjects will have a physical examination and ECG performed, and vitals and clinical laboratory specimens collected.

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 their premedication of fexofenadine 180 mg orally. The day of initial dosing of study drug will be designated Day 0. On the morning (Day 0) subjects will report to the clinic for 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 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 [Section 1.1]). 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 [Section 1.1]). 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 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 [Section 1.1]). 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 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 [Section 1.1]). 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 [Section 1.1]). 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: 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.

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-110, subjects will receive methylprednisolone 40 mg (or equivalent drug) intravenously. Eligible subjects who have been assigned to Cohorts 3-8, 10, 11, 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 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 SEL-037 (0.2 mg/kg for Cohorts 3, 5, 7, and 11; 0.4 mg/kg for Cohorts 4, 6, 8, 10, and 12) 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 [Section 1.1]). 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-110, subjects will receive methylprednisolone 40 mg (or equivalent drug) intravenously. Eligible subjects who have been assigned to Cohorts 3-8, 10, 11, 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 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 SEL-037 (0.2 mg/kg for Cohorts 3, 5, 7, and 11; 0.4 mg/kg for Cohorts 4, 6, 8, 10, and 12) 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 [Section 1.1]). 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-110, subjects will receive methylprednisolone 40 mg (or equivalent drug) intravenously. Eligible subjects who have been assigned to Cohorts 3-8, 10, 11, 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 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 SEL-037 (0.2 mg/kg for Cohorts 3, 5, 7, and 11; 0.4 mg/kg for Cohorts 4, 6, 8, 10, and 12) 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 [Section 1.1]). 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-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 SEL-037 (0.2 mg/kg for Cohorts 3, 5, 7, and 11; 0.4 mg/kg for Cohorts 4, 6, 8, 10, and 12) diluted into 100 mL of normal saline over 60 minutes (+/- 2 minutes) by infusion pump. 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-037 for safety evaluations and PK blood draws (see Schedule of Events [Section 1.1]). 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-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 SEL-037 (0.2 mg/kg for Cohorts 3, 5, 7, and 11; 0.4 mg/kg for Cohorts 4, 6, 8, 10, and 12) diluted into 100 mL of normal saline over 60 minutes (+/- 2 minutes) by infusion pump. 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-037 for safety evaluations and PK blood draws (see Schedule of Events [Section 1.1]). 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.

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: 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.

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 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 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 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.

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

6.2. Number of Subjects

Number of patients (planned): In Part A and Part B, approximately 100 subjects will be divided into 11 dosing cohorts, each consisting of 6-20 subjects. Cohorts 1-10 are closed to enrollment but are permitted to be re-opened to increase the enrollment to the maximum total number of subjects permitted. Cohorts 11 and 12 will continue enrolling up to 20 subjects per cohort. 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), 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 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.

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: 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.)

Subjects who withdraw early or have significant protocol deviations 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.

6.3. Treatment Assignment

All enrolled subjects will be randomized initially to Cohorts 1, 2, 3 and 4 such that upon reaching 12 subjects total for all 4 cohorts, each cohort will contain 3 subjects. The experience of these 12 subjects has guided 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 treatment 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.

6.3.1. Stopping Rules in an Individual Subject or in a Cohort

For this clinical trial a treatment period is defined as period of time from the beginning of dosing of the first study drug on a given dosing day (ie, Either saline placebo or SEL-110 during Part A of the study and SEL-037 during Part B of the study) to the beginning of the next scheduled dose of study drug, and has a typical duration of 28 days.

For Part C (Cohorts 13, 15, and 17), a treatment period is defined as the period of time from the beginning of dosing of SEL-212 to the beginning of the next scheduled dose of study drug.

Individual

For subjects in Cohorts 1 and 2, any subject who has a weekly serum uric acid value ≥6 mg/dl or >50% of their baseline (where baseline value refers to the pre-dose serum uric acid level from visit 4, Day 0, treatment period 1) at Day 21 of their current treatment cycle will not be eligible for the next dosing of SEL-037. The subject will be followed for 30 days post the last dose of study drug at which time they will have an End of Study assessment and their participation in the study will be terminated.

In Cohorts 3-8, 10-13, 15, and 17 only subjects whose ambient blood samples indicate a serum uric acid (sUA) value less than or equal to 1.0 mg/dL at any of the Day 21 visits will be eligible for the next dosing of SEL-212 (or SEL-037). All other subjects will be followed for 30 ± 2 days post the last dose of study drug at which time all of the End of Study assessments will be completed and their participation in the study will be terminated.

Cohort

If 5 subjects in any of Cohorts 1-5 or 7, or if 10 subjects in any of Cohorts 6, 8, 10, 11, or 12 have met the requirements for individual stopping of their participation in the trial as described above or have been stopped based on Section 6.4 then that cohort will no longer have any additional subjects enrolled in it. Those subjects who have been enrolled will continue until they fulfill the requirements

for individual stopping or complete the clinical trial treatment periods. If they continue to meet the requirements for continued participation they may continue in Part B of the study.

In Part C, if 10 subjects in either of Cohorts 13, 15, or 17 have met the requirements for individual stopping of their participation in the trial as described above or have been stopped based on Section 6.4 then the cohort will no longer have any additional subjects enrolled in it. Those subjects who have been enrolled will continue until they fulfill the requirements for individual stopping or complete the clinical trial treatment periods. If they continue to meet the requirements for continued participation they may continue in the clinical trial.

The medical monitor, Investigator, IRB, or regulatory agency may also stop additional dosing or dose escalation based on any condition that warrants termination such as the discovery of an unexpected, serious or unacceptable risk to subjects or an unacceptable incidence of an expected event (e.g., unacceptable incidence or severity of infusion reactions) which suggests additional dosing is not warranted.

6.3.2. Safety committee

Safety data will be monitored on an ongoing basis by the Investigators and medical monitor. If two or more subjects in a single cohort experience SAEs that are assessed as related or possibly related to study drug, then the safety committee will review all relevant safety information for all subjects in that cohort. The data will include the accumulated data through the time of the scheduled meeting. At minimum, this committee will include the Investigators, or their representatives, who have had subjects dosed at their site in the cohort of interest, the medical monitor and a sponsor representative.

6.4. Criteria for Study Termination

The study will be terminated when the subjects have completed follow-up assessments as per Section 1.1 or the medical monitor, Sponsor, Investigators, safety committee, IRB or regulatory agencies have determined there is an unacceptable risk to subjects or additional dosing or procedures are not warranted or necessary.

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

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

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject 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.

7.2. Subject 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.

7.3. Subject Restrictions and Requirements

7.3.1. Medication and Therapy Restrictions

See Section 8.2.

7.3.2. Contraception

Females must be of non-childbearing potential, where childbearing potential is defined as being: (a) <6 weeks after surgical bilateral salpingooperhectony with or without hysterectomy or (b) pre or perimenopausal (< less than 24 months of natural amenorrhea).

All males with female partners with childbearing potential agree to use effective contraception and agree to continue doing so for four months after study drug dosing. Effective contraception is defined (for male subjects with a female partner with childbearing potential) as (a) two separate forms of contraception simultaneously, one of which must be a male condom with spermicide; or (b) be non-heterosexually active.

7.3.3. Subject Confinement

Subjects will undergo multiple blood draws and safety assessments as dictated by the schedule of events. There will be no overnight clinic stays. Subjects will need to remain in the clinic for a minimum of 9 hours after the start of dosing of study drug infusion.

7.3.4. Blood and Sperm Donations

Subjects will be advised that they should not donate blood and males should not donate sperm until after completion of this study.

7.3.5. Foods, Meals, Beverages and Fluid Intake

Subjects will be given a standardized low-purine diet during the In-Clinic Phase (dosing of study drug). There are no other food, meal, and beverage or fluid intake restrictions. Subjects should maintain a normal routine and diet as much as possible.

7.4. Subject Completion and Withdrawal

7.4.1. Screen Failures

An evaluation of the subject's eligibility occurs from consent through the predose assessments and a subject will not be considered enrolled in the study until dosed with study drug. Any subject that is screened but not dosed will be considered a screen failure and the reason for failure will be documented.

7.4.2. Subject Completion

A subject will be considered to have completed the study when the subject has completed the Treatment Period 5, Day 30 visit. Enrolled subjects who prematurely discontinue for any reason before completion of the study will be treated as outlined in the following section.

7.4.3. Enrolled Subject Withdrawal and Discontinuations

7.4.3.1. Withdrawal Procedures

Early terminations are when an enrolled subject withdraws consent or the Investigator terminates a subject. The reason for withdrawal will be evaluated and recorded in the case report form (CRF) and source documents. Subjects that withdraw may be replaced (see Replacement of Subjects, Section 7.4.4).

Subjects may withdraw consent at any time. A documented effort must be made to determine why a subject withdraws consent, fails to return for the necessary visits, or is dropped from the study. All subjects that withdraw early upon termination should have the Early Termination visit assessments completed (i.e., End of Study assessments), if the assessments pose no risk to the subject and the subject allows such assessments.

The Investigator should consult with the Sponsor/medical monitor prior to withdrawing any subject. Since this is a multiple dose safety study, once dosed, subjects generally should not be terminated by the Investigator and should be followed through 30 days after last dose of study drug unless the subject withdraws consent or is lost to follow-up. In situations where continued participation in certain aspects of the study pose a risk to the subject, with consultation with the medical monitor, the Investigator should discontinue those procedures that pose a risk and should continue to collect data and conduct those assessments that do not put the subject at risk through 30 days after last study drug (e.g., End of Study). Subjects with compliance issues or major deviations that effect data quality will also continue to be followed through 30 days after last study drug collecting as much data on the subject as possible, unless otherwise indicated by the Sponsor.

7.4.3.2. Subjects Lost To Follow-Up

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

7.4.4. Replacement of Subjects

An excessive rate of withdrawal of subjects and missing data within a cohort can have a negative impact on this study given the small cohort size. Subjects may be replaced at the discretion of the Sponsor based on a review of withdrawal rates within a cohort, the impact of missing or unusable data, out of window blood draws and protocol deviations or other unanticipated events. No additional subjects will be replaced or dosed if the reason for withdrawal was the fulfilment of the stopping rules for individuals or cohorts.

8. TREATMENT OF SUBJECTS

8.1. Description of Study Drug

The investigational products are listed in Table 8. The first one is lyophilized SEL-037 supplied as 6 mg SEL-037, with phosphate buffer and mannitol as excipients, in a 2 ml borosilicate glass vial with a bromobutyl rubber stopper and an aluminum-plastic combination cap. The second product is SEL-110, a frozen suspension of synthetic biodegradable polymeric nanoparticles encapsulating rapamycin in PBS, supplied at a 2 mg/mL rapamycin concentration in a 10 mL borosilicate glass vial filled to provide a deliverable dose of 5mL with a coated butyl rubber stopper and aluminum-plastic combination cap.

Table 8: Investigational Product

	Investigational Product	Investigational Product
Product Name:	SEL-037	SEL-110
Dosage Form:	Lyophilized product	Frozen nanoparticle suspension
Unit Dose	6 mg SEL-037 per vial diluted to final dose in normal saline	10 mg / 5 ml in the thawed state
Route of Administration	Intravenous infusion	IV infusion
Physical Description	2 ml borosilicate glass vial with rubber stopper and aluminum-plastic combination cap	10 mL borosilicate glass vial with rubber stopper and aluminum-plastic combination cap
Manufacturer	Manufactured for Selecta Biosciences by 3SBio	Manufactured for Selecta Biosciences by Emergent BioSolutions

8.2. Concomitant Medications and Therapies

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

Uric acid lowering therapy:

1. Uric acid lowering therapy of allopurinol, febuxostat (Uloric®), and probenecid is allowed if the dose was stable (no clinically significant dose change or therapy started or stopped) for at least the month prior to the Visit 1 Screening Visit and remains stable throughout the trial.
2. No new uric acid therapy should be initiated or existing therapy stopped until after the study.
3. Subjects cannot have any prior exposure to or be presently be taking any experimental or marketed uricase therapy (e.g., rasburicase (Elitek®, Fasturtec®), pegloticase (Krystexxa®), pegsiticase (SEL-037)).

