Phase 2 dose-finding study in patients with gout using SEL-212, a novel PEGylated uricase (SEL-037) combined with tolerogenic nanoparticles (SEL-110)

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Supplementary Material

Full inclusion/exclusion criteria

Inclusion criteria:

1. Provided written informed consent prior to study-specific procedures and throughout the study
2. Willing and able to comply with study requirements (follow-up visits, compliance with study requirements, etc.)
3. Male aged 21–75 years (inclusive) or female aged 21-75 years of non-child bearing potential at Screening
4. Serum uric acid (sUA) ≥ 6 mg/dL at Screening, with established or symptomatic gout (≥1 of the following: ≥1 tophus; ≥1 gout flare within the last 6 months; chronic gouty arthropathy)
5. Use of allopurinol, febuxostat (Uloric®), or probenecid as uric acid- (UA-) lowering therapy only if dosing has been stable for at least the month prior to Screening and remains stable during the Screening Phase
6. Negative anti-polyethylene glycol (PEG) antibody test at Screening
7. Has not participated/has agreed not to participate in a clinical trial within 30 days of Screening and throughout the study
8. Negative serology for HIV-1/-2 and hepatitis C virus
9. Adequate venous access; able to receive IV therapy
10. Fully recovered from prior surgery (if applicable)
11. Not participating in a vaccination scheme and has not 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
3. Treatment with known CYP3A4 inhibitors or inducers MAY be exclusionary

4. Treatment with drugs known to interact with sirolimus (e.g. cyclosporine, diltiazem, erythromycin, antifungals, calcium channel blockers, rifampin, verapamil) unless they are stopped 2 weeks prior to starting the trial

5. Women of childbearing potential (less than 24 months of natural amenorrhea)

6. Initiation/change in dose of hormone-replacement therapy for menopausal women <1 month prior to Screening/during the Screening Phase

7. Uncontrolled diabetes with baseline glycated hemoglobin (HbA1c) ≥8%

8. Fasting glucose >240 mg/dL

9. Fasting triglyceride >300 mg/dl

10. Fasting low-density lipoprotein cholesterol >200 mg/dl

11. Glucose-6-phosphate dehydrogenase deficiency

12. Uncontrolled hypertension (blood pressure >170/100 mmHg at Screening and 1 week prior to dosing)

13. White blood cell count <3.5 x10^9 /L; serum aspartate aminotransferase/alanine amino transferase >3x upper limit of normal (ULN) in the absence of known active liver disease; glomerular filtration rate <40 ml/min/1.73 m^2; hemoglobin <9 gm/dL; serum phosphate <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. Electrocardiogram (ECG) with evidence of prior myocardial infarction, clinically significant arrhythmia, or other abnormalities that, in the opinion of the investigator, are consistent with significant underlying cardiac disease

18. History of hematological or autoimmune disorders; currently immunosuppressed or immunocompromized

19. Use of dabigatran (Pradaxa®), rivaroxaban (Xarelto®), edoxaban (Savaysa®), warfarin (Coumadin®) or apixaban (Eliquis®)

20. Prior exposure to experimental/marketed uricases (e.g., rasburicase [Elitek, Fasturtec], pegloticase [Krystexxa®], SEL-037)

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

22. Subjects with a condition that compromises their safety or makes study completion unlikely

Bioanalytical methods

Anti-SEL-037 antibodies were detected using a validated sequential bridging immunoassay using MesoScale Discovery technology. Serum samples were added to SEL-037 coated plates and incubated overnight. After washing, sulfo-Tag SEL-037 was added to form a complex with anti-SEL-037 antibodies bound to the SEL-037 coated plates. The immune complexes were detected using tripolyamine read buffer and an MSD Sector 6000 instrument. Anti-SEL-037 antibodies were confirmed using the tagged SEL-037 and confirmed samples, titered. The immune complexes were further characterized using KLH-PEG competition to detect the presence of anti-PEG antibodies. The sensitivity of the assay was determined to be 13 ng/mL.

A validated direct bind enzyme-linked immunosorbent assay (ELISA) was used to detect anti-PEG antibodies. Plates were coated with PEG 30K overnight. After washing, serum samples were diluted a minimum of 40-fold before adding to the plate. Anti-PEG antibodies were then detected using rabbit anti-human IgG and IgM horseradish peroxidase (HRP) antibodies. The presence of anti-PEG antibodies was colorimetrically visualized using 3,3',5,5'-tetramethylbenzidine (TMB). Plates were read at 450 nm. The sensitivity of this assay was estimated to be 4 ng/mL.

Anti-uricase antibodies were detected using a previously described validated direct bind ELISA [1].

A validated assay was used to measure SEL-037 uricase activity in serum. The assay used SEL-037 as the reference standard and the HRP and fluorescent probe from Cell Biolabs (Uric acid/Uricase assay kit, Reference No. STA-375). Uric acid added to the samples was converted to allantoin, hydrogen peroxide and carbon dioxide. Hydrogen peroxide reacts with the fluorescence probe in the presence of HRP to produce a fluorescent product. The fluorescent product was detected on a fluorescence reader using an excitation of 530-560 nm and an emission of 590 nm. The lower limit of quantitation of the assay was 0.2 mU/mL.

Human whole blood samples were analyzed quantitatively using a validated liquid chromatography mass spectrometry (LC-MS) method to determine the concentration of SEL-110 (sirolimus) with a lower limit of quantitation of 0.65. Sirolimus from human whole

blood was extracted using protein precipitation followed by liquid-liquid extraction, with sirolimus-$^{13}C,D_3$ added as an internal standard. Both calibration and quality control samples were prepared by spiking SEL-110 reference material into pooled human whole blood and extracted in the same manner as study samples. Extracted sirolimus was separated from interfering components with reverse-phase liquid chromatography and detected via tandem MS detection using an Applied Biosystems Triple Quad API 5500 LC/MS/MS system with Applied Biosystems 'Analyst' software for data acquisition and processing.

