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ORIGINAL RESEARCH

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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ABSTRACT

Introduction: SEL-212 is a developmental treatment for uncontrolled gout characterized by serum uric acid (sUA) levels ≥ 6 mg/dl despite treatment. It comprises a novel PEGylated uricase (SEL-037; also called pegadricase) co-administered with tolerogenic nanoparticles containing sirolimus (rapamycin) (SEL-110; also called ImmTOR®), which mitigates the formation of anti-drug antibodies (ADAs) against uricase and SEL-037 (PEGylated uricase), thereby enabling sustained sUA control (sUA < 6 mg/dl). The aim of this study was to identify appropriate dosing for SEL-037 and SEL-110 for use in phase 3 clinical trials.

Methods: This open-label phase 2 study was conducted in adults with symptomatic gout and sUA ≥ 6 mg/dl. Participants received five monthly infusions of SEL-037 (0.2 or 0.4 mg/kg) alone or in combination with three or five monthly infusions of SEL-110 (0.05–0.15 mg/kg). Safety, tolerability, sUA, ADAs, and tophi were monitored for 6 months.

Results: A total of 152 adults completed the study. SEL-037 alone resulted in rapid sUA reductions that were not sustained beyond 30 days in most participants due to ADA formation and loss of uricase activity. Levels of ADAs decreased with increasing doses of SEL-110 up to 0.1 mg/kg, with anti-uricase titers < 1080 correlating with sustained sUA control and reductions in tophi. Overall, 66% of evaluable participants achieved sUA control at week 20 following five monthly doses of SEL-037 0.2 mg/kg + SEL-110 0.1–0.15 mg/kg, whereas only 26% achieved sUA control at week 20 when SEL-110 was withdrawn after week 12. Compared to other dose combinations, SEL-037 0.2 mg/kg + SEL-110 0.15 mg/kg achieved the greatest sUA control at week 12 and was well-tolerated with no safety concerns.

Conclusion: Results provide continued support for the use of multiple monthly administrations

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of SEL-037 0.2 mg/kg + SEL-110 0.1-0.15 mg/kg in clinical trials for SEL-212.
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Keywords: Gout; Hyperuricemia; ImmTOR®; Polyethylene glycols; SEL-212; Uric acid; Urate oxidase

Key Summary Points

Why carry out the study?

Uncontrolled gout is a painful, debilitating inflammatory arthritis caused by persistently high levels of serum uric acid (sUA ≥ 6 mg/dl) leading to crystal formation (tophi) in joints and other areas of the body.

Although recombinant uricases effectively reduce sUA levels in the short term, long-term use is restricted by the formation of anti-drug antibodies (ADAs).

SEL-212 is a novel sUA-lowering therapy comprising SEL-037 (a fungal PEGylated uricase, also called pegadricase) and SEL-110 (tolerogenic nanoparticles containing rapamycin that instruct the immune system to specifically tolerate co-administered biologics without broad immunosuppression) that mitigates ADA formation thereby prolonging SEL-037 activity, enabling repeat dosing and reducing the risk of adverse events.

What was learned from the study?

Multiple monthly infusions of SEL-037 0.2–0.4 mg/kg with SEL-110 0.05–0.15 mg/kg (in particular SEL-110 0.1 mg/kg and 0.15 mg/kg) were well tolerated in adults with symptomatic gout and sUA ≥ 6 mg/dl at baseline and provided sustained sUA control that correlated with low levels of ADAs (anti-uricase titers < 1080) and reduced tophi.

Results provide continued support for the use of multiple monthly co-administrations of SEL-037 0.2 mg/kg + SEL-110 0.1–0.15 mg/kg in the phase 2 COMPARE trial and the ongoing phase 3 clinical trials for SEL-212.