Anticoagulants use:

1. The use of the following anticoagulants are prohibited during the trial
   a. dabigatran (Pradaxa®),
   b. rivaroxaban (Xarelto®)
   c. apixaban (Eliquis®)
   d. edoxaban (Savaysa®)
   e. warfarin (Coumadin®).

Hormone replacement therapy:

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

Drugs which have an effect on CYP3A4

The use of CYP3A4 inducers or inhibitors are prohibited during the trial.

Examples of inducers would be carbamazepine-Tegretol®, phenobarbital, phenytoin-Dilantin®, rifampin/rifampicin-Rifadis®, rifabutin-Mycobutin®, St. John's Wort-Hypericum perforatum.

Examples of inhibitors would benefazodone-Serazone®, itraconazole-Sporanox®, ketoconazole-Nizoral®, voricinazole-Vfend®, atraznavir-Reyataz®, indinavir-Crixvan®, nelfinavir-Viracept®, ritonavir-Norvir, saquinavir-Invirase®, clarithromycin-Biaxin®,telithomycin-Ketek® and grapefruit juice.

8.2.1. Premedication with Antihistamines and Steroids

All subjects in the study will be pre-medicated with oral 180 mg fexofenadine two times (evening before (-12 h ± 2h, self-administered) and -2 h ± 1 hours before receiving study drug) and 40 mg methylprednisolone (or equivalent drug, for example prednisone 50 mg IV or dexamethasone 8 mg IV) intravenously -1 h ± 0.5 hours before receiving study drug (ie. prior to SEL-037 for Cohorts 1 and 2 and Part B of all cohorts or prior to SEL-110 for Cohorts 3-8, 10, 11, and 12) to reduce infusion reactions. These medications will be supplied by the clinic.

In Part C (Cohorts 13, 15, and 17), the premedication schedule described above will apply.

8.2.2. Management and Treatment of Infusion Reactions

The following steps will be implemented in this protocol to either reduce the risk of infusion reactions or manage infusion reactions.

- Subjects with immunoreactivity to PEG will be ineligible for the study
- Subjects with prior exposure to uricase therapy will be ineligible
- Each subject will be observed for infusion reactions after dosing of study drug in the clinic for 9 hours from the start of study drug infusion (SEL-110 or saline for Part A or SEL-037 for Part B). Subjects will be instructed on the signs or symptoms of infusion reaction and told to notify the PI immediately if they feel they are experiencing one.

- SEL-110 will be administered via syringe pump to control the infusion rate of the small volume of material
- SEL-037 will be administered by slow infusion over an hour only in a healthcare setting and by healthcare providers sufficiently equipped and prepared to manage infusion reactions including anaphylaxis.
- Subjects will be pre-medicated with 180 mg fexofenadine orally two times before dosing and 40 mg methylprednisolone (or equivalent drug) intravenously -1 ± 0.5h before dosing in an attempt to reduce infusion reactions in subjects.
- Subjects with a history of anaphylaxis, angioedema or previous infusion reactions will be excluded from the trial.
- Only sites with immediate capability to appropriately respond to a reaction of this severity will be allowed to participate in the trial to reduce the risk to any subject

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

8.2.3. Gout Flares (Prevention and Treatment)

All subjects that meet all inclusion and exclusion criteria will be given premedication for gout flare prevention. The regimen will begin 1 week prior to the first dosing of study drug and continue for as long as the subject is enrolled in the clinical study. Subjects will be given colchicine 1.2 mg as a single loading dose. Then they will continue with colchicine 0.6 mg QD for the remainder of their participation in the trial. If there is a contraindication to colchicine, the subject will receive ibuprofen 600 mg TID or an equivalent NSAID unless the subject has a contraindication to NSAID. If the subject has a contraindication to colchicine and to NSAIDs then no premedication will be given. The gout flare prevention medication should continue as long as the subject is enrolled in the clinical study. Subjects who began receiving a NSAID as gout flare prevention medication due to a contraindication to colchicine or under a previous version of this protocol should continue to receive the NSAID as long as the subject is enrolled in the study. These medications will be supplied by the clinic.

As gout flares are expected to happen despite the subject receiving preventative premedication they (the gout flare) are to be recorded as an adverse event and treated at the discretion of the investigator to provide adequate patient care. Investigators should consult with the medical monitor if a change in the subject's uric acid lowering medication is needed.

8.3. Treatment Compliance

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

8.4. Randomization

This is an open label clinical study. 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.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

This study has two study drugs, SEL-037 and SEL-110. SEL-037, lyophilized pegylated uricase, is supplied in stoppered 2 mL vials.

SEL-110 is a biodegradable polymeric nanoparticle encapsulating rapamycin which is supplied as a frozen suspension in stoppered 10 ml vials.

9.2. Study Drug Packaging and Labeling

Study drug will be supplied in vials in bulk boxes with boxes and vials unassigned to a subject.

9.3. Study Drug Storage

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

Upon receipt of the SEL-110 vials at the clinical site, the vials should be stored in a secured way at -15 to -25 °C within the primary or secondary box container in order to protect the SEL-110 from long-term light exposure.

9.4. Study Drug Preparation

Detailed procedures and sample calculations for dosing are found in the appendix (Section 19.3). Doses are calculated on a mg/kg basis according to a patient's weight. For the first treatment period dosing day (Visit 4), the weight used for dose preparation should be the subject's weight at screening. For later dosing, weight used for dose preparation should be the subject's weight at the Day 21 visit from the preceding treatment period.

9.4.1. SEL-037 Preparation

Each vial of SEL-037 will be reconstituted with 1.1 ml of sterile water for injection, USP (United States Pharmacopeia) which forms a 6 mg/mL concentrated solution and then diluted for administration in 100 ml of room temperature 0.9% sodium chloride for injection, USP. The full resultant volume of the SEL-037-normal saline solution (100 mL saline + required volume of reconstituted SEL-037) will be administered in the allotted time. Reconstituted SEL-037 is stable at room temperature and normal light conditions for 8 hours and the diluted SEL-037-normal saline solution for infusing should be used (i.e., infusion completed) within 6 hours of dilution.

9.4.2. SEL-110 Preparation

Each vial of SEL-110 will be thawed at room temperature and brought to room temperature over a 2 hour period before being drawn into appropriate size syringe/syringes for IV infusion with syringe pump. Thawed SEL-110 is stable for 24 hours at room temperature at normal light conditions.

SEL-110 should be administered as soon as possible after thawing; however, overnight thawing of SEL-110 at room temperature is permitted as long as the SEL-110 dose is completely administered within 24 hours of removal from its frozen storage conditions.

Doses are calculated on a mg/kg basis according to a patient's weight as described in Section 19.3.2. In cohorts receiving SEL-110 doses <0.10 mg/kg, the maximum dose per study visit, irrespective of the patient's weight, is 12 mg (equivalent to 6.0 mL of SEL-110). In cohorts receiving SEL-110 doses ≥0.10 mg/kg, there is no maximum dose; however, the rate of SEL-110 infusion will be restricted as described in Section 9.5, with an initial infusion rate of 5.5 mL/hour.

9.5. Administration

The thawed SEL-110 will be withdrawn from the vial and dosed via IV infusion 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 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.

The diluted SEL-037 in 0.9% sodium chloride for injection, USP 100 ml will be infused intravenously with an infusion pump over a 60 minute period.

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

Only if medically warranted in response to an AE will the Investigator modify the infusion parameters (decrease the rate of infusion, interrupt the infusion, or reduce the dose volume infused). The Investigator will notify the study team of any changes in infusion parameters.

9.6. Study Drug Accountability

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

9.7. Study Drug Disposal

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

10. PHARMACOKINETIC, PHARMACODYNAMIC AND RADIOLOGIC ASSESSMENTS

10.1. Sample Collection

Multiple blood samples will be collected from a venous access which is different and on an alternative limb than the site where study drug has been administered. The blood samples will be processed for a determination of whole blood levels of rapamycin, serum levels of SEL-037, uricase activity, serum uric acid levels, antibody (anti-PEG, anti-pegsiticase and anti-uricase) levels, inflammatory marker assessments and T-cell recall assessments according to the procedures in the study laboratory manual and in Section 1.1 (the schedule of events by cohort).

For Part C (Cohorts 13, 15, and 17), at each timepoint specified in the schedule of events (Section 1.1, Table 5), 2 blood samples will be collected for sUA measurement. One sample will be stored and shipped under ambient temperature and one sample will be stored and shipped under frozen conditions. Refer to the Laboratory Manual for details about sample handling.

The target blood collection time for the follow-up visits will be approximately the same time of day as the start of study drug dosing. Blood draws should be collected as close to the times specified, as possible. The acceptable window of collecting samples is:

- All dosing day (Treatment Periods 1, 2, 3, 4 and 5 Day 0) samples: target collection time ± 5 minute window
- Follow-up visit (Treatment Periods 1, 2, 3, 4 and 5 Day 1): the target collection time ± 2 hour window from D0 0 hour
- Follow-up visits (All except Day 1): the target collection time ± 8 hour window from D0 0 hour

- Dosing day (Treatment Periods 2, 3, 4 and 5, Day 0) and EOS visit: target day ± 1 day window
- Infusion reaction labs ± 5 minute window

The actual date and time that blood samples were drawn will be captured.

10.1.1. Additional Observational Visit

We have noted in the open label portion of the SEL-212/101 clinical trial and the initial portion of this SEL-212/201 clinical trial a persistent and beneficial effect on serum uric acid (sUA) when subjects are given SEL-212. This effect had persisted beyond 30 days in 17 of 31 subjects as of November 28, 2016. Based on these results, our goal is to follow subjects in Cohorts 3-8, 10, 11, and 12 beyond the current protocol Treatment Period 5, Day 30 Visit so that we may monitor and characterize the continued effect of SEL-212. Since there is a lag between lab results and the visits we would propose to see the subject for an additional visit if the sUA at the Treatment Period 5 Day 21 (Visit 32) is below 6 mg/dL. The additional visit would be 60 ± 1 days after the Treatment Period 5 Day 0 dosing day (Visit 28) at which time we would have the value of the sUA for the Day 21 (Visit 32) visit and their end of study visit (EOS P5 Day 30) value. The beneficial effect on the sUA is an unexpected, positive event which is beneficial to the subject and would likely be beneficial to the projected treatment population in the future.

In Part C (Cohorts 13, 15, and 17), subjects will be followed as described above.

Blood samples will be taken at the observational visits for assessments that will include: serum uric acid, and serum samples for anti-pegsiticase, anti-uricase and anti-PEG.

10.2. Analytical Procedures

Serum samples for SEL-037, for uricase activity and for uric acid determinations and whole blood samples for rapamycin determinations will be measured by validated methods. Serum samples for antibody (anti-PEG, anti-uricase, and anti-pegsiticase) determinations will be measured by validated methods. Procedures for processing samples will be included in the Study Manual.

Anti-pegsiticase, anti-uricase and anti-PEG samples will be sampled as per the schedule of events. At minimum, the samples to be analyzed will include the Day 14 and pre-dose samples for each treatment period as well as the Day 7, 14, 21 and EOS/Early Termination visit for the final treatment period for each subject.

10.3. Pharmacokinetic Assessments

The following PK parameters will be calculated on SEL-037, uricase activity and SEL-110 and assessed: the maximum observed serum concentration (C_{max}), the time at which C_{max} occurred (T_{max}), area under the serum concentration-time curve from time 0 to the time of last quantifiable concentration (AUC_{last}), area under the serum concentration-time curve from time 0 to infinity

(AUC_{inf}), the terminal elimination rate constant (K_{el}), terminal half-life ($t_{1/2}$), serum clearance of drug (CL), and apparent volume of distribution at equilibrium (V_{ss}).

10.4. Radiologic Assessments

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.

Procedures for the dual energy CT scan and analysis can be found in the study procedure manual.