Statistical analyses

Pharmacodynamic analyses

Pharmacodynamic (PD) parameters for SEL-037 and SEL-110 were calculated using actual sUA concentrations and percent changes from baseline over time. The number and percentage of subjects maintaining sUA <6 mg/dL each week were summarized. Key PD parameters based on actual sUA concentrations and percent changes from baseline over time, $\%CFB_{min}$, $AUE_{\%CFBlast}$, and TA. $AUE_{\%CFBlast}$, UA concentration and percentage change from baseline on Day 21 of each TP were analyzed using a linear mixed model for the response to SEL-110 dose levels co-administered with either SEL-037 0.2 or 0.4 mg/kg. The dose level of SEL-110 for Cohorts 1 and 2 was assigned as 0. Additionally, the contribution of SEL-110 to the PD effect of SEL-037 was tested to compare the following (test – reference). For PD parameters based on actual measured values, the baseline concentration of UA was incorporated into the model as a covariate. Correlations between PD endpoints (C_{min}, CFB_{min}, $AUE_{CFBlast}$, and TA_$AUE_{CFBlast}$) and pharmacokinetic (PK) parameters (C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$) for both SEL-110 and SEL-037 were explored using Spearman correlation analysis. The effect of co-administering various SEL-110 doses on the PK parameters of SEL-037 for serum concentrations or uricase activity was investigated using a linear mixed-effect model.

Pharmacokinetic analyses

Most PK parameters were calculated for SEL-037 and sirolimus concentrations or uricase activity separately using a noncompartmental IV infusion log-linear model for each cohort and TP where possible using WinNonLin 6.4 or higher. PK parameters for SEL-110 and SEL-037 were analyzed by examining all available measurements from all TPs where the participant received SEL-110 0.05-0.15 mg/kg in combination with SEL-037 0.2 mg/kg or 0.4 mg/kg. This was performed stratified by TP (Table S2 and Table S3), and across TP 1-5 combined (Table 4 and Table S4). For the analyses stratified by TP, data were summarized as geometic mean (SD) and geometric coefficient of variation. For the analyses combining TP 1-5, linear mixed models were fitted to estimate the geometric mean and the between- and within-subject geometric coefficient of variation %. For each PK parameter except T_{max} and $T_{1/2}$, a separate linear mixed model was fitted for each SEL-110/SEL-037 dose combination group. The outcome for each linear mixed model was the log of the PK parameter. Cohort was included in the model as a fixed effect for models where analysis set contained more than one cohort, whilst subject was included as a random effect. The least-square mean on the log scale was calculated across cohorts for the dose group under consideration in the model. Given that each cohort contributes a different number of observations, the least-square mean was weighted by the number of available measurements within each cohort. The exponential of the least-squares mean was taken to obtain the presented geometric mean. The geometric coefficient of variation percentages were calculated from the estimate of the within- and between-subject variance from the linear mixed models. PK parameters T_{max} and $T_{1/2}$ were summarized by combining all available measurements across TPs for each SEL-110 dose, presenting median and maximum values. In addition, geometric mean (95% confidence interval) SEL-110 concentrations were estimated from linear mixed models for 2 SEL-110/SEL-037 dose combinations (SEL-110 0.1mg/kg and SEL-110 0.15mg/kg with SEL-037 0.2mg/kg). The outcome in the linear mixed model was $\log_e$(SEL-110 concentration), with a fixed effect time variable, fitted as a categorical variable and subject included as a random effect. The exponential of the least square means (95% confidence intervals) from the model at each time point are present in Figure 3.

Antibody transiency analyses

To examine antibody transience for anti-PEG, anti-SEL-037 and anti-uricase antibodies (Figure S3), we examined whether participants a) remained antibody negative throughout

follow-up (antibody titers ≤0.5) b) became positive (titers >0.5) before returning to negative or c) became antibody positive and remained positive until their last antibody measurement. Given that anti-uricase titers <1080 correlated with sustained sUA control at Week 20, the same analysis was performed using anti-uricase titers ≥1080. For anti-PEG and anti-SEL-037 antibodies, the thresholds were considered to be the median antibody titer for participants testing positive for the respective antibodies.

References

1. Sands E, Kivitz A, DeHaan W. et al. Tolerogenic nanoparticles mitigate the formation of anti-drug antibodies against pegylated uricase in patients with hyperuricemia. Nat Commun 2022;13:272. doi: 10.1038/s41467-021-27945-7.

Table S1. Pharmacokinetic parameters for SEL-110 0.05-0.15 mg/kg when combined with A. SEL-037 0.2 mg/kg (TP1, 3 and 5) and B. SEL-037 0.4 mg/kg (TP1 and 3) based on SEL-110 serum concentration (Pharmacokinetic Analysis Set)

a.

SEL-110 dose		**NA**	**0.05 mg/kg TP1-3**	**0.08 mg/kg TP1-3**	**0.1 mg/kg TP1-3**	**0.1 m/kg TP1-5**	**0.15 mg/kg TP1-3**	**0.15 mg/kg TP1-5**	**0.15-0.1 mg/kg TP1-5**
Cohort		**1**	**3**	**5**	**7**	**17**	**11**	**13**	**15**
TP1									
C_{max} (ng/mL)	N	0	9	6	11	11	13	23	11
	Geo mean	NA	192.9	359.8	362.9	704.6	1037.4	1109.6	1180.3
	Geo CV%	NA	186.3	28.2	30.2	66.4	84.6	58.5	30.3
T_{max} (h)	N	NA	9	6	11	11	13	23	11
	Median (range)	-	1 (0.3-166)	0.85 (0.6-1.0)	1.0 (0.8-3.0)	1.0 (0.3-1.9)	1.0 (0.5-1.5)	1.0 (0.3-2.0)	1.0 (0.8-1.7)
$AUC_{0\text{-}last}$ (h·ng/mL)	N	0	9	6	11	11	13	23	11
	Geo mean	NA	4211.2	6127.1	6781.1	9451.1	10359.9	17057.1	16503.9
	Geo CV%	NA	35.6	25.3	39.2	118.4	172.1	96.4	66.5