INTRODUCTION

Gout is a chronic metabolic disorder characterized by serum uric acid (sUA) levels exceeding the physiologic limit of solubility [1–3]. This results in the formation of monosodium urate crystals (tophi) in joint fluid and soft tissues, leading to bone remodeling, intermittent inflammatory arthritis, and/or an increased risk of renal calculi, cardiovascular disease, and death [3–6]. Treatment guidelines for uncontrolled gout recommend managing arthritic flares using non-steroidal anti-inflammatory drugs (NSAIDs), colchicine or glucocorticoids, while reducing sUA levels to < 6 mg/dl using a combination of nonpharmacological therapy (diet and lifestyle), xanthine oxidase inhibitors (e.g., allopurinol and febuxostat) to inhibit uric acid (UA) production, and/or uricosuric agents (e.g., probenecid) to improve UA renal clearance [1, 7]. Up to 6% of gout patients have chronic refractory disease, defined as symptomatic gout with sUA ≥ 6 mg/dl despite treatment, or intolerance/contraindications to standard therapy [8, 9].

Unlike most mammals, humans lack the functional uricase enzyme [10] that converts urate to more soluble (and therefore more easily eliminated) allantoin [11]. Although intravenous (IV) infusions of non-human uricases effectively reduce sUA levels in people with hyperuricemia, uricases are highly immunogenic in humans and are rapidly cleared from the circulation [12]. Two uricases are currently approved for the treatment of hyperuricemia; rasburicase (ELITEK®) is licensed as a single course of treatment for chemotherapy-related hyperuricemia [13] and pegloticase (Krystexxa®) (a PEGylated uricase [14]) is approved as a biweekly treatment for gout that is refractory to conventional therapy [1, 15, 16]. Although pegloticase reduces sUA and tophi formation in the short term [15, 17–19], anti-drug antibodies (ADAs) develop in up to 90% of patients resulting in an increased risk of infusion reactions, increased pegloticase clearance, and reduced efficacy over time. Only 42% of pegloticase-treated patients maintain sUA control (sUA < 6 mg/dl) after 6 months [17, 18] unless pegloticase is co-administered with methotrexate [20].

SEL-212 is a developmental IV therapy comprising SEL-037 (pegadricase, formerly known as pegsiticase) and SEL-110 [21]. SEL-037 is a PEGylated uricase that differs from pegloticase in terms of source (*Candida utilis* as opposed to porcine/baboon), formulation, and type of PEGylation [22, 23]. SEL-110 consists of tolerogenic nanoparticles containing sirolimus (rapamycin) that instruct the immune system to specifically tolerate co-administered biologics without broad immunosuppression [21, 24–26]. Preclinical studies show that co-administration of SEL-110 with SEL-037 prevents the formation of ADAs and prolongs uricase activity in uricase-deficient mice and wild-type non-human primates, resulting in sustained sUA control [24]. In phase I studies, a single infusion of SEL-037 0.1–1.2 mg/kg and/or SEL-110 $\leq$ 0.3 mg/kg was well tolerated in healthy adults with baseline sUA $\geq$ 6 mg/dl [25]. Moreover, a single co-administration of SEL-037 0.4 mg/kg with SEL-110 0.03–0.3 mg/kg rapidly reduced sUA levels to < 0.1 mg/dl and dose-dependently reduced or prevented the formation of ADAs up to 60 days post-treatment.

The aim of this study was to evaluate the safety, tolerability, pharmacodynamic (PD) and pharmacokinetic (PK) profile of multiple monthly IV infusions of SEL-037 with or without SEL-110 in patients with hyperuricemia and symptomatic gout, and to further explore the relationship between sUA reductions, ADA titers and tophi. Results were used to identify the most appropriate dose of each component of SEL-212 for further study in the ongoing phase 3 studies (NCT04596540 and NCT04513366) and the COMPARE trial (NCT03905512), the first head-to-head study comparing the efficacy and safety of SEL-212 with pegloticase.

METHODS

Study Design

This phase 2, open-label, multiple ascending dose study (NCT02959918) took place at 15 US sites between October 2016 and January 2019. The study met US regulatory and International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, was approved by the Institutional Review Board (IRB), and was conducted in accordance with the Declaration of Helsinki and/or Federal regulations. The study was approved by Copernicus Group IRB, Cary, NC, USA. Written informed consent was obtained from all participants.