10.5. Inflammatory Marker Assessments

Assessments of inflammatory markers will be performed as an exploratory measure for all subjects enrolled in each cohort at the predose visit for Treatment Period 1 (Visit 4/Day 0) and one additional inflammatory marker sample is to be collected for Treatment Period 5 – this may be collected at Visit 32/Day 21, between Visit 32/Day 21 and the EOS Visit, or at the EOS Visit/Day 30, or at Early Termination to investigate changes to inflammatory markers. No inflammatory marker assessments will be performed on subjects who have received their first treatment period dose under prior protocol versions not subject to inflammatory marker assessments. Procedures for the assessments and analysis can be found in the study procedure laboratory manual.

In Part C (Cohorts 13, 15, and 17), assessments of inflammatory markers will be performed as an exploratory measure for all subjects at the predose visit and day 7 visit for all Treatment Periods 1-5 and one additional inflammatory marker sample is to be collected near the end of Treatment Period 5 – this may be collected at Visit 32/Day 21, between Visit 32/Day 21 and the EOS Visit, or at the EOS Visit/Day 30, or at Early Termination to investigate changes to inflammatory markers.

10.6. T-cell recall Assessments

Assessments of T-cell recall responses to pegsiticase will be performed as an exploratory measure for all subjects in each cohort to investigate changes to T-cell recall response to pegsiticase. Assessments will be performed for each subject at 3 time points as per the schedules of events and at Early Term visit. If a predose T-cell recall specimen is not available this will not preclude the drawing of a specimen for T-cell recall at v18, v30 or at Early Term. Procedures for the assessments and analysis can be found in the study procedure manual.

11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

11.1.1. Demographic/Medical History

Demographic and significant medical history will be documented. Medical history will be recorded up to the time of dosing.

11.1.2. Vital Signs

Blood pressure, pulse and respiratory rate, temperature will be assessed at times indicated in the schedule of events ± 2.5 minutes. Blood pressure and heart rate will be recorded after at least 5 minutes of rest in a sitting position. If a conflict occurs during a visit because of multiple assessments needing to occur at the same time point, the ECG may be performed +/- 30 minutes from the designated time so that the vital signs and the blood draws may occur within the stated parameters.

11.1.3. Weight and Height

Height and weight will be recorded at the Screening Visit. Weight will also be recorded at Day 21 visits for each treatment period, ie. at Visits 8, 14, 20, 26 and 32.

11.1.4. Physical Examination

Physical examinations will be conducted at visits indicated in the schedule of events. Breast, rectal and urogenital exams are not required unless warranted based on the clinical judgment of the subject's medical history or current medical condition. The physical exam should be done by a physician or physician's assistant or similarly qualified individual.

11.1.5. Electrocardiogram (ECG)

ECG will be recorded with the subject in a semi-recumbent position after at least 5 minutes of rest and until 4 regular consecutive complexes are available depending on heart rate. If a conflict occurs during a visit because of multiple assessments needing to occur at the same time point, the ECG may be performed +/- 30 minutes from the designated time so that the vital signs and the blood draws may occur within the stated parameters. ECGs will be recorded at times indicated in the schedule of events. Twelve-lead ECGs will be recorded at paper speed of 25 mm/sec. ECG intervals RR, PR, QRS, QT, QTcB and QTcF will be calculated.

11.1.6. Laboratory Assessments

Fasting blood samples collected as indicated in the schedule of events will include a complete blood count (CBC) with differential, clinical chemistry (serum comprehensive metabolic panel including electrolytes – sodium, potassium, chloride, bi-carbonate, phosphate and magnesium),

lipid panel and coagulation parameters (international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen) and urinalysis.

Screening tests for glucose-6-phosphate dehydrogenase deficiencies, HbA1c, HIV and hepatitis C will be conducted at the Screening Visit.

The collection date, time, and study day will be documented.

11.1.7. Immunogenicity

Blood samples will be collected per the schedule of events. Procedures for processing samples will be included in the study laboratory manual.

11.2. Adverse and Serious Adverse Events

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of a non-serious adverse events (AE), serious adverse events (SAE) as provided in this protocol.

11.2.1. Definitions

11.2.1.1. Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug (i.e., study drug) in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An AE can arise with use of any drug or medicinal product.

Subjects will be considered enrolled in the study upon dosing of study drug for the first time. AEs (and thus SAEs) will be collected from the time the subject is dosed (infusion is started) until the end of the End of Study Visit. During the Screening Phase (from time informed consent is signed to immediately before dosing) any clinically significant changes in the subject's health will be recorded in the subject's medical history.

11.2.1.2. Unexpected Adverse Events and Unexpected Suspected Drug Reaction

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

11.2.1.3. Serious Adverse Event

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

- results in death;
- is life-threatening;

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

11.2.2. Recording Adverse Events

Subjects will be encouraged to spontaneously report any changes in health from the time of informed consent signing through completion of the study. Study staff will also inquire about any changes in the subject's health.

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

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

11.2.2.1. Adverse Event Term/Name/Description

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

11.2.2.2. Relationship to Study Drug

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

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

- Not Related (If no valid reason exists for suggesting a relationship to study drug or the AE was more likely explained by causes other than study drug).

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

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

11.2.2.3. Adverse Event Intensity/Severity Grading

AEs will be classified according to the Rheumatology Common Toxicity Criteria, version 2.0 (Woodworth et al. 2007). The general framework for grading AEs is provided below, and the full scale is provided in Section 19.1 of the protocol.

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

For an assessment of anaphylaxis, the clinical criteria for the diagnosis of anaphylaxis will be based on the National Institute of Allergy and Infectious Diseases (NIAID)/ Food Allergy & Anaphylaxis Network (FAAN) Symposium criteria for anaphylaxis diagnosis (Section 19.2).

11.2.2.4. Assessment of Outcome

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

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

11.2.2.5. Action taken with study drug

The action taken in regards to study drug will be assessed by the investigator as:

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

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

11.2.2.6. Laboratory and Diagnostic Abnormalities as Adverse Events

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

11.2.2.7. Pregnancy

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

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

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

11.3. Reporting Adverse Events

11.3.1. Adverse Event Reporting Period

The study period during which AEs must be reported is from the time the subject is dosed until the End of Study. During the Screening Phase (from time informed consent is signed up to the time of dosing) any clinically significant changes in the subject's health will be recorded in the subject's medical history.

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

11.3.2. SAE Reporting Procedures

If SAEs occur, all investigators should immediately, but not later than 24 hours of observing or learning of the event, complete and fax the SAE form to INC Drug Safety.
Facsimile (for SAE only): 877-464-7787
Email (for SAE only): INCDrugSafety@INCResearch.com
The investigator will complete the SAE form and provide all case information available at the time of the initial report. The investigator must include the following mandatory case information:

i. the subject identification number
ii. the event description
iii. the seriousness criteria
iv. the investigator's causality assessment

The reporting investigator must send the written and signed SAE report by facsimile or email, within 24 hours of observing, notification of, or learning of the SAE to INC Drug Safety as described above. Follow-up information regarding an SAE and the supporting data, including

laboratory findings and discharge summaries, should be sent by facsimile or email to INC Drug Safety within 24 hours of receipt of the information.

If the Investigator does not have all information regarding an SAE, the Investigator will not wait to receive additional information before completing as much of the form as possible and notifying the safety group. The form will be updated when additional information is received. The Investigator will always provide at minimum: 1) AE term or event name/description, 2) subject identifier, 3) an assessment of causality (see Section 11.2.2.2).

11.3.3. Regulatory Reporting Requirements for SAEs

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

11.3.4. Reporting Safety Information to the IRB

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

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

11.4. Follow-up of Adverse Events

The Investigator is required to proactively follow each subject and provide further information to in regards to AEs and SAEs. All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the appropriate CRF entries and event reporting forms will be updated, as appropriate.

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

The Sponsor or the Sponsor's designee may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The Investigator is obligated to assist. If a subject

dies during participation in the study or during a recognized follow-up period, the Sponsor will be provided with a copy of any post-mortem findings, including histopathology.

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

12. STATISTICS

12.1. Sample Size Determination

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 and pharmacokinetics, pharmacodynamics of a multiple IV infusions of SEL-212 and the safety, tolerability, pharmacokinetics, and pharmacodynamics of SEL-037 after multiple infusions.

12.2. Safety Analysis Set

All dosed subjects with any available post dose safety information will be included in the safety analysis.

12.3. PK Analysis Set

The PK analysis dataset will include all dosed subjects for which PK data is available with no significant protocol 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. All subjects and samples excluded from the analysis will be clearly documented in the study report.

12.4. PK Analyses

Data will be listed for all individual subjects with available SEL-037 serum concentrations and rapamycin whole blood levels. All concentrations below the lower limit of quantification (LLOQ) or missing data will be labeled as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in the estimation of pharmacokinetic parameters.

For each dose, descriptive statistics, including arithmetic mean, standard deviation, geometric mean, coefficient of variation, median, minimum, and maximum will be calculated for rapamycin in whole blood and SEL-037 serum concentrations at each sampling time and for all PK parameters.

Graphical representations of the results will include (but are not limited to) the following graphs as appropriate:

- Log-linear and linear-linear concentration-time profiles for each individual

- Log-linear and linear-linear concentration-time profiles for the mean values per dose
- Log-linear and linear-linear concentration-time profiles for the median values per dose
- Log-linear and linear-linear overlay plots of the individual concentration-time profiles for each dose

In addition, the relationship between PK parameters and dose will be evaluated graphically.

12.5. Pharmacodynamic Analyses

Pharmacodynamic analysis will be as described in the Statistical Analysis Plan.

Data will be listed for all individual subjects with available uric acid serum concentrations. For each dose, descriptive statistics, including arithmetic mean, standard deviation, and geometric mean, coefficient of variation, median, minimum, and maximum will be calculated at each sampling time.

The relationship of PK and PD will be explored and may be analyzed by Spearman rank-order correlations between serum uricase concentration and serum uric acid concentrations by each time point and overall time points. The corresponding p-values will also be provided.

12.6. Radiologic Analysis

Radiologic analysis will be as described in the Study procedure manual.

12.7. Inflammatory Markers Analysis

Change from baseline will be analyzed as described in the Study procedure manual.

12.8. Safety Analyses

Includes subjects in the safety analysis population. Baseline for all laboratory evaluations, vital signs, and ECG measurements will be defined as the last evaluation done before study drug administration.

12.8.1. Demographic and Baseline Characteristics

Baseline characteristics and demographics will be listed and summarized. Medical history will be listed only.

Extent of exposure to study drug will be listed by dose.

12.8.2. Adverse Events

The verbatim AE terms in the CRFs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). By definition, the study only collects treatment-emergent adverse events (TEAE) so all AEs are TEAEs. The percentage of subjects with specific TEAEs will be summarized for each dose.

All adverse events will be listed sorted by dose, subject, system organ class and preferred term.

TEAEs will be summarized (number of events, number and % of subjects having experienced at least one event) by dose, system organ class and preferred term. TEAEs will be also summarized by intensity, and by causality. SAEs will be only listed. A narrative will be produced for those subjects who have discontinued treatment due to an adverse event or who experienced a Grade 3 or higher events.

12.8.3. Clinical Laboratory Tests

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 each 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.

12.8.4. Cardiovascular Safety

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 ± standard error of the mean (SEM)) on changes from baseline over time will be provided. Listing of abnormal clinically significant evaluation as well as a listing of subjects with abnormal QTc values (>450, >480 and >500ms) and of subjects with abnormal QTc 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 reported.

12.8.5. Vital Signs

Pulse, temperature, respiration rate, and systolic blood pressure 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± SEM) on changes from baseline over time will be given as appropriate.

12.8.6. Physical Examination

Results of physical examinations will be listed and frequency tables computed.

12.8.7. Immunogenicity

Immunogenicity data will be listed.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

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

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

At study closure, monitors will also conduct all activities described in Section 16.3.

13.2. Audits and Inspections

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

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

13.3. Institutional Review Board (IRB)

This study will be conducted in full compliance with the Institutional Review Board (IRB) regulations in 21 CFR 56 and applicable local regulatory guidance, in accordance with ICH-GCP.