$t_{1/2}$ (h)	N	0	8	6	11	11	12	19	11
	Geo mean	NA	198.8	167.8	205	227.6	102.7	172.5	139.7
	Geo CV%	NA	12.6	30.6	12.1	11.5	380.2	96	149.9
$AUC_{0\text{-}inf}$ (h·ng/mL)	N	0	8	6	11	10	11	19	11
	Geo mean	NA	5117.6	6897.7	7798.2	1394 0.3	13180.7	17215	18056.3
	Geo CV%	NA	29.5	22.9	38.2	34.9	135.7	86.4	60.6
CL (L/h)	N	0	8	6	11	10	11	19	11
	Geo mean	NA	1175.3	1368.1	1384	842.1	1168.1	899.2	833.9
	Geo CV%	NA	34.7	30.2	35.4	38.1	128.5	75.9	63.5
Vd (L)	N	0	8	6	11	10	11	19	11
	Geo mean	NA	337072.7	331205.5	409321.3	284068.4	157339.7	223730.2	168055.7
	Geo CV%	NA	35.1	36.9	36.6	38.3	105.7	131.2	159.6
TP3									
C_{max} (ng/mL)	N	0	3	5	7	6	9	12	5
	Geo mean	NA	236.6	334.5	246.6	999.1	1398	1651.9	820.9
	Geo CV%	NA	39.8	23.6	603.4	14.5	26.2	25.8	47.6
T_{max} (h)	n	NA	3	5	7	6	9	12	5
	Median (range)	-	0.8 (0.8-1.0)	1.0 (0.8-1.1)	0.8 (0.8- 1.0)	1.0 (1.0- 2.0)	1.0 (0.3-1.5)	1.0 (1.0-2.0)	1.0 (0.8-1.0)
$AUC_{0\text{-}last}$ (h·ng/mL)	N	0	3	5	7	6	9	12	5
	Geo mean	NA	5076.3	6274	6626.5	15287.1	17999	32093.6	10203.1
	Geo CV%	NA	18.6	23	116.4	36.8	46.7	69.6	36.2

$t_{1/2}$ (h)	N	0	3	5	7	3	7	12	5
	Geo mean	NA	196.6	206	224.4	166.1	177.6	200.4	191
	Geo CV%	NA	13.9	5.1	22.6	23.4	33.5	34	15
$AUC_{0\text{-}inf}$ (h·ng/mL)	N	0	3	5	6	3	7	12	4
	Geo mean	NA	5995.6	7259.6	10256.2	13258.5	19219	34722	12784.4
	Geo CV%	NA	14.7	24.1	52.5	22.3	49.6	62.8	24.5
CL (L/h)	N	0	3	5	6	3	7	12	4
	Geo mean	NA	1496.7	1258.3	1075.2	832.7	846.8	484.3	800.2
	Geo CV%	NA	9.2	30.3	65.3	14.4	56.1	55.6	21.8
Vd (L)	N	0	3	5	6	3	7	12	4
	Geo mean	NA	424495.3	373887.6	323307.7	199563	216977.4	140026.3	225769.2
	Geo CV%	NA	21	31.5	55.8	23.1	80.7	80.2	30.8
TP5									
C_{max} (ng/mL)	N	0	0	0	0	6	0	11	4
	Geo mean	NA	NA	NA	NA	928.5	NA	2209.6	784.6
	Geo CV%	NA	NA	NA	NA	55	NA	97.2	29
T_{max} (h)	n	NA	NA	NA	NA	6	NA	11	4
	Median (range)	-	-	-	-	1.0 (0.5-1.5)	-	1.0 (1.0-3.0)	1.0 (0.8-1.0)
$AUC_{0\text{-}last}$ (h·ng/mL)	N	0	0	0	0	6	0	11	4
	Geo mean	NA	NA	NA	NA	17511.6	NA	37471.6	11295.2
	Geo CV%	NA	NA	NA	NA	77.5	NA	52.4	22.2

$t_{1/2}$ (h)	N	0	0	0	0	5	0	9	3
	Geo mean	NA	NA	NA	NA	137	NA	218.9	191.3
	Geo CV%	NA	NA	NA	NA	56.7	NA	13.3	19.5
$AUC_{0\text{-}inf}$ (h·ng/mL)	N	0	0	0	0	5	0	9	3
	Geo mean	NA	NA	NA	NA	18324.1	NA	44015.6	12482.8
	Geo CV%	NA	NA	NA	NA	87.9	NA	43.5	18.6
CL (L/h)	N	0	0	0	0	5	0	9	3
	Geo mean	NA	NA	NA	NA	610	NA	387.9	742.5
	Geo CV%	NA	NA	NA	NA	88.9	NA	41.6	15
Vd (L)	N	0	0	0	0	5	0	9	3
	Geo mean	NA	NA	NA	NA	120532.6	NA	122495.4	204926.6
	Geo CV%	NA	NA	NA	NA	169.7	NA	30.8	5.8

b.

SEL-110 dose		**NA**	**0.05 mg/kg TP1-3**	**0.08 mg/kg TP1-3**	**0.1 mg/kg TP1-3**	**0.125 mg/kg TP1-3**	**0.15 mg/kg TP1-3**
Cohort		**2**	**4**	**6**	**8**	**10**	**12**
TP 1							
C_{max} (ng/mL)	N	0	10	11	12	14	14
	Geo mean	NA	121.4	344.4	371.6	977.7	1436.6
	Geo CV%	NA	368.6	159.4	60.8	68.1	48.4
T_{max} (h)	n	NA	10	11	12	14	14
	Median (min, max)	-	1.0 (0.5-2.1)	0.8 (0.3-1.1)	1.0 (0.3-1.5)	1.0 (0.4-2.0)	1.0 (0.8-1.9)
$AUC_{0\text{-last}}$ (h·ng/mL)	N	0	10	11	12	14	14
	Geo mean	NA	1705.4	3325	7290.9	12917.5	25513.8
	Geo CV%	NA	2767.5	296.7	96.2	381.2	59.9
$t_{1/2}$ (h)	N	0	8	8	11	12	14
	Geo mean	NA	209	229.2	197	186.5	190.1
	Geo CV%	NA	27.7	12.7	29.4	49.3	39.1
$AUC_{0\text{-inf}}$ (h·ng/mL)	N	0	8	7	11	12	14
	Geo mean	NA	4611.6	7679.1	8671.8	22822.1	27057.2
	Geo CV%	NA	28.5	27.4	97.5	73	59.8