Participants

The study included men and women aged 21–-75 years with sUA $\geq$ 6 mg/dl and established or symptomatic gout (at least one of the following: $\geq$ 1 tophus; $\geq$ 1 gout flare within the last 6 months; gouty arthropathy). All participants were required to have negative serology at screening for anti-PEG antibodies, HIV-1/-2 and hepatitis C virus. Subjects receiving stable doses of ULT for $\geq$ 1 month prior to screening and throughout the screening phase were required to continue with their existing therapy throughout the study. Subjects with previous or current exposure to uricase (rasburicase, pegloticase, or SEL-037 in clinical trials) were excluded. Full inclusion and exclusion criteria are listed in the Supplementary Material.

Interventions

Subjects were screened up to 45 days prior to study drug dosing. Eligible participants were randomized to one of 14 dosing cohorts (Table 1). Cohorts 1 and 2 were scheduled to receive five Q4-week doses of SEL-037 alone; cohorts 3–8 and 10–12 received three Q4-week ascending doses of SEL-212 (Part A) followed by

Table 1 Study design

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

Cohort	TPs 1–5 (Part C)	
	SEL-037	SEL-110
13	0.2 mg/kg	0.15 mg/kg
15	0.2 mg/kg	Dose 1: 0.15 mg/kg
		Dose 2–5: 0.1 mg/kg
17	0.2 mg/kg	0.1 mg/kg

Participants were randomized to one of 14 dosing cohorts and each cohort entered five consecutive TPs with study drug dosing on day 0 of each TP and 28 ± 1 day between each dose. *TP* treatment period

two Q4-week doses of SEL-037 alone (Part B), and cohorts 13, 15 and 17 received five Q4-week ascending doses of SEL-212 (Part C). Cohort numbers 9, 14, and 16 were omitted from the protocol to ensure that that odd-numbered cohorts received SEL-037 0.2 mg/kg and even-numbered cohorts received 0.4 mg/kg.

Each cohort consisted of five consecutive treatment periods (TPs), with study drug dosing on day 0 of each TP and 28 days between doses. Unless contraindicated, participants received gout flare prophylaxis comprising either a single dose of colchicine 1.2 mg followed by colchicine 0.6 mg QD or an NSAID (ibuprofen 600 mg TID or equivalent) one week prior to study drug dosing in TP1 and throughout the study. Participants also received an antihistamine (60–180 mg oral fexofenadine) 12 ± 2 h and 2 ± 1 h before each study drug dosing in TPs 1–5 and a steroid (IV methylprednisolone 16–40 mg or equivalent) 1 ± 0.5 h before each dosing to reduce the risk of infusion reactions.

Assessments

Participants remained in the clinic for 9 h after the start of each infusion for safety evaluations and PK blood draws and returned to the clinic for PK and PD blood draws on days 1, 7, 14 and

Table 2 Patient characteristics at baseline (Safety Analysis Set)