IRB approval for the investigation must be obtained before the study is initiated. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

14. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, the Sponsor (or Sponsor representative) may conduct a quality assurance audit. Please see Section 13.2 and Section 16.5 for more details regarding the audit process at any time during the conduct of the study or after study completion.

14.1. Regulatory Authority Approval

The Sponsor will obtain approval to conduct the study from the Food and Drug Administration (FDA) in accordance with FDA regulatory requirements prior to conducting the study.

14.2. Protocol Modifications

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

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

15. ETHICS

15.1. Ethics Review

The Investigator is responsible for ensuring that this protocol, the site's informed consent form (ICF), and any other information that will be presented to potential subjects (e.g., advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate IRB. The Investigator agrees to allow the IRB direct access to all relevant documents. The IRB must be constituted in accordance with all applicable regulatory requirements. The Sponsor or contract research organization (CRO) will provide the Investigator with relevant document(s)/data that are needed for IRB review and approval of the study. The IRB must approve the study and ICF before study drug(s) and other study material can be shipped to the site.

If the protocol, the ICF, or any other information that the IRB has approved for presentation to potential subjects is amended during the study, the Investigator is responsible for ensuring the IRB reviews and approves these amended documents, where applicable. The Investigator must follow all applicable regulatory requirements pertaining to the use of an amended ICF including

obtaining IRB approval of the amended form before new subjects consent to take part in the study using this version of the form. Copies of the IRB approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to the Sponsor or CRO managing the study, as appropriate.

15.2. Ethical Conduct of the Study

This study will be conducted in accordance with ICH-GCP guidelines and all applicable regulatory requirements, including, where applicable, the Declaration of Helsinki.

15.3. Written Informed Consent

This study will be conducted in full compliance with the informed consent regulations in 21 CFR 50. The consent form must be reviewed and approved by the Sponsor prior to submission to the IRB. The consent form must be approved by the IRB prior to initiation of the study. The Investigator is responsible for obtaining written consent (signed and dated ICF) from potential subjects prior to performing any trial tests or assessments required by the protocol. A copy of the signed consent document will be given to the patient and the original retained by the Investigator.

No Investigator may involve a human being as a subject in research unless the Investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An Investigator may seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether to participate and that minimize the possibility of coercion or undue influence. The information given to the subject or the representative must be in a language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the Investigator, the institution, the Sponsor, or its agents from liability for negligence.

An IRB-approved consent form should inform each prospective subject or the legally authorized representative of each prospective subject of the purpose and the nature of the study, its possible hazards and benefits, and the subject's right to withdraw from the study at any time without prejudice to further treatment. Exemptions to the requirement for informed consent in the United States are described in 21 CFR 50.23.

The Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

16. DATA HANDLING AND RECORDKEEPING

16.1. Case Report Form Completion and Source Documentation

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record observations and other data pertinent to the study for each study participant. Subject data are collected by the investigator or designee using source documents that are entered into a CRF, defined by the Sponsor. Subject data necessary for analysis and reporting will be first collected in the source documents and then entered into the validated CRF database system.

All information recorded on CRFs must be consistent with the subject's source documentation (i.e., medical records). The Investigator is responsible for the accuracy of the data transcribed from all source documentation. All CRF entries should be made within a reasonable timeframe from the time of a subject's visit. A monitor representing the sponsor will verify the CRF documentation for each patient against the source documents at the study center. Instances of missing or uninterpretable data will be brought to the attention of the investigator and/or sponsor for resolution.

16.2. Data Management

Clinical data management will be performed in accordance with applicable study standards and data cleaning procedures. Database lock will occur when data management quality control procedures are completed.

16.3. Study Site Close-Out

Upon completion of the study, the monitor may conduct the following activities in conjunction with the investigator or site staff, as appropriate:

1. Resolve data queries.
2. Accountability, reconciliation, and return of unused study drug(s).
3. Review of final site study records for completeness.
4. Return all study-specific equipment to the appropriate vendor as required.

16.4. Retention of Study Documents and Records

Following closure of the study, the Investigator must maintain all site study records in a safe and secure location. All CRF data will be retained by and are the sole property of the Sponsor. The investigator will retain a copy of all source documents and CRF data (i.e., either hard copies if a paper CRF or DVD-ROM containing pdf files of CRFs provided by the sponsor) for the subjects enrolled at the site. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection). Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is

taken. The Investigator must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the Investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The Sponsor will inform the Investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or the Sponsor standards/procedures; otherwise, the retention period will default to 15 years.

The Investigator must notify the Sponsor of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the Investigator leaves the site.

16.5. Inspection of Records

The Sponsor (or Sponsor representative) will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

17. PUBLICATION POLICY

In the event of a conflict between the provisions of this section and a written contract regarding the conduct of Study between Sponsor (or a contract research organization) and the site, the Investigator or any person assisting Investigator with the Study, the terms of that contract shall control.

17.1. Ownership

All information provided by or on behalf of Sponsor and all data and information generated by the site, the Investigator or any person assisting Investigator with the Study as part of or in connection with the Study (other than a subject's medical records), is the sole and exclusive property of Sponsor. All rights, title, and interests in and to any inventions, discoveries or know-how made, conceived, learned or first reduced to practice by the site, Investigator or any person assisting Investigator with the Study during the course of, in relation to, or as a result of the Study (and any intellectual property rights related thereto) are the sole and exclusive property of the Sponsor, and are hereby assigned to Sponsor.

17.2. Confidentiality

All information provided by the Sponsor and all data and information generated by the site as part of or in relation to the Study (other than a subject's medical records) will be kept confidential by the Investigator, the site, and any person assisting Investigator with the Study.

This information and data shall not be used by the site, Investigator, or any person assisting Investigator with the Study for any purpose other than conducting the Study. These restrictions do not apply to: 1) information which becomes publicly available through no fault of the site, Investigator or any person assisting Investigator with the Study; 2) information which it is necessary to disclose in confidence to an IRB solely for the evaluation of the Study; 3) information which it is necessary to disclose in order to provide appropriate medical care to a Study subject; or 4) Study results which are permitted to be published as described in the next section.

17.3. Publication

If the Study is a multi-center study, the first publication or disclosure of Study results shall include data from all sites.

Investigator may publish the results of the Study only for noncommercial, educational or academic purposes provided that: 1) said publication is made after the multi-center publication; and 2) prior to making the publication, or otherwise disclosing the Study results, Investigator provides Sponsor with a copy of the proposed publication and allows Sponsor a reasonable period to review. Proposed publications shall not include the Sponsor confidential information (other than the Study results) or personal data with respect to any subject (such as name or initials) and if the Sponsor identifies any such the Sponsor confidential information in a proposed publication, it shall be removed.

At the Sponsor's request, the submission, publication or other disclosure of a proposed publication will be delayed a sufficient time to allow the Sponsor to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights contained in such proposed publication.

18. LIST OF REFERENCE

Barlow, A. D., Nicholson, M. L. and Herbert, T. P. (2013). "Evidence for rapamycin toxicity in pancreatic beta-cells and a review of the underlying molecular mechanisms." Diabetes **62**(8): 2674-2682;

Biggers, K. and Scheinfeld, N. (2008). "Pegloticase, a polyethylene glycol conjugate of uricase for the potential intravenous treatment of gout." Curr Opin Investig Drugs **9**(4): 422-429;

Bomalaski, J. S., Holtsberg, F. W., Ensor, C. M. and Clark, M. A. (2002). "Uricase formulated with polyethylene glycol (uricase-PEG 20): biochemical rationale and preclinical studies." J Rheumatol **29**(9): 1942-1949;

Cammalleri, L. and Malaguarnera, M. (2007). "Rasburicase represents a new tool for hyperuricemia in tumor lysis syndrome and in gout." Int J Med Sci **4**(2): 83-93;

Campion, E. W., Glynn, R. J. and DeLabry, L. O. (1987). "Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study." Am J Med **82**(3): 421-426;

Chen, Y., Zhang, Z., Lin, Y., Lin, H., Li, M., Nie, P., Chen, L., Qiu, J., Lu, Y., Chen, L., Xu, B., Lin, W., Zhang, J., Du, H., Liang, J. and Zhang, Z. (2013). "Long-term Impact of Immunosuppressants at Therapeutic Doses on Male Reproductive System in Unilateral Nephrectomized Rats: A Comparative Study." BioMed Res Int 2013:690382. doi: 10.1155/2013/690382;

Choi, H. (2006). "Epidemiology of crystal arthropathy." Rheum Dis Clin North Am **32**(2): 255-273, v;

Cortes, J., Moore, J. O., Maziarz, R. T., Wetzler, M., Craig, M., Matous, J., Luger, S., Dey, B. R., Schiller, G. J., Pham, D., Abboud, C. N., Krishnamurthy, M., Brown, A., Jr., Laadem, A. and Seiter, K. (2010). "Control of plasma uric acid in adults at risk for tumor Lysis syndrome: efficacy and safety of rasburicase alone and rasburicase followed by allopurinol compared with allopurinol alone--results of a multicenter phase III study." J Clin Oncol **28**(27): 4207-4213;

Deutsch, M.A., Kaczmarek, I., Huber, S., Schmauss, D., Beiras-Fernandez, A., Schmoeckel, M., Ochsenkuehn, R., Meiser, B., Mueller-Hoecker, J. and Reichart, B. (2007). " Sirolimus-associated infertility: case report and literature review of possible mechanisms." Am J Transplant. 7(10):2414-21.

Fishburn, C. S. (2008). "The pharmacology of PEGylation: balancing PD with PK to generate novel therapeutics." J Pharm Sci **97**(10): 4167-4183;

Ghisdal, L., Van Laecke, S., Abramowicz, M. J., Vanholder, R. and Abramowicz, D. (2012). "New-onset diabetes after renal transplantation: risk assessment and management." Diabetes Care **35**(1): 181-188;

Goldman, S. C., Holcenberg, J. S., Finklestein, J. Z., Hutchinson, R., Kreissman, S., Johnson, F. L., Tou, C., Harvey, E., Morris, E. and Cairo, M. S. (2001). "A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis." Blood **97**(10): 2998-3003;

Gray, L.E., Wilson, V., Noriega, N., Lambright, C., Furr, J., Stoker, T.E., Laws, S.C., Goldman, J., Cooper, R.L. and Foster, P.M.D. (2004). "Use of the Laboratory Rat as a Model in Endocrine Disruptor Screening and Testing." ILAR J 45: 425-437;

Hakeam, H. A., Al-Jedai, A. H., Raza, S. M. and Hamawi, K. (2008). "Sirolimus induced dyslipidemia in tacrolimus based vs. tacrolimus free immunosuppressive regimens in renal transplant recipients." Ann Transplant **13**(2): 46-53;

Johnston, O., Rose, C. L., Webster, A. C. and Gill, J. S. (2008). "Sirolimus is associated with new-onset diabetes in kidney transplant recipients." J Am Soc Nephrol **19**(7): 1411-1418;

Khanna, D., Fitzgerald, J. D., Khanna, P. P., Bae, S., Singh, M. K., Neogi, T., Pillinger, M. H., Merill, J., Lee, S., Prakash, S., Kaldas, M., Gogia, M., Perez-Ruiz, F., Taylor, W., Liote, F., Choi, H., Singh, J. A., Dalbeth, N., Kaplan, S., Niyyar, V., Jones, D., Yarows, S. A., Roessler, B., Kerr, G., King, C., Levy, G., Furst, D. E., Edwards, N. L., Mandell, B., Schumacher, H. R., Robbins, M., Wenger, N., Terkeltaub, R. and American College of, R. (2012a). "2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia." Arthritis Care Res (Hoboken) **64**(10): 1431-1446;