CL (L/h)	N	0	8	7	11	12	14
	Geo mean	NA	1183.9	1128.5	1146	527.3	540.2
	Geo CV%	NA	28.6	28.5	133	80.5	60.3
Vd (L)	N	0	8	7	11	12	14
	Geo mean	NA	356993	359499.4	325759.3	141909	148172.2
	Geo CV%	NA	55.3	35.3	112.2	134.3	42.2
TP 3							
C_{max} (ng/mL)	N	0	1	7	8	7	10
	Geo mean	NA	195.1	260.1	529.1	1442.2	1572.6
	Geo CV%	NA	NA	96.3	16.8	23.6	36.7
T_{max} (h)	n		1	7	8	7	10
	Median (min, max)		1.0 (1.0-1.0)	1.0 (0.8-2.0)	1.0 (0.8-1.6)	1.0 (0.9-1.5)	1.05 (0.8-1.6)
$AUC_{0\text{-last}}$ (h·ng/mL)	N	0	1	7	8	7	10
	Geo mean	NA	3524.6	6421.4	10176.6	28390.4	31209.5
	Geo CV%	NA	NA	43.4	36.6	75.7	66.2

$t_{1/2}$ (h)	N	0	1	6	8	7	10
	Geo mean	NA	177.1	195.9	222.1	203.5	196.3
	Geo CV%	NA	NA	27.5	13.5	10.9	19.3
$AUC_{0\text{-inf}}$ (h·ng/mL)	N	0	1	6	8	7	10
	Geo mean	NA	4047	7237.8	11713.6	30542.2	33061.2
	Geo CV%	NA	NA	46.9	34.4	71.8	63.5
CL (L/h)	N	0	1	6	8	7	10
	Geo mean	NA	1451.7	1102.3	848.9	411.1	467.7
	Geo CV%	NA	NA	52.7	24.1	93.3	56.9
Vd (L)	N	0	1	6	8	7	10
	Geo mean	NA	370963.8	311517.2	271997.8	120687.6	132476.8
	Geo CV%	NA	NA	41.9	29.5	90.8	56

$AUC_{0\text{-inf}}$, area under the serum concentration-time curve from time 0 to infinity; $AUC_{0\text{-last}}$, area under the serum concentration-time curve from time 0 to the last quantifiable sample; CL, serum clearance of drug; C_{max}, maximum observed concentration of drug; CV, coefficient of variation; geo mean, geometric mean; max, maximum; min, minimum; n, number of observations; NA, not applicable; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; T_{max}, time of occurrence for maximum (peak) drug concentration; TP, treatment period. Subjects with unreliable λ_z (ie, R-square adjusted > 0.85, interval for λ_z calculation shorter than $t_{1/2}$, number of points to calculate λ_z < 3), had λ_z with its related PK parameters excluded from summary statistics. Subjects with unreliable $AUC_{0\text{-}\infty}$ (because of extrapolation > 20%), had $AUC_{0\text{-inf}}$ with its related PK parameters excluded from summary statistics.

Table S2. Pharmacokinetic parameters for SEL-110 (sirolimus) 0.05-0.15 mg/kg when combined with SEL-037 0.2 mg/kg or 0.4 mg/kg (TPs 1-5 combined) (Pharmacokinetic Analysis Set)

		SEL-037 0.2 mg/kg				SEL-037 0.4 mg/kg				
SEL-110 dose (mg/kg)		**0.05**	**0.08**	**0.1**	**0.15**	**0.05**	**0.08**	**0.1**	**0.125**	**0.15**
C_{max}	n (values)	18	17	83	116	13	26	29	30	36
(ng/mL)	n (subjects)	9	6	28	47	10	11	12	14	14
	Geo mean	213	342	608	1249	121	317	398	989	1479
	Geo CV% (between)	22	19	43	41	367	0	61	65	31
	Geo CV% (within)	100	13	59	43	7	100	15	25	31
T_{max} (h)	n (values)	18	17	83	116	13	26	29	30	36
	n (subjects)	9	6	28	47	10	11	12	14	14
	median	1	1	1	1	1	0.95	1	1	1
	minimum	0.3	0.6	0.3	0.3	0.5	0.3	0.3	0.4	0.8
	maximum	166	1.1	3	3	2.1	2	1.6	2	1.9
$AUC_{0\text{-last}}$	n (values)	18	17	83	116	13	26	29	30	36
(h·ng/mL)	n (subjects)	9	6	28	47	10	11	12	14	14
	Geo mean	4028	6302	8942	16074	1734	3634	7291	13407	26945
	Geo CV% (between)	33	18	66	99	2780	301	44	374	58
	Geo CV% (within)	41	13	63	40	12	29	102	32	43

$AUC_{0\text{-}inf}$	n (values)	17	17	70	102	11	20	27	27	33
(h·ng/mL)	n (subjects)	9	6	26	44	9	9	11	12	14
	Geo mean	4789	7163	12152	29392	4561	8037	9257	24241	28984
	Geo CV% (between)	36	18	32	85	24	28	94	77	56
	Geo CV% (within)	36	12	40	38	12	28	15	28	43
$t_{1/2}$ (h)	n (values)	17	17	75	104	11	22	27	27	34
	n (subjects)	9	6	27	45	9	9	11	12	14
	median	200	193	213	207	223	214	231	214	210
	minimum	10	106	5	2	117	120	109	45	53
	maximum	265	255	350	322	274	297	277	268	301
CL (mL/h)	n (values)	17	17	70	102	11	20	27	27	33
	n (subjects)	9	6	26	44	9	9	11	12	14
	Geo mean	1361	1317	904	820	1158	1021	1075	497	508
	Geo CV% (between)	24	25	30	75	23	27	130	84	45
	Geo CV% (within)	39	12	40	38	12	28	15	28	43