		Cohort								
		1 *N* = 3	**2** *N* = 3	**3** *N* = 9	**4** *N* = 10	**5** *N* = 6	**6** *N* = 11	**7** *N* = 11	**8** *N* = 12	**10** *N* = 14
Age (years)	Mean (SD)	49.3 (3.79)	54.3 (11.93)	55.7 (9.89)	52.0 (8.65)	58.5 (5.47)	59.4 (9.67)	51.5 (12.84)	53.3 (9.90)	59.7 (9.39)
Gender										
Male	*n* (%)	3 (100)	3 (100)	9 (100)	9 (90.0)	6 (100)	8 (72.7)	10 (90.9)	10 (83.3)	12 (85.7)
Race										
Asian	*n* (%)	0	0	0	1 (10.0)	0	0	0	0	2 (14.3)
Black/African American	*n* (%)	1 (33.3)	2 (66.7)	2 (22.2)	2 (20.0)	2 (33.3)	2 (18.2)	3 (27.3)	4 (33.3)	2 (14.3)
Pacific	*n* (%)	0	0	0	1 (10.0)	0	0	0	0	0
White	*n* (%)	2 (66.7)	0	7 (77.8)	5 (50.0)	4 (66.7)	9 (81.8)	8 (72.7)	8 (66.7)	10 (71.4)
Other	*n* (%)	0	1 (33.3)	0	1 (10.0)	0	0	0	0	0
Ethnicity										
Non-Hispanic/Latino	*n* (%)	3 (100)	3 (100)	7 (77.8)	9 (90.0)	5 (83.3)	11 (100)	11(100)	12 (100)	13 (92.9)
Height (cm)	Median (range)	180.30 (178.0–181.6)	168.40 (165.1–178.0)	174.00 (169.0–182.0)	176.50 (157.5–187.1)	177.25 (171.0–187.9)	171.00 (149.8–182.9)	180.00 (152.4–185.4)	172.85 (152.0–185.4)	171.00 (160.0–195.0)
Weight (kg)	Median (range)	135.50 (100.5–150.0)	111.80 (101.1–119.2)	110.70 (88.7–225.8)	113.45 (70.8–137.5)	117.85 (101.8–138.8)	106.30 (76.4–133.5)	98.90 (83.8–157.5)	99.25 (65.9–185.1)	89.65 (73.3–167.7)
BMI (kg/m^2)	Median (range)	41.70 (31.7–45.5)	37.10 (35.3–42.0)	37.00 (29.3–68.2)	35.90 (26.0–43.0)	37.30 (34.2–41.6)	33.90 (28.9–45.7)	32.10 (27.8–54.7)	31.95 (27.7–58.4)	30.30 (25.5–44.1)
Tophi present (yes)	*n* (%)	0	0	0	0	0	1 (9.1)	1 (9.1)	0	1 (7.1)
Diabetes present (yes)	*n* (%)	0	0	4 (44.4)	0	2 (33.3)	1 (9.1)	1 (9.1)	2 (16.7)	1 (7.1)

Table 2 continued

		Cohort					
		11 *N* = 13	**12** *N* = 14	**13** *N* = 23	**15** *N* = 11	**17** *N* = 12	**All cohorts** *N* = 152
Age (years)	Mean (SD)	52.5 (6.97)	57.7 (8.72)	56.0 (7.53)	49.3 (7.16)	52.9 (13.57)	54.8 (9.51)
Gender							
Male	*n* (%)	12 (92.3)	11 (78.6)	22 (95.7)	11 (100)	12 (100)	138 (90.8)
Race							
Asian	*n* (%)	0	0	1 (4.3)	0	0	4 (2.6)
Black or African American	*n* (%)	6 (46.2)	4 (28.6)	7 (30.4)	1 (9.1)	2 (16.7)	40 (26.3)
Pacific	*n* (%)	1 (7.7)	0	1 (4.3)	0	0	3 (2.0)
White	*n* (%)	6 (46.2)	10 (71.4)	14 (60.9)	10 (90.9)	10 (83.3)	103 (67.8)
Other	*n* (%)	0	0	0	0	0	2 (1.3)
Ethnicity							
Non-Hispanic/Latino	*n* (%)	13 (100)	13 (92.9)	22 (95.7)	8 (72.7)	12 (100)	142 (93.4)
Height (cm)	Median (range)	177.00 (150.7–190.0)	175.25 (166.0–194.0)	178.00 (162.0–190.5)	173.00 (165.1–187.9)	179.50 (170.5–194.5)	176.00 (149.8–195.0)
Weight (kg)	Median (range)	103.20 (72.5–169.9)	101.50 (77.4–143.8)	105.50 (71.6–146.6)	106.20 (74.3–120.0)	121.45 (79.3–164.5)	105.25 (65.9–225.8)
BMI (kg/m^2)	Median (range)	32.90 (25.4–54.2)	30.10 (25.1–38.8)	33.80 (26.3–44.6)	33.60 (24.8–41.3)	37.40 (25.7–51.3)	33.70 (24.8–68.2)
Tophi present	*n* (%)	0	1 (7.1)	1 (4.3)	2 (18.2)	2 (16.7)	9 (5.9)
Diabetes present (Yes)	*n* (%)	2 (15.4)	2 (14.3)	1 (4.3)	0	4 (3.3)	20 (13.2)