Khanna, D., Khanna, P. P., Fitzgerald, J. D., Singh, M. K., Bae, S., Neogi, T., Pillinger, M. H., Merill, J., Lee, S., Prakash, S., Kaldas, M., Gogia, M., Perez-Ruiz, F., Taylor, W., Liote, F., Choi, H., Singh, J. A., Dalbeth, N., Kaplan, S., Niyyar, V., Jones, D., Yarows, S. A., Roessler, B., Kerr, G., King, C., Levy, G., Furst, D. E., Edwards, N. L., Mandell, B., Schumacher, H. R., Robbins, M., Wenger, N., Terkeltaub, R. and American College of, R. (2012b). "2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis." Arthritis Care Res (Hoboken) **64**(10): 1447-1461;

Koyama, Y., Ichikawa, T. and Nakano, E. (1996). "Cloning, sequence analysis, and expression in Escherichia coli of the gene encoding the Candida utilis urate oxidase (uricase)." J Biochem **120**(5): 969-973;

Lipsky, P. E., Calabrese, L. H., Kavanaugh, A., Sundy, J. S., Wright, D., Wolfson, M. and Becker, M. A. (2014). "Pegloticase immunogenicity: the relationship between efficacy and

antibody development in patients treated for refractory chronic gout." Arthritis Res Ther **16**(2): R60;

Mehvar, R. (2000). "Modulation of the pharmacokinetics and pharmacodynamics of proteins by polyethylene glycol conjugation." J Pharm Pharm Sci **3**(1): 125-136;

Oda, M., Satta, Y., Takenaka, O. and Takahata, N. (2002). "Loss of urate oxidase activity in hominoids and its evolutionary implications." Mol Biol Evol **19**(5): 640-653;

Oldfield, V. and Perry, C. M. (2006). "Rasburicase: a review of its use in the management of anticancer therapy-induced hyperuricaemia." Drugs **66**(4): 529-545;

Pereira, M. J., Palming, J., Rizell, M., Aureliano, M., Carvalho, E., Svensson, M. K. and Eriksson, J. W. (2012). "mTOR inhibition with rapamycin causes impaired insulin signalling and glucose uptake in human subcutaneous and omental adipocytes." Mol Cell Endocrinol **355**(1): 96-105;

Roa, J., Garcia-Galiano, D., Varela, L., Sanchez-Garrido, M. A., Pineda, R., Castellano, J. M., Ruiz-Pino, F., Romero, M., Aguilar, E., Lopez, M., Gaytan, F., Dieguez, C., Pinilla, L. and Tena-Sempere, M. (2009). "The mammalian target of rapamycin as novel central regulator of puberty onset via modulation of hypothalamic Kiss1 system." Endocrinology **150**(11): 5016-5026;

Rovira J., Diekmann F., Ramírez-Bajo M.J., Bañón-Maneus E., Moya-Rull D., and Campistol J.M. (2012). "Sirolimus-associated testicular toxicity: detrimental but reversible." Transplantation **93**(9):874-9;

Sampson, H. A., Munoz-Furlong, A., Campbell, R. L., Adkinson, N. F., Jr., Bock, S. A., Branum, A., Brown, S. G., Camargo, C. A., Jr., Cydulka, R., Galli, S. J., Gidudu, J., Gruchalla, R. S., Harlor, A. D., Jr., Hepner, D. L., Lewis, L. M., Lieberman, P. L., Metcalfe, D. D., O'Connor, R., Muraro, A., Rudman, A., Schmitt, C., Scherrer, D., Simons, F. E., Thomas, S., Wood, J. P. and Decker, W. W. (2006). "Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium." J Allergy Clin Immunol **117**(2): 391-397;

Sherman, M. R., Saifer, M. G. and Perez-Ruiz, F. (2008). "PEG-uricase in the management of treatment-resistant gout and hyperuricemia." Adv Drug Deliv Rev **60**(1): 59-68;

Shivaswamy, V. (2013). "Immunosupppression and Endocrine Dysfunction." Journal of Transplantation Technologies & Research **01**(S2);

Skrzypek, J. and Krause, W. (2007). " Azoospermia in a renal transplant recipient during sirolimus (rapamycin) treatment." Andrologia. 39(5):198-9;

So, A. (2008). "Developments in the scientific and clinical understanding of gout." Arthritis Res Ther **10**(5): 221;

Soefje, S.A.,Karnad, A., Brenner, A.J.(2011)."Common toxicities of mammalian target rapamycin inhibitors." Target Oncology **6**:125-129

Sundy, J. S., Baraf, H. S., Yood, R. A., Edwards, N. L., Gutierrez-Urena, S. R., Treadwell, E. L., Vazquez-Mellado, J., White, W. B., Lipsky, P. E., Horowitz, Z., Huang, W., Maroli, A. N., Waltrip, R. W., 2nd, Hamburger, S. A. and Becker, M. A. (2011). "Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials." JAMA **306**(7): 711-720;

Sundy, J. S., Ganson, N. J., Kelly, S. J., Scarlett, E. L., Rehrig, C. D., Huang, W. and Hershfield, M. S. (2007). "Pharmacokinetics and pharmacodynamics of intravenous PEGylated recombinant mammalian urate oxidase in patients with refractory gout." Arthritis Rheum **56**(3): 1021-1028;

Veronese, F. M. and Mero, A. (2008). "The impact of PEGylation on biological therapies." BioDrugs **22**(5): 315-329;

Woodworth, T., Furst, D. E., Alten, R., Bingham, C. O., 3rd, Yocum, D., Sloan, V., Tsuji, W., Stevens, R., Fries, J., Witter, J., Johnson, K., Lassere, M. and Brooks, P. (2007). "Standardizing assessment and reporting of adverse effects in rheumatology clinical trials II: the Rheumatology Common Toxicity Criteria v.2.0." J Rheumatol **34**(6): 1401-1414;

Wortmann, R. L., Firestein, G. S., Budd, R. C., Gabriel, S. E., McInnes, I. B. and O'Dell, J. R. (2008). Gout and Hyperuricemia. Kelley's Textbook of Rheumatol, Elsevier**:** 1481-1506.

Wu, X. W., Lee, C. C., Muzny, D. M. and Caskey, C. T. (1989). "Urate oxidase: primary structure and evolutionary implications." Proc Natl Acad Sci U S A **86**(23): 9412-9416;

Wu, X. W., Muzny, D. M., Lee, C. C. and Caskey, C. T. (1992). "Two independent mutational events in the loss of urate oxidase during hominoid evolution." J Mol Evol **34**(1): 78-84;

Zalipsky, S. and Lee, C. (1992). Use of Functionalized Poly(Ethylene Glycol)s for Modification of Polypeptides. Poly(Ethylene Glycol) Chemistry. J. M. Harris, Springer US**:** 347-370.

Zuber, J., Anglicheau, D., Elie, C., Bererhi, L., Timsit, M.O., Mamzer-Bruneel, M.F., Ciroldi, M., Martinez, F., Snanoudj, R., Hiesse, C., Kreis, H., Eustache, F., Laborde, K., Thervet, E. and Legendre, C. (2008). "Sirolimus may reduce fertility in male renal transplant recipients." Am J Transplant. 8(7):1471-9.

19. APPENDICES

19.1. Common Toxicity Criteria for Rheumatology, version 2.0

(Woodworth, 2007)

	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-Threatening)
	Asymptomatic, or transient	Symptomatic	Prolonged symptoms, reversible	At risk of death
	Short duration (< 1 week)	Duration 1–2 weeks	Major functional impairment	Substantial disability, especially if permanent
	No change in lifestyle	Alter lifestyle occasionally		
	No medication or over-the-counter medications	Medications give relief (may be prescription)	Prescription medications/partial relief; hospitalized <24 hours	Hospitalized >24 hours
			Temporary or permanent study drug discontinuation	Permanent study drug discontinuation

19.1.1. Clinical Signs and Symptoms

A. Allergic/Immunologic

	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-Threatening)
A1. Allergic reaction/ hypersensitivity (includes drug fever)	Transient rash; drug fever <38°C; transient, asymptomatic bronchospasm	Generalized urticaria responsive to meds; drug fever >38°C; reversible bronchospasm	Symptomatic bronchospasm requiring meds; symptomatic urticaria persisting with meds; allergy-related edema/angioedema	Anaphylaxis; laryngeal/ pharyngeal edema requiring resuscitation
A2. Autoimmune reaction	Serologic or other evidence of autoimmune reaction, but patient asymptomatic, all organ function normal and no treatment is required (e.g. vitiligo)	Evidence of autoimmune reaction involving a non-essential organ or functions, requiring treatment other than immunosuppressive drugs (e.g. hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or toxicity requiring short term immunosuppressive treatment (e.g. transient colitis or anemia)	Causes major organ dysfunction; or progressive, not reversible, or requires long term administration of high dose immunosuppressive therapy
A3. Rhinitis (including sneezing, nasal stuffiness, post-nasal discharge)	Transient, non-prescription meds relieve	Prescription med required, slow response to meds	Corticosteroids or other prescription med with persistent disabling symptoms such as impaired exercise tolerance	N/A
A4. Serum sickness	Transient, non-prescription meds relieve	Symptomatic, slow response to meds (e.g. oral corticosteroids)	Prolonged; symptoms only partially relieved by meds; parenteral corticosteroids required	Major organ dysfunction, requires long-term high-dose immunosuppressive therapy
A5. Vasculitis	Localized, not requiring treatment; or rapid response to meds; cutaneous	Symptomatic, slow response to meds (e.g. oral corticosteroids)	Generalized, parenteral corticosteroids required or/and short duration hospitalization	Prolonged, hospitalization, ischemic changes, amputation

B. Cardiac

	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-Threatening)
B1. Arrhythmia	Transient, asymptomatic	Transient, but symptomatic or recurrent, responds to meds	Recurrent/persistent; maintenance prescription	Unstable, hospitalization required; parenteral meds
B2. Cardiac function decreased	Asymptomatic decline in resting ejection fraction by >10%, but <20% of baseline value	Asymptomatic decline of resting ejection fraction ≥20% of baseline value	CHF responsive to treatment	Severe or refractory CHF
B3. Edema	Asymptomatic (e.g. 1+ feet/calves), self-limited, no therapy required	Symptomatic (e.g. 2+ feet/calves), requires therapy	Symptoms limiting function (e.g. 3+ feet/calves, 2+ thighs), partial relief with treatment, prolonged	Anasarca; no response to treatment
B4. Hypertension (new onset or worsening)	Asymptomatic, transient increase by >20 mm Hg (diastolic) or to >150/100 if previously normal, no therapy required	Recurrent or persistent increase >150/100 or by >10 mm Hg (diastolic), requiring and responding readily to treatment	Symptomatic increase >150/100, >20 mm Hg, persistent, requiring multi-agent therapy, difficult to control	Hypertensive crisis
B5. Hypotension (without underlying diagnosis)	Transient, intermittent, asymptomatic, orthostatic decrease in blood pressure >20 mm Hg	Symptomatic, without interference with function, recurrent or persistent >20 mm Hg decrease, responds to treatment	Syncope or symptomatic, interferes with function, requiring therapy and sustained medical attention, dose adjustment or drug discontinuation	Shock
B6. Myocardial ischemia	Transient chest pain/ECG changes; rapid relief with nitro	Recurring chest pain, transient ECG ST-T changes; treatment relieves	Angina with infraction, no or minimal functional compromise, reduce dose or discontinue study drug	Acute myocardial infarction, arrhythmia and/or CHF
B7. Pericarditis/ pericardial effusion	Rub heard, asymptomatic	Detectable effusion by echocardiogram, symptomatic NSAID required	Detectable on chest X-ray, dyspnea; or pericardiocentesis; requires corticosteroids	Pulsus alternates with low cardiac output; requires surgery
B8. Phlebitis/ thrombosis/ embolism (excludes injection site)	Asymptomatic, superficial, transient, local, or no treatment required	Symptomatic, recurrent, deep vein thrombosis, no anticoagulant therapy required	Deep vein thrombosis requiring anticoagulant therapy	Pulmonary embolism