PK and TP data were combined for each of the SEL-110 doses administered with SEL-037 0.2 mg/kg. $AUC_{0\text{-}inf}$, area under the serum concentration-time curve from time 0 to infinity; $AUC_{0\text{-}last}$, area under the serum concentration-time curve from time 0 to the last quantifiable sample; CL, serum clearance of drug; C_{max}, maximum observed concentration of drug; Geo CV, geometric coefficient of variation; Geo mean, geometric mean; max, maximum; min, minimum; n, number of observations; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; T_{max}, time of occurrence for maximum (peak) drug concentration; TP, treatment period. Subjects with unreliable λ_z (ie, R-square adjusted > 0.85, interval for λ_z calculation shorter than $t_{1/2}$, number of points to calculate λ_z < 3), had λ_z with its related PK parameters excluded from summary statistics. Subjects with unreliable $AUC_{0\text{-}\infty}$ (because of extrapolation > 20%), had $AUC_{0\text{-}inf}$ with its related PK parameters excluded from summary statistics.

Table S3 Pharmacokinetic parameters for A. SEL-037 0.2 mg/kg and B. SEL-037 0.4 mg/kg with or without SEL-110 0.05-0.15 mg/kg (TPs 1, 3 and 5) based on SEL-037 serum concentration (Pharmacokinetic Analysis Set)

a.

SEL-110 dose		**NA**	**0.05 mg/kg TP1-3**	**0.08 mg/kg TP1-3**	**0.10 mg/kg TP1-3**	**0.10 mg/kg TP1-5**	**0.15 mg/kg TP1-3**	**0.15 mg/kg TP1-5**	**0.15 - 0.1 mg/kg TP1-5**
Cohort		**1**	**3**	**5**	**7**	**17**	**11**	**13**	**15**
TP1									
C_{max} (ng/mL)	N	3	9	6	11	12	13	23	11
	Geo mean	6.3	5.7	5.7	5.1	4.5	4.7	4.5	4.3
	Geo CV%	26.8	36.5	16.7	24.4	13.3	20.9	15.6	16
T_{max} (h)	n	3	9	6	11	12	13	23	11
	Median (range)	2 (1.1-5.1)	22.2 (20.2-23.8)	23.6 (20.3-24.9)	22.4 (21.1-31.7)	22.5 (0.0-25.3)	22.8 (0.0-28.8)	23 (0.0-24.6)	22.5 (21.0-23.9)
$AUC_{o\text{-}last}$ (h.ng/mL)	N	3	9	6	11	10	10	22	11
	Geo mean	112.9	337.9	247.7	275.8	283.7	149.2	155.6	93.6
	Geo CV%	13.3	244.5	179.5	229.8	199.4	204.5	217.4	195.1

TP3									
C_{max} (ng/mL)	N	0	3	5	7	6	9	12	5
	Geo mean	NA	7.7	6.1	5.3	5.1	4.4	4.9	4.8
	Geo CV%	NA	33	17.3	17.3	7.6	16.6	15.7	9.7
T_{max} (h)	n	NA	3	5	7	6	9	12	5
	Median (range)	- -	22.2 (22.0-22.3)	22.2 (21.6-23.9)	21.6 (21.0-23.6)	22.5 (20.5-26.6)	22.2 (21.1-25.1)	22.4 (0.0-25.0)	22.1 (19.1-28.1)
$AUC_{o\text{-}last}$ (h.ng/mL)	N	0	3	5	7	6	9	11	5
	Geo mean	NA	467	719.8	226.3	288.7	110.9	200.3	618.5
	Geo CV%	NA	402.3	12	249.9	211.5	216.2	217	5.3
TP5									
C_{max} (ng/mL)	N	0	1	1	6	6	7	11	4
	Geo mean	NA	4.8	4.4	5.6	5.5	4.1	4.7	3.9
	Geo CV%	NA	NA	NA	16.5	15.5	8.5	13.6	24.8
T_{max} (h)	n	NA	1	1	6	6	7	11	4
	Median (range)	- -	2.0 3.0 (NA)	24.1 (NA)	22.5 (0.0-28.8)	21.8 (20.8-22.7)	22.6 (0.0-24.1)	22.8 (0.0-52.3)	21.95 (21.8-28.6)

$AUC_{o\text{-}last}$ (h.ng/mL)	N	0	1	1	5	6	6	11	4
	Geo mean	NA	98.7	53.1	172	448.3	47.1	221.4	82.7
	Geo CV%	NA	NA	NA	196	143.2	9.9	208.8	243.5

b.

SEL-110 dose		**NA**	**0.05 mg/kg TP1-3**	**0.08 mg/kg TP1-3**	**0.10 mg/kg TP1-3**	**0.125 mg/kg TP1-3**	**0.15 mg/kg TP1-3**
Cohort		**2**	**4**	**6**	**8**	**10**	**12**
TP1							
C_{max} (ng/mL)	N	3	10	11	12	14	14
	Geo mean	6.9	9.7	10.7	9	8.2	9.8
	Geo CV%	78.9	25.5	8.5	16.4	34.8	29.3
T_{max} (h)	n	3	10	11	12	14	14
	Median (range)	1.0 (1.0-8.0)	23.0 (20.6-24.1)	22.0 (0.0-27.2)	21.6 (0.0-26.1)	23.2 (0.0-167)	23.0 (20.7-51.1)
$AUC_{o\text{-}last}$ (h.ng/mL)	N	3	10	9	11	13	14
	Geo mean	402.2	1337.4	1777.8	1500.9	1505.6	1881.3
	Geo CV%	359.1	152.2	22.2	36.3	50	48.7