C. General (Constitutional)

	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-Threatening)
C1. Fatigue/malaise (asthenia)	Increase over baseline; most usual daily functions maintained, short term	Limits daily function intermittently over time	Interferes with basic ADL, persistent	Unable to care for self, bed or wheelchair bound >50% of day debilitating, hospitalization
C2. Fever (pyrexia) (note: fever due to drug allergy should be coded as allergy)	Transient, few symptoms 37.7-38.5°C	Symptomatic, recurrent 38.6-39.9°C; relieved by meds	≥40°C; ≤24h, persistent symptoms; partial response to meds.	≥40°C, debilitating, >24 hr, hospitalization; no relief with meds
C3. Headache	Transient or intermittent, no meds or relieved with OTC	Persistent, recurring, non-narcotic analgesics relieve	Prolonged with limited response to narcotic medicine	Intractable, debilitating, requires parenteral meds.
C4. Insomnia	Difficulty sleeping, short term, not interfering with function	Difficulty sleeping, short term, interfering with function, use of prescription med.	Prolonged symptoms, with limited response to narcotic meds.	Debilitating, hospitalization; no relief with meds
C5. Rigors, chills	Asymptomatic, transient, no meds, or non-narcotic meds relieve	Symptomatic, narcotic meds relieve.	Prolonged symptoms, with limited response to narcotic meds.	Debilitating, hospitalization; no relief with meds
C6. Sweating (diaphoresis)	Episodic, transient	Frequent, short term	Frequent, drenching, disabling	Dehydration, requiring IV fluids/ hospitalization >24 hr
C7. Weight gain	5-9.9%	10-19.9%	20-30%	N/A
C8. Weight loss	5-9.9%	10-19.9%	20-30%	N/A

D. Dermatologic

	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-Threatening)
D1. Alopecia	Subjective, transient	Objective, fully reversible	Patchy, wig used, partly reversible	Complete, or irreversible even if patchy
D2. Bullous eruption	Localized, asymptomatic	Localized, symptomatic, requiring treatment	Generalized, responsive to treatment, reversible	Prolonged, generalized, or requiring hospitalization for treatment
D3. Dry skin	Asymptomatic, controlled with emollients	Symptoms eventually (1-2 wks) controlled with emollients	Generalized, interfering with ADL >2 wks, persistent pruritis, partially responsive to treatment	Disabling for extended period, unresponsive to ancillary therapy and requiring study drug discontinuation for relief
D4. Injection site reaction	Local erythema, pain, pruritis, <few days	Erythema, pain, edema, may include superficial phlebitis, 1-2 wks	Prolonged induration, superficial ulceration; includes thrombosis	Major ulceration necrosis requiring surgery
D5. Petechiae (without vasculitis)	Few, transient asymptomatic	Dependent areas, persistent up to 2 wks	Generalized, responsive to treatment; reversible	Prolonged, irreversible, disabling
D6. Photosensitivity	Transient erythema	Painful erythema and edema requiring topical treatment	Blistering or desquamation, requires systematic corticosteroids	Generalized exfoliation or hospitalization
D7. Pruritis	Localized, asymptomatic, transient, local treatment	Intense or generalized, relieved by systematic medication	Intense or generalized, poorly controlled despite treatment	Disabling, irreversible
D8. Rash (not bullous)	Erythema, scattered macular/popular eruption; pruritis transient; TOC or no meds	Diffuse macular/popular eruption or erythema with pruritis; dry desquamation; treatment required	Generalized, moist desquamation, requires systematic corticosteroids; responsive to treatment; reversible	Exfoliative or ulcerating; or requires hospitalization; or parenteral corticosteroids
D9. Indurartion/fibrosis/ thickening (not sclerodermal)	Localized, high density on palpation, reversible, no effect on ADL and not disfiguring	Local areas <50% body surface, not disfiguring, transient interference with ADL, reversible	Generalized, disfiguring, interferes with ADL, reversible	Disabling, irreversible, systemic symptoms

E. Ear/Nose/Throat

	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-Threatening)
E1. Hearing loss	Transient, intermittent, no interference with function	Symptomatic, treatment required, reversible	Interferes with function, incomplete response to treatment	Irreversible deafness
E2. Sense of smell	Slightly altered	Markedly altered	Complete loss, reversible	Complete loss, without recovery
E3. Stomatitis	Asymptomatic	Painful, multiple, can eat	Interferes with nutrition. Slowly reversible	Requires enteral support; residual dysfunction
E4. Taste disturbance (dysgeusia)	Transiently altered; metallic	Persistently altered, limited effect on eating	Disabling, effect on nutrition	N/A
E5. Tinnitus	Intermittent, transient, no interference with function	Requires treatment, reversible	Disabling, or associated with hearing loss	Irreversible deafness
E6. Voice changes (includes hoarseness, loss of voice, laryngitis)	Intermittent hoarseness, able to vocalize	Persistent hoarseness, able to vocalize	Whispered speech, slow return of ability to vocalize	Unable to vocalize for extended period
E7. Xerostomia (dry mouth)	Transient dryness	Relief with meds	Interferes with nutrition, slowly reversible	Extended duration interference with nutrition, requires parenteral nutrition

F. Eye/Ophthalmologic

	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-Threatening)
F1. Cataract	Asymptomatic, no change in vision, non-progressive	Symptomatic, partial visual loss, progressive	Symptoms impairing function, vision loss requiring treatment, including surgery	N/A
F2. Conjunctivitis	Asymptomatic, transient, rapid response to treatment	Symptomatic, responds to treatment, changes not interfering with function	Symptoms prolonged, partial response to treatment, interferes with function	N/A
F3. Lacrimation increased (tearing, watery eyes)	Symptoms not requiring treatment, transient	Symptomatic, treatment required, reversible	Unresponsive to treatment with major effect on function	N/A
F4. Retinopathy	Asymptomatic, non-progressive, no treatment	Reversible change in vision; readily responsive to treatment	Disabling change in vision ophthalmological findings reversible, sight improves over time	Loss of sight
F5. Vision changes (e.g. blurred, photophobia, night blindness, vitreous floaters)	Asymptomatic, transient, no treatment required	Symptomatic, vision changes not interfering with function, reversible	Symptomatic, vision changes interfering with function	Loss of sight
F6. Xerophtalmia (dry eyes)	Mild scratchiness	Symptomatic without interfering with function, requires artificial tears	Interferes with vision/function, corneal ulceration	Loss of sight

G. Gastrointestinal

	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-Threatening)
G1. Anorexia	Adequate food intake, minimal weight loss	Symptoms requiring oral nutritional supplementation	Prolonged, requiring IV support	Requires hospitalization for nutritional support
G2. Constipation	Asymptomatic, transient, responds to stool softener, OTC laxatives	Symptomatic, requiring prescription laxatives, reversible	Obstipation requiring medical intervention	Bowel obstruction, surgery required.
G3. Diarrhea	Transient, increase of 2-3 stools/day over pre-treatment (no blood or mucus), OTC agents relieve	Symptomatic, increase 4-6 stools/day, nocturnal stools, cramping, requires treatment with prescription meds.	Increase >6 stools/day, associated with disabling symptoms, e.g. incontinence, severe cramping, partial response to treatment.	Prolonged, dehydration, unresponsive to treatment, requires hospitalization.
G4. Dyspepsia (heartburn)	Transient, intermittent, responds to OTC antacids, H-2 blockers	Prolonged, recurrent, requires prescription meds. relieved by meds	Persistent despite treatment, interferes with function, associated with GI bleeding	N/A
G5. GI bleed (gastritis, gastric or duodenal ulcer diagnosed-defined etiology)	Asymptomatic, endoscopic finding, hemocult + stools, no transfusion, responds rapidly to treatment	Symptomatic, transfusion ≤2 units needed; responds to treatment	Hematemesis, transfusion 3-4 units, prolonged interference with function	Recurrent, transfusion > 4 units, perforation, requiring surgery, hospitalization
G6. Hematochezia (rectal bleeding)	Hemorrhodial, asymptomatic, no transfusion	Symptomatic, transfusion ≤ 2 units, reversible	Recurrent, transfusion >3-4 units	> 4 units, hypotension, requiring hospitalization
G7. Hepatitis	Laboratory abnormalities, asymptomatic, reversible	Symptomatic laboratory abnormalities, not interfering with function, slowly reversible	Laboratory abnormalities persistent > 2 wks, symptoms interfere with function	Progressive, hepato-renal, anasarca, pre-coma or coma
G8. Nausea or nausea/vomiting (use diagnostic term)	Transient, intermittent, minimal interference with intake, rapid response to meds.	Persistent, recurrent, requires prescription meds, intake maintained	Prolonged, interferes with daily function and nutritional intake, periodic IV fluids	Hypotensive, hospitalization, parenteral nutrition, unresponsive to out-patient management
G9. Pancreatitis	Amylase elevation, intermittent nausea/vomiting, transient, responds rapidly to treatment	Amylase elevation with abdominal pain, nausea, occasional vomiting, responsive to treatment	Severe, persistent abdominal pain with pancreatic enzyme elevation, incomplete or slow response to treatment	Complicated by shock, haemorrhage (acute circulatory failure)
G10. Procitis	Perianal pruritus, haemorrhoids (new onset), transient, or intermittent, relieved by OTC meds	Tenesmus or ulcerations, anal fissure, responsive to treatment, minimal interference with function	Unresponsive to treatment, marked interference with function	Mucosal necrosis with haemorrhage, infection, surgery required

H. Musculoskeletal

	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-Threatening)
H1. Avascular necrosis	Asymptomatic MRI changes, non-progressive	MRI changes and symptoms responsive to rest and analgesia	MRI changes, symptoms requiring surgical intervention	Wheelchair bound; surgical repair not possible
H2. Arthralgia	Intermittent transient symptoms, no meds or relieved by OTC meds	Persistent or recurrent symptoms, resolve with meds, little effect on function	Severe symptoms despite meds, impairs function	Debilitating, hospitalization required for treatment
H3. Leg cramps	Transient, intermittent, does not interfere with function	Recurrent symptoms, minimally interferes with function or sleep, responds to meds	Persistent, prolonged interference with function or sleep, partial or no response to meds	N/A
H4. Myalgia	Occasional; does not interfere with function	Frequent, requires meds (non-narcotic); minor effects on function	Major change in function/lifestyle, narcotic pain meds	Debilitating, profound weakness, requires wheelchair, unresponsive to meds

I. Neuropsychiatric

	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-Threatening)
I1. Anxiety or Depression (mood alteration)	Symptomatic, does not interfere with function; no meds	Frequent symptoms, responds to meds; interferes with ADL at times	Persistent, prolonged symptoms, partial or no response to meds, limits daily function	Suicidal ideation or danger to self
I2. Cerebrovascular ischaemia	N/A	Single transient ischemic event, responsive to treatment	Recurrent transient ischemic events	Cerebrovascular accident with permanent disability
I3. Cognitive disturbance	Subjective symptoms, transient, intermittent, not interfering with function	Objective symptoms, persisting, interferes with daily function occasionally	Persistent or worsening objective symptoms; interferes with routine daily	Debilitating/disabling and permanent; toxic psychosis
I4. Depressed consciousness (somnolence)	Observed, transient, intermittent, not interfering with function	Somnolence or sedation, interfering with function	Persistent, progressive, obtundation, stupor	Coma
I5. Inability to concentrate	Subjective symptoms, does not interfere with function	Objective findings, interferes with function	Persistent, prolonged objective findings or organic cause	N/A
I6. Insomnia (in absence of pain)	Occasional difficulty sleeping, transient intermittent, not interfering with function	Recurrent difficulty sleeping; requires meds for relief; occasional interference with function	Persistent or worsening difficulty sleeping; severely interferes with routine daily function	N/A
I7. Libido decreased	Decrease in interest	Loss of interest; influences relationship	Persistent, prolonged interfering with relationship	N/A
I8. Peripheral motor neuropathy	Subjective or transient loss of deep tendon reflexes; function maintained	Objective weakness, persistent, no significant impairment of daily function	Objective weakness with substantial impairment of function	Paralysis
I9. Peripheral sensory neuropathy (sensory disturbance)	Subjective symptoms without objective findings, transient, not interfering with function	Objective sensory loss, persistent, not interfering with function	Prolonged sensory loss or paraesthesias interfering with function	N/A
I10. Seizure	N/A	Recurrence of old seizures, controlled with adjustment of medication	Recurrence/exacerbation with partial response to medication	Recurrence not controlled, requiring hospitalization; new seizures
I11. Vertigo (dizziness)	Subjective symptoms, transient, intermittent, no treatment	Objective findings, recurrent, meds relieve, occasionally interfering with function	Persistent, prolonged, interfering with daily function; partial response to medication	Debilitating without response to medication, hospitalization