TP3							
C_{max} (ng/mL)	N	0	1	7	8	7	10
	Geo mean	NA	14	10	9.7	9.1	10.4
	Geo CV%	NA	NA	23.3	23.6	20.8	50.3
T_{max} (h)	n	NA	1	7	8	7	10
	Median (range)	- -	20.9 (NA)	23.8 (22.0-159)	21.9 (0.0-27.9)	22.7 (21.4-24.7)	23.3 (21.6-29.3)
$AUC_{o\text{-}last}$ (h.ng/mL)	N	0	1	7	7	7	10
	Geo mean	NA	2815.7	1477.9	1516.6	1752.5	1687.2
	Geo CV%	NA	NA	38.2	39.8	47.1	61.3
TP5							
C_{max} (ng/mL)	N	0	1	5	6	7	8
	Geo mean	NA	10.7	10	9.1	7.8	10.4
	Geo CV%	NA	NA	26.8	26.9	35.5	25.2
T_{max} (h)	n	NA	1	5	6	7	8
	Median (range)	- -	23.1 (NA)	24.6 (3.0-24.6)	23.4 (22.3-25.5)	23.9 (22.1-26.2)	24.1 (22.5-27.3)
$AUC_{o\text{-}last}$ (h.ng/mL)	N	0	1	5	6	7	8
	Geo mean	NA	2092.3	1297.6	1332.1	792.4	1381.1
	Geo CV%	NA	NA	30.7	54.7	162.2	33.5

$AUC_{0\text{-last}}$, area under the serum concentration-time curve from time 0 to the last quantifiable sample; C_{max}, maximum observed concentration of drug; Geo CV, geometric coefficient of variation; Geo mean, geometric mean; max, maximum; min, minimum; n, number of observations; NA, not applicable; PK, pharmacokinetic; SD, standard deviation; T_{max}, time of occurrence for maximum (peak) drug concentration.

Subjects with unreliable λ_z (ie, R-square adjusted > 0.85, interval for λ_z calculation shorter than $t_{1/2}$, number of points to calculate λ_z < 3), had λ_z with its related PK parameters excluded from summary statistics. Subjects with unreliable $AUC_{0\text{-inf}}$ (because of extrapolation > 20%), had $AUC_{0\text{-inf}}$ with its related PK parameters excluded from summary statistics.

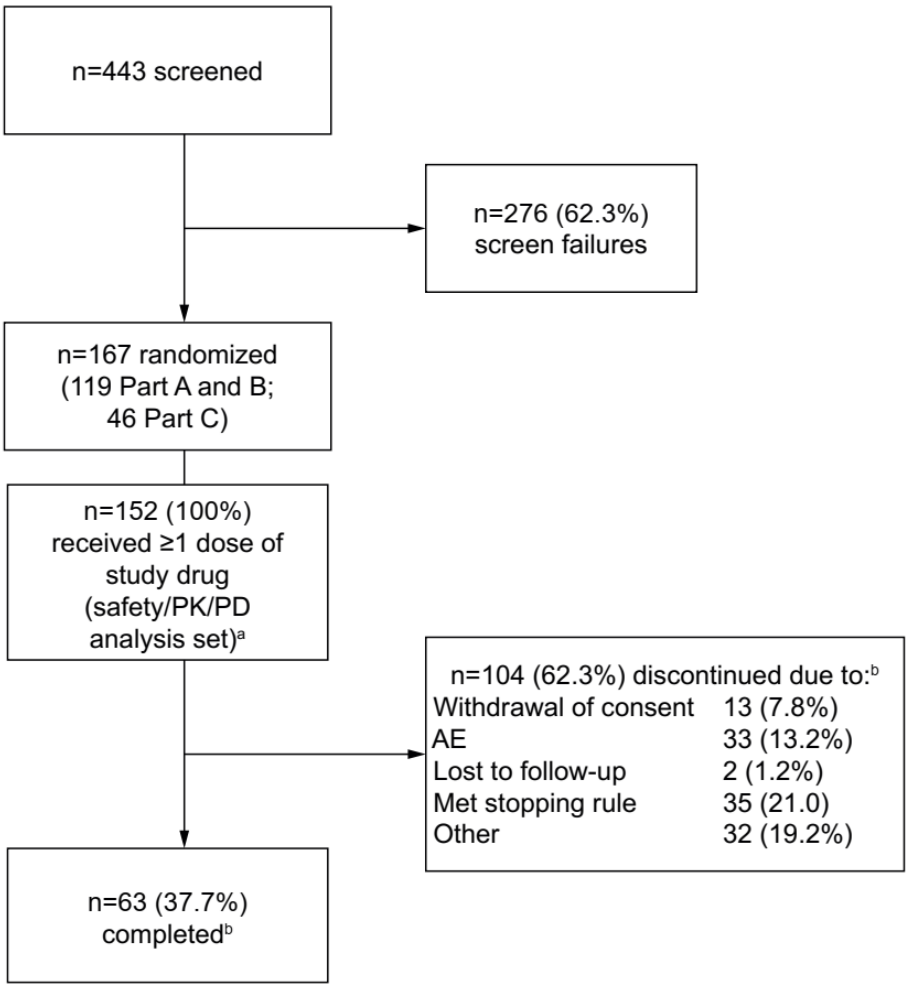

Figure S1. Participant disposition.

n, number of subjects; PD, pharmacodynamic; PK, pharmacokinetic; [a] Percentages are based on the number of dosed subjects for each treatment group; safety, PK and PD analysis sets were identical [b]Percentages are based on the number of subjects randomized.