J. Pulmonary

	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-Threatening)
J1. Asthma	Occasional wheeze, no interference with activities	Wheezing, requires oral meds, occasional interference with function	Debilitating requires nasal O_2	Requires ventilator assistance
J2. Cough	Transient, intermittent, occasional OTC meds relieve	Persistent, requires narcotic or other prescription meds for relief	Recurrent, persistent coughing spasms without consistent relief by meds, interferes with function	Interferes with oxygenation; debilitating
J3. Dyspnea	Subjective, transient, no interference with function	Symptomatic, intermittent or recurring, interferes with exertional activities	Symptomatic during daily routine activities, interferes with function, treatment with intermittent nasal O_2 relieves	Symptomatic at rest, debilitating, requires constant nasal O_2
J4. Pleuritic pain (pleurisy)	Transient, intermittent symptoms, no treatment or OTC meds relieve	Persistent symptoms, requires prescription meds for relief	Prolonged symptoms, interferes with function, requires frequent narcotic pain relief	Debilitating, requiring hospitalization
J5. Pneumonitis (pulmonary infiltrates)	Asymptomatic radiographic changes, transient, no treatment required	Symptomatic, persistent, requiring corticosteroids	Symptomatic, requiring treatment including O2	Debilitating, not reversible; or requiring assisted ventilation
J6. Pulmonary function decreased (FVC or carbon monoxide diffusion capacity-DLCO)	76 - 90 % of pre-treatment value	51-75 % of pre-treatment value	26-50 % of pre-treatment value	≤25 % of pre-treatment value

19.1.2. Laboratory Data

K. Hematology

	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-Threatening)
K1. Hgb (g/dL) decrease from pre-treatment	1.0-1.4	1.5-2.0	2.1-2.9, or Hgb <8.0, >7.0	≥3.0; or Hgb <7.0
K2. Leukopenia (total WCB) X 1000	3.0-3.9	2.0-2.9	1.0-1.9	<1.0
K3. Neutopenia (X 1000)	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
K4. Lymphopenia (X 1000)	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
K5. Platelets (X 1000)	75-LLN	50-74.9	20-49.9; platelet transfusion required	<20; recurrent platelet transfusions

L. Chemistry

	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-Threatening)
L1. Hypercalcaemia (mg/dL)	1.1 x ULN-11.5	11.6-12.5	12.6-13.5; or symptoms present	>13.5; or associated coma
L2. Hyperglycemia (mg/dL) (fasting)	140-160	161-250	251-500	>500, or associated with ketoacidosis
L3. Hyperkalaemia (mg/dL)	5.50-5.9	6.0-6.4	6.5-7.0 or any ECG change	>7.0 or any arrhythmia
L4.	-	--	--	--
L5. Hypocalcaemia (mg/dL)	0.9 X LLN-7.8	7.7-7.0	6.9-6.5; or associated with symptoms	6.5 or occurrence of tetany
L6. Hypoglycemia (mg/dL)	55-64 (no symptoms)	40-54 (or symptoms present)	30-39 (symptoms impair function)	<30 or coma
L7. Hyponatraemia (mg/dL)	N/A	125-129	120-124	<120
L8. Hypokalaemia (mg/dL)	N/A	3.0-3.4	2.5-2.9	<2.5
L9. CPK (also if polymyosis)	1.2-1.9 X ULN	2.0-4.0 X ULN	4.0 X ULN with weakness but without life-threatening signs or symptoms	>4.0 X ULN with signs or symptoms of rhabdomyolsis or life-threatening
L10. Serum uric acid	1.2-1.6 X ULN	1.7-2.9 X ULN	3.0-5.0 X ULN or gout	N/A
L11. Creatinine (mg/dL)	1.1-1.3 X ULN	1.3-1.8 X ULN	1.9-3.0 X ULN	>3.0 X ULN
L12. SGOT (AST)	1.2-1.5 X ULN	1.6-3.0 X ULN	3.1-8.0 X ULN	>8.0 X ULN
L13. SGPT (ALT)	1.2-1.5 X ULN	1.6-3.0 X ULN	3.0-8.0 X ULN	>8.0 X ULN
L14. Alkaline phosphatase	1.1-2.0 X ULN	1.6-3.0 X ULN	3.0-5.0 X ULN	>5.0 X ULN
L15. Total bilirubin	1.1-1.4 X ULN	1.5-1.9 X ULN	2.0-3.0 X ULN	>3.0 X ULN
L16. LDH	1.3-2.4 X ULN	2.5-5.0 X ULN	5.1-10 X ULN	>10 X ULN

M. Urinalysis

	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-Threatening)
M1. Hematuria	Micro only	Gross, no clots	Clots, transfusion <2 units	Transfusion required
M2. Proteinuria (per 24 h)	300–500 mg (tr/1+)	501–1999 mg (2+)	2-5.0 g (3+) nephrotic syndrome	5.0 g (4+) anasarca
M3. WBC in urine	N/A	N/A	Indicating acute interstitial nephritis	Associated with acute renal failure
M4. Uric acid crystals	Present without symptoms	N/A	With stones or symptoms of stones (e.g. renal colic)	Causing renal outflow obstruction and hospitalization

OTC: over-the-counter medication; ADL: activities of daily living; IV: intravenous; ECG: electrocardiogram; CHF: congestive heart failure; MRI: magnetic resonance imaging; Hb: hemoglobin; LLN: upper limit of normal; ULN: upper limit of normal; WBC: white blood cells; SLE: systemic lupus erythematosus; ANA: antinuclear antibodies;H-2: histamine-2 blockers; FVC: forced vital capacity

19.2. NIAID/FAAN Clinical Criteria for Anaphylaxis

From the Second Symposium on the Definition and Management of Anaphylaxis (Sampson, 2006).

*Anaphylaxis is highly likely when any **one** of the following 3 criteria are present*

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   c. Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced blood pressure after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure
   b. Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

***Note**: Item 1 will generally apply to subjects in this study since SEL-037 will not be a known or a likely antigen for these subjects.

19.3. Reconstitution and Dilution for Infusion Instructions

19.3.1. SEL-037 Instructions

Follow instructions below:

1. Convert weight of subject to kg, as needed (weight in pounds divided by 2.2046).
2. Calculate the mL of reconstituted SEL-037 required for a subject

Volume (ml) reconstituted SEL-037 required for each infusion = *(dose in mg/kg) x (subject weight in kg) / (concentration of SEL-037 per ml in vial i.e., 6 mg/mL)*

3. Since each vial, once reconstituted, will yield about 1 mL of product that can be withdrawn from the vial, the number of vials required for a subject equals the number of ml of reconstituted SEL-037 needed for the infusion rounded up to the next whole number.
4. Reconstitute the required number of vials each with 1.1 mL of room temperature sterile water for injection, USP. Invert (don't shake) each vial several times to ensure product is reconstituted. Do not use any vials with visible clumping. Reconstituted SEL-037 should be diluted as in Step 5 as soon as possible but reconstituted SEL-037 is stable at room temperature and normal light conditions for 8 hours.
5. Dilute required volume of reconstituted SEL-037 by adding it to 100 mL of 0.9% saline for injection, USP.
6. Infuse total volume of the SEL-037-normal saline solution 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. The SEL-037-normal saline solution is stable for up to 6 hours at room temperature (i.e., the infusion should be completed within 6 hours of dilution) but it is recommended that the infusion of SEL-037 be started as soon as possible to account for any potential interruptions in dosing. No infusion of the SEL-037-normal saline solution should start if 5 hours have lapsed between diluting SEL-037 and the start of infusion.
7. At the conclusion of the infusion, using the port closest to the IV pump, flush the IV drip set using a volume of 0.9% normal saline equal to the prime volume of the tubing.

Example for subject weighing 200 pounds in Cohort 2 (0.4 mg/kg group)

Step 1: If not already done convert weight to kg:	*= 200 pounds / 2.2046 = 90.7 kg*
Step 2: Calculate volume of reconstituted SEL-037 needed:	*= (0.4 mg/kg) x (90.7 kg) / (6 mg/mL)*

= 36.29/6 = 6.0 mL
Step 3: number of vials needed: *= Round up 6.048 mL = 7 vials*
Step 4 and 5: Reconstitute 7 vials and add 6.0 mL to 100 mL of 0.9% normal saline for injection, USP.
Step 6: Infuse 106.0 mL 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
Step 7: At the conclusion of the infusion, using the port closest to the IV pump, flush the IV drip set using a volume of 0.9% normal saline equal to the prime volume of the tubing

19.3.2. SEL-110 Instructions

Follow instructions below:

1. Convert weight of subject to kg, as needed (weight in pounds divided by 2.2046).
2. Calculate the volume (mL) of SEL-110 required for a subject, with a maximum volume of 6.0 mL (equivalent to 12 mg of rapamycin in SEL-110) per study visit per individual in cohorts receiving SEL-110 doses <0.10 mg/kg. If calculated required dose volume exceeds 6.0 mL, dose volume should be set to 6.0 mL. In cohorts receiving SEL-110 ≥0.10 mg/kg, there is no maximum volume of SEL-110, however their initial rate of SEL-110 is restricted to 5.5 mL/hr as described in section 9.5. If calculated required dose volume exceeds 6.0 mL, for cohorts receiving SEL-110 ≥0.10 mg/kg, the full calculated dose volume should be used.

Volume (mL) SEL-110 required =
(dose in mg/kg) x (subject weight in kg) / (concentration of SEL-110 per ml in vial i.e., 2 mg/mL)

3. Calculate the number of vials of SEL-110 required for a subject. Round the calculation up to the next whole number.

Number of SEL-110 vials required =
[Volume (mL) SEL-110 required + priming volume (mL)]/ (5 mL/vial)

4. Thaw the required number of vials at room temperature for at least 2 hours. Once the vials are thawed, invert slowly (don't shake) each vial twenty times to ensure product is uniform. Do not use any vials with visible clumping. Thawed SEL-110 should be administered as soon as possible but thawed SEL-110 is stable at room temperature and normal light conditions for 24 hours.
5. Load a syringe with the appropriate size for the dose. In order to prime the line between the syringe and the injection site valve, an additional priming volume of SEL-110 (approximately 1.5mL), equal to the volume of the connecting line used (approximately 0.65mL) and the prime volume of the 5 micrometer membrane filter (Pall Medical, PN HP1050; 0.85 mL) used, should be added to the syringe. When loading syringes, do not bubble air through the product to avoid the formation of foam.
6. Start an infusion of 125 mL of normal saline solution over 60 minutes using an IV set with an injection site valve.
7. Start an infusion of SEL-110 as described below concurrently with the saline infusion of Step 6:
   a) For cohorts receiving SEL-110 doses <0.1 mg/kg, using the injection site valve, immediately after starting the normal saline IV, slowly inject the SEL-110 using a syringe infusion pump at a single steady rate to deliver the dose over a period of 55 minutes. A 5 µm syringe filter (5 µm syringe filter Supor (PES) membrane, Pall Medical P/N HP1050) for single use must be included in the SEL-110 line downstream of the syringe and proximal to the injection site valve.
   b) For cohorts receiving SEL-110 doses ≥0.1 mg/kg, using the injection site valve, immediately after starting the normal saline IV, slowly inject the SEL-110 using a syringe

infusion pump at an initial infusion rate equal to 5.5 mL/hour for the first 30 minutes of infusion and, then, change to a steady rate sufficient to deliver the remainder of the dose volume for the additional 25 minutes. A 5 µm syringe filter (5 µm syringe filter Supor (PES) membrane, Pall Medical P/N HP1050) for single use must be included in the SEL-110 line downstream of the syringe and proximal to the injection site valve.

At the end of the 55 minutes, continue the saline infusion for the additional 5 minutes after the SEL-110 infusion stops to flush the main line. Do not flush the line between the syringe and the injection site valve.

Example for subject weighing 200 pounds in Cohort _5__ (0.08 mg/kg group)

Step 1: If not already done convert weight to kg:

= 200 pounds / 2.20462 = 90.7 kg

Step 2: Calculate volume of SEL-110 needed, with a maximum volume of 6.0 mL (equivalent to 12 mg of rapamycin in SEL-110) per study visit per individual, since the example cohort 5 is receiving <0.1 mg/kg SEL-110. If calculated required dose volume exceeds 6.0 mL, dose volume should be set to 6.0 mL:

= (0.08 mg/kg) x (90.7 kg) / (2 mg/mL)

= 7.26/2 = 3.6 mL SEL-110

Step 3: Calculate number of vials needed (assumes 1.5 mL prime volume):

= [3.6 mL SEL-110 required + 1.5mL]/ (5 mL/vial)

= 1.02 vials. Round up to 2 vials.

Step 4 and 5: Thaw 2 vials and load syringe with 3.6 mL SEL-110 plus the priming volume (approximately 1.5 mL).

Step 6: Start infusion of 125 mL of normal saline solution over 60 minutes.

Step 7: Immediately after the start of the normal saline infusion, slowly inject 3.6 mL of SEL-110 at a single steady rate over 55 minutes, using a 5 µm syringe filter proximal to the injection site valve. At the end of the 55 minutes, continue the saline infusion for the additional 5 minutes after the SEL-110 infusion stops to flush the main line.

19.4. Laboratory Schedules by Cohort

Table 9: Laboratory Schedule - Cohorts 1 & 2 (SEL-037)

Labs for SEL-037 Cohorts 1&2		Treatment 1-5					EOS / Early Termination
Labs	screen	predose	D7	D14	D21		D30
Safety labs							
Alkaline phosphatase	x	x		x			x
ALT	x	x		x			x
APTT	x	x					x
AST	x	x		x			x
Electrolytes	x	x					x
Total Bilirubin	x	x					x
BUN	x	x					x
Calcium	x						
Total Complement[2]	x						
Creatinine	x	x					x
eGFR	x						
Fibrinogen[1]	x	x					
Glucose(fasting)	x	x		x			x
Hct	x	x					x
Hgb	x	x					x
HbA1c	x						
Hep C Ab	x						
HIV 1/2	x						
INR	x	x					x
Phosphorous	x						
CBC with platelets	x	x		x			x
WBC c diff	x	x		x			x
Lipid Panel							
total cholesterol	x	x					x
HDL	x	x					x
LDL	x	x					x
Triglycerides	x	x					x
Urinalysis	x						
G6PD	x						
Immunogenicity							
Anti-Pegsiticase		x	x	x	x		x
Anti-Uricase		x	x	x	x		x
Anti-PEG	x	x	x	x	x		x
PK/PD							
SEL-110 PK							
SEL-037 PK		x[2]	x	x	x		x
Uricase Activity		x[3]	x	x	x		x
Uric Acid	x	x[2]	x	x	x		x

[1] Collected at screening, results not required to determine eligibility

[2] Additional samples collected during D0 and D1 as per Schedule of Events timing

[3] Additional sample collected D1 as per Schedule of Events timing

Table 10: Laboratory Schedule - Cohorts 3-8, 10, 11, and 12 (SEL-212)

Labs for SEL-212 Cohorts 3-8, 10, 11, & 12		Treatment Period 1-3					Treatment Period 4-5					EOS / Early Termination
Labs	screen	predose	D7	D14	D21		predose	D7	D14	D21		D30
Safety labs												
Alkaline phosphatase	x	x		x			x		x			x
ALT	x	x		x			x		x			x
APTT	x	x					x					x
AST	x	x		x			x		x			x
Electrolytes	x	x					x					x
Total Bilirubin	x	x					x					x
BUN	x	x					x					x
Calcium	x											
Total Complement[1]	x											
Creatinine	x	x					x					x
eGFR	x											
Fibrinogen[1]	x	x		x			x					
Glucose(fasting)	x	x	x	x	x		x		x			x
Hct	x	x	x	x	x		x					x
Hgb	x	x	x	x	x		x					x
HbA1c	x											
Hep C Ab	x											
HIV 1/2	x											
INR	x	x					x					x
Phosphorous	x	x	x	x	x		x		x			x
CBC with platelets	x	x	x	x	x		x	x	x	x		x
WBC c diff	x	x	x	x	x		x	x	x	x		x
Lipid Panel												
total cholesterol	x	x	x	x	x		x		x			x
HDL	x	x	x	x	x		x		x			x
LDL	x	x	x	x	x		x		x			x
Triglycerides	x	x	x	x	x		x		x			x
Urinalysis	x											
G6PD	x											
Immunogenicity												
Anti-Pegsiticase		x	x	x	x		x	x	x	x		x
Anti-Uricase		x	x	x	x		x	x	x	x		x
Anti-PEG	x	x	x	x	x		x	x	x	x		x
PK/PD												
SEL-110 PK		x[2]	x	x	x		x[4]					x
SEL-037 PK		x[2]	x	x	x		x[2]	x	x	x		x
Uricase Activity		x[3]	x	x	x		x[3]	x	x	x		x
Uric Acid	x	x[2]	x	x	x		x[2]	x	x	x		x
Exploratory												
Inflammatory markers		x[5]										x
T-cell recall		x[5]	x[6]					x[7]				x

[1] Collected at screening, results not required to determine eligibility

[2] Additional samples collected during D0 and D1 as per Schedule of Events timing

[3] Additional sample collected D1 as per Schedule of Events timing

[4] Predose sample only collected on Treatment Period 4 only

[5] Predose sample only collected on Treatment Period 1 (Visit 4) only

[6] Sample collected on Treatment Period 3 (Visit 18) only

[7] Sample collected on Treatment Period 5 (Visit 30) only

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.

Table 11 Laboratory Schedule – Part C: Cohorts 13, 15, and 17 (SEL-212)

Labs for SEL-212		Treatment Period 1-5					EOS / Early Termination
Labs	Screen	Predose	D7	D14	D21		D30
Safety labs							
Alkaline phosphatase	x	x		x			x
ALT	x	x		x			x
APTT	x	x					x
AST	x	x		x			x
Electrolytes	x	x					x
Total Bilirubin	x	x					x
BUN	x	x					x
Calcium	x						
Total Complement[1]	x						
Creatinine	x	x					x
eGFR	x						
Fibrinogen[1]	x	x		x			
Glucose(fasting)	x	x	x	x	x		x
Hct	x	x	x	x	x		x
Hgb	x	x	x	x	x		x
HbA1c	x						
Hep C Ab	x						
HIV 1/2	x						
INR	x	x					x
Phosphorous	x	x	x	x	x		x
CBC with platelets	x	x	x	x	x		x
WBC c diff	x	x	x	x	x		x
Lipid Panel							
total cholesterol	x	x	x	x	x		x
HDL	x	x	x	x	x		x
LDL	x	x	x	x	x		x
Triglycerides	x	x	x	x	x		x
Urinalysis	x						
G6PD	x						
Immunogenicity							
Anti-Pegsiticase		x	x	x	x		x
Anti-Uricase		x	x	x	x		x
Anti-PEG	x	x	x	x	x		x
PK/PD							
SEL-110 PK		x[2]	x	x	x		x
SEL-037 PK		x[3]	x	x	x		x
Uricase Activity		x[2]	x	x	x		x
Uric Acid[7]	x	x[2]	x	x	x		x
Exploratory							
Inflammatory markers		x	x				x
T-cell recall		x[5]	x[6]				x

[1] Collected at screening, results not required to determine eligibility

[2] Additional samples collected during D0 and D1 as per Schedule of Events timing

[3] Additional sample collected D1 as per Schedule of Events timing

[4] Predose sample only collected on Treatment Period 4 only

[5] Predose sample only collected on Treatment Period 1 (Visit 4) only

[6] Sample collected on Treatment Period 3 (Visit 18) and Treatment Period 5 (Visit 30) only

[7] 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 this protocol in order to maintain the cohort numbering convention of associating odd numbered cohorts with the 0.2 mg/kg SEL-037 dose.

Table 12. Laboratory Schedule for Suspected Infusion Reaction, All Cohorts

Phases: Cohorts 1,2, 3-8, 10, 11, 12, 13, 15, & 17											
Hour (h)	At Event	Post event (time after suspected IR[a])									
		0.25h	0.5h	0.75h	1h	1.5h	2h	3h	6h	12h	24h
Safety Labs											
Safety Labs - As indicated from predose in individual schedules	X										
Tryptase (total serum)	X		X				X		X		X
Histamine (plasma)	X	X					X				
Anti-Pegsiticase	X										
Anti-Uricase	X										
Anti-PEG	X										
[a] All times are ± 5 minutes from suspected IR											

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. 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.

19.5. New York Heart Association Functional Classification

Class I: Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain

Class II: Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain

Class III: Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain

Class IV: Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

Revision History

Version	Reason for Change	Date
01	Original protocol	28JUL2016
02	Revised SEL-110 highest dose from 0.1 mg/kg to 0.08 mg/kg Updated Schedule of Events, Figure 1, Tables 7-9 Updated description of potential risks of SEL-110	05SEP2016
03	Revised methylprednisolone premedication dose from 16mg to 40mg, its route of administration from oral to intravenous and its timing from 2 hours to 1 hour prior to study drug administration Updated Individual and cohort stopping rules	07DEC2016
04	Revised fexofenadine premedication dose to 180 mg Revised gout flare premedication to colchicine 0.6mg QD Revised windows for screening and vital signs Updated Schedules of Events, Table 7 and dosing instructions Updated previous human clinical experience Updated Figure 1 for closure of Cohorts 1 and 2 Updated cohort randomization and opening criteria Added observational visit and T-cell recall assay	22DEC2016
05	Added Cohort 7 and 8 Adding optional alternative premedication for methylprednisolone Added weight measurement at all Day 21 visits Clarified T-cell recall sample collection schedule and requirements for sampling Revised inflammatory marker schedule Updated Schedules of Events and Table 8 Updated Figure 1 for inclusion of Cohorts 7 and 8 Clarified windows for dosing and infusion reaction kit samples	07FEB2017

05.1	Increased number of subjects in Cohorts 5, 6, 7 & 8 Clarified time windows for SEL-037 and SEL-110 dose administration and for suspected infusion reaction labs Updated Individual and cohort stopping rules	04Apr2017
06.0	Added Cohorts 10 and 12 Clarified randomization and cohort enrollment process Clarified infusion rates for SEL-110 doses >0.10 mg/kg Clarified dosing volumes Updated nonclinical and clinical data from completed studies Clarified inflammatory marker assessment time points	12JUN2017
06.1	Removed Cohorts 10 and 12 Increased number of subjects in Cohorts 6 & 8 Updated enrollment status Clarified infusion rates for SEL-110 doses of 0.10 mg/kg Updated cohort stopping rules Updated nonclinical animal study information Updated dose selection rationale Clarified SEL-110 infusion preparation instructions	28JUN2017
06.2	Added Cohorts 10 and 12 Clarified infusion rates for SEL-110 doses ≥0.10 mg/kg Updated nonclinical and clinical data from completed studies	09AUG2017
06.3	Added Cohort 11 Updated enrollment status Clarified DECT scanning for Cohorts 10, 11, and 12 and for re-opened cohorts. Added DECT scan at Treatment Period 3 for Cohorts 10, 11, and 12.	20OCT2017
07.0	Addition of Part C (Cohorts 13 and 15) Updated enrollment status Updated dose selection rationale	21DEC2017

07.1	Added Cohort 17 to Part C Clarified that for Part C, sUA used for individual stopping rules will be measured in blood samples stored at ambient temperatures similar to Parts A and B. Updated dose rationale Update Phase I study information	19MAR2018