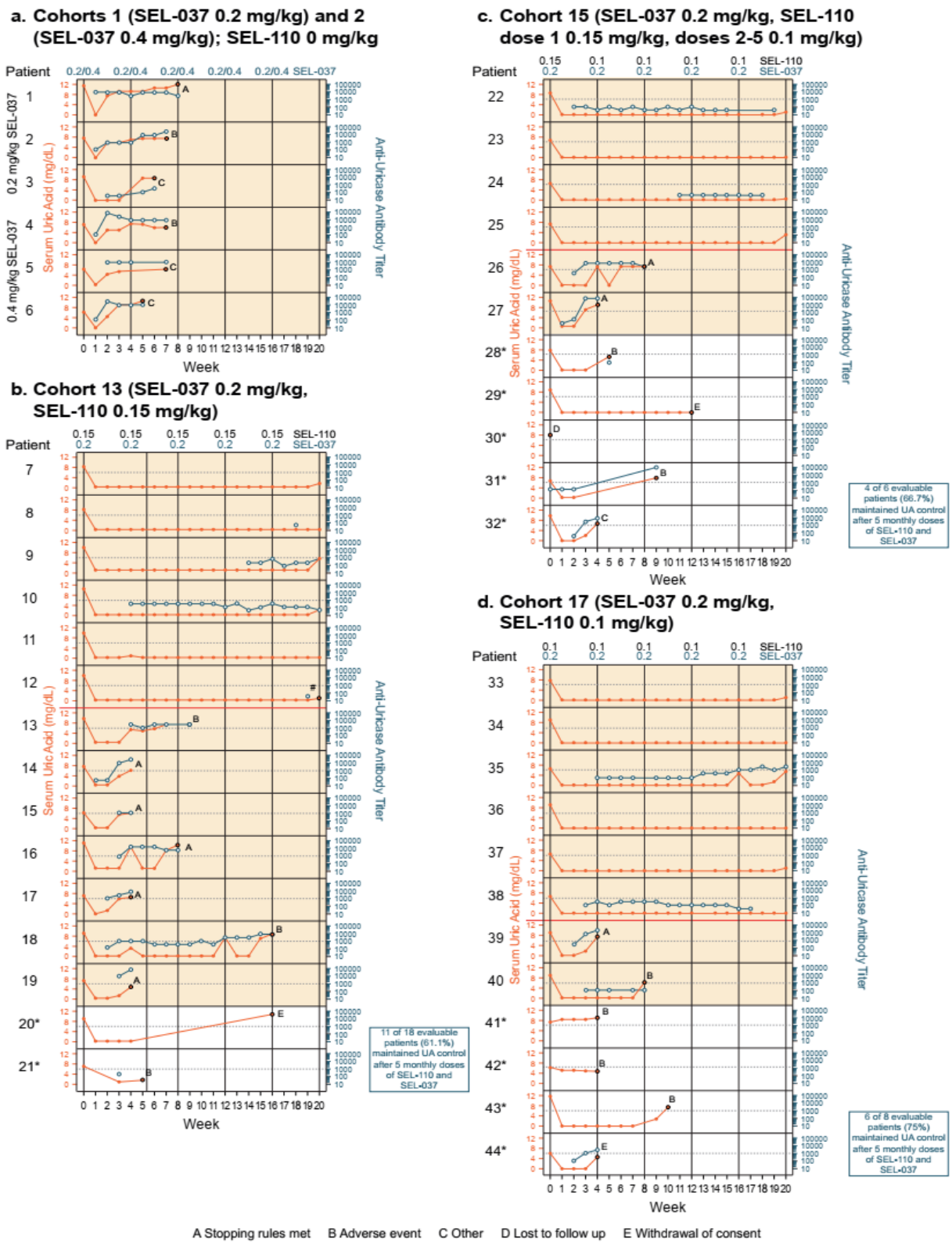

Figure S2. Plot of individual serum uric acid (sUA) levels and anti-uricase antibody titer over time in a. Cohorts 1-2, b. Cohort 13, c. Cohort 15 and d. Cohort 17.

*non-evaluable patient (the plots for the evaluable patients have background shading). #Frozen uric acid sample result used in place of missing ambient uric acid sample for the same timepoint. Orange solid markers represents sUA concentration. Blue open markers represent anti-uricase antibody titer results. The red horizontal line separates subjects who achieved and maintained sUA levels less than 6 mg/dL through Week 20 (End of Study).

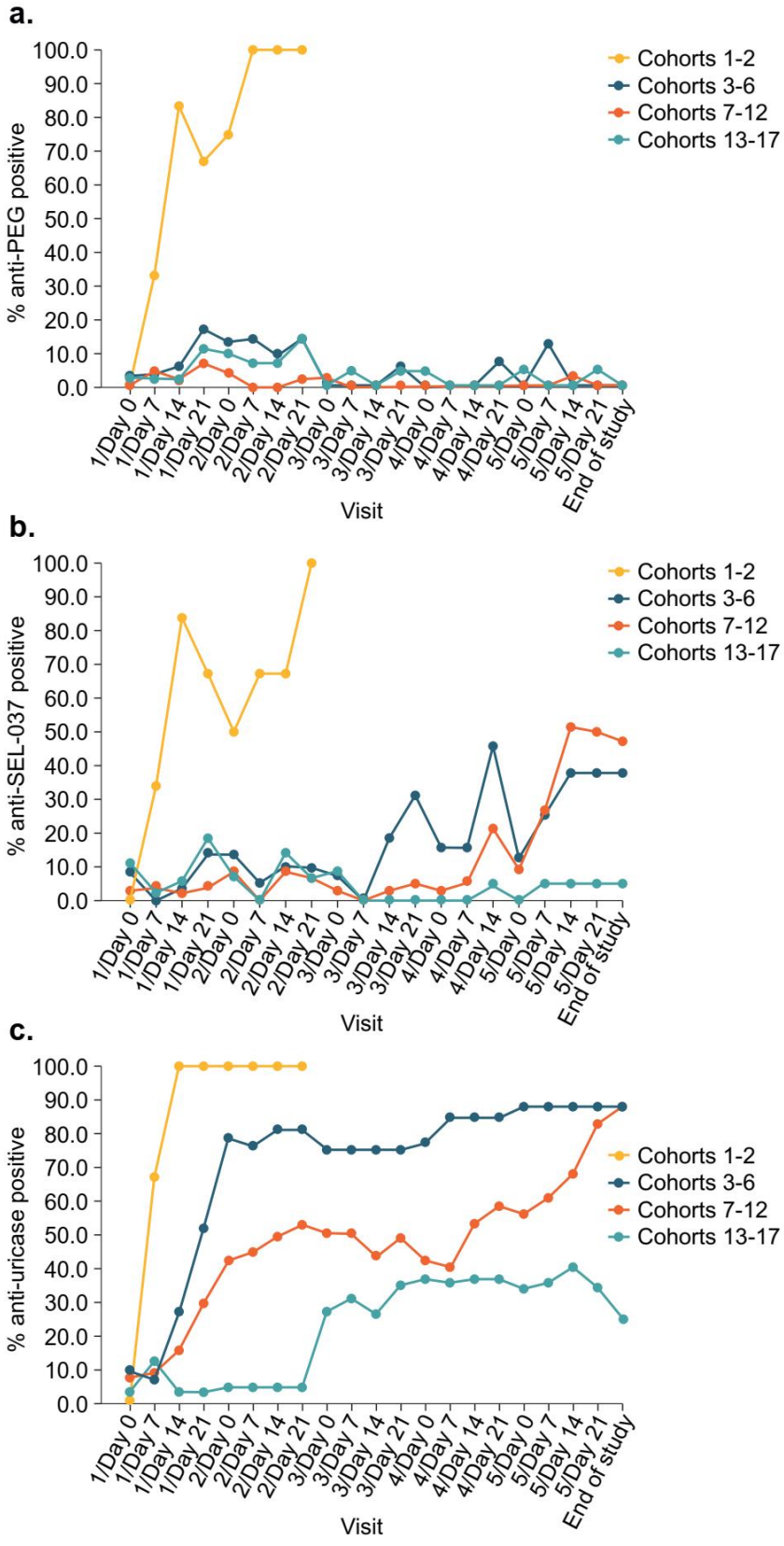

Figure S3. Changes in the percentage of a. Anti-PEG, b. Anti-SEL-037 and c. Anti-uricase positive participants over time.

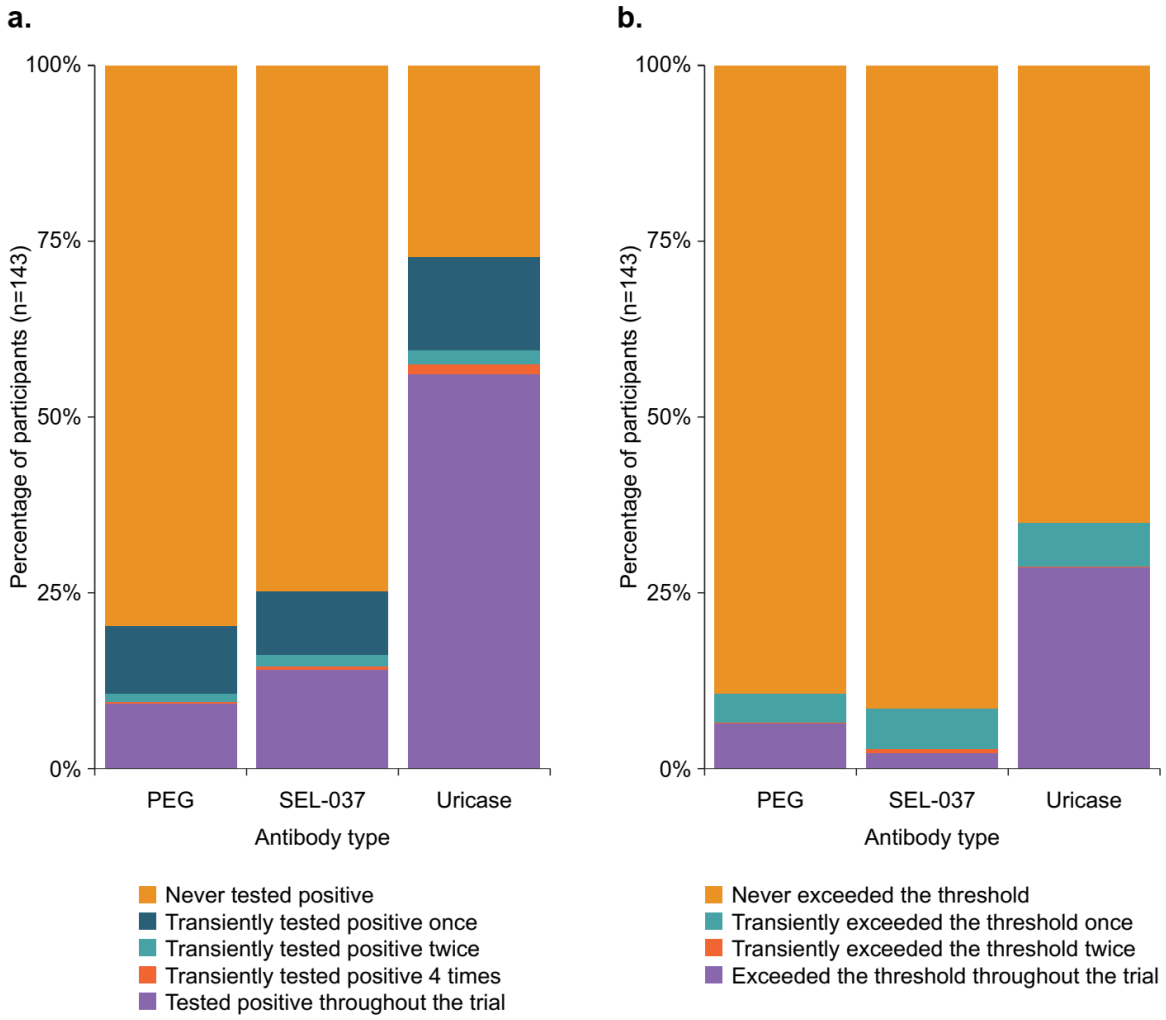

Figure S4. Percentage of participants treated with SEL-037 in combination with SEL-110 (Cohorts 3-17) who a. Never tested positive for antibodies or had transient or sustained increases in antibodies and b. Had anti-PEG antibody titers >475, anti-SEL-037 (anti-pegsiticase) antibody titers >4, and anti-uricase antibody titers >1080.

For Panel b, the thresholds for anti-PEG and anti-SEL-037 antibody titers are considered to be the median value for participants with anti-PEG and anti-SEL-037 antibodies, respectively. The threshold for anti-uricase antibodies is the level below which participants demonstrated sustained sUA control at Week 20.