Percentages are based on the number of dosed subjects. Cohort 1 = SEL-037 0.2 mg/kg; cohort 2 = SEL-037 0.4 mg/kg; cohort 3 = SEL-037 0.2 mg/kg + SEL-110 0.05 mg/kg; cohort 4 = SEL-037 0.4 mg/kg + SEL-110 0.05 mg/kg; cohort 5 = SEL-037 0.2 mg/kg + SEL-110 0.08 mg/kg; cohort 6 = SEL-037 0.4 mg/kg + SEL-110 0.08 mg/kg; cohort 7 = SEL-037 0.2 mg/kg + SEL-110 0.1 mg/kg; cohort 8 = SEL-037 0.4 mg/kg + SEL-110 0.1 mg/kg; cohort 10 = SEL-037 0.4 mg/kg + SEL-110 0.125 mg/kg; cohort 11 = SEL-037 0.2 mg/kg + SEL-110 0.15 mg/kg; cohort 12 = SEL-037 0.4 mg/kg + SEL-110 0.15 mg/kg; cohort 13 = SEL-037 0.2 mg/kg + SEL-110 0.15 mg/kg; cohort 15 = SEL-037 0.2 mg/kg + SEL-110 0.15 (0.10) mg/kg; cohort 17 = SEL-037 0.2 mg/kg + SEL-110 0.1 mg/kg

BMI body mass index, *n* number of subjects, *SD* standard deviation

Table 3 Summary of TEAEs and most frequently reported TEAEs possibly related or related to study treatment for a. TPs 1–3 and b. TPs 4–5 (Safety Analysis Set)

a	Cohort										
	1 n = 3	2 n = 3	3 n = 9	4 n = 10	5 n = 6	6 n = 11	7 n = 11	8 n = 12	10 n = 14	11 n = 13	12 n = 14
Subjects with ≥ 1 TEAE, n (%)	3 (100)	2 (66.7)	8 (88.9)	8 (80.0)	6 (100)	10 (90.9)	10 (90.9)	12 (100)	14 (100)	12 (92.3)	14 (100)
Severe TEAE	1 (33.3)	1 (33.3)	1 (11.1)	0	1 (16.7)	1 (9.1)	2 (18.2)	3 (25.0)	1 (7.1)	1 (7.7)	3 (21.4)
Life-threatening TEAE	0	0	1 (11.1)	0	0	0	1 (9.1)	1 (8.3)	0	0	0
Drug-related TEAE	3 (100)	1 (33.3)	6 (66.7)	3 (30.0)	5 (83.3)	9 (81.8)	9 (81.8)	7 (58.3)	10 (71.4)	9 (69.2)	13 (92.9)
Serious TEAE	1 (33.3)	1 (33.3)	2 (22.2)	0	0	1 (9.1)	2 (18.2)	3 (25.0)	2 (14.3)	0	1 (7.1)
Drug-related serious TEAE	1 (33.3)	1 (33.3)	2 (22.2)	0	0	1 (9.1)	1 (9.1)	1 (8.3)	0	0	0
Fatal TEAE	0	0	0	0	0	0	0	0	0	0	0
TEAE leading to study drug discontinuation	1 (33.3)	1 (33.3)	2 (22.2)	0	0	2 (18.2)	2 (18.2)	2 (16.7)	2 (14.3)	1 (7.7)	2 (14.3)
Drug-related TEAEs in ≥ 5 subjects, n (%)	3 (100)	1 (33.3)	6 (66.7)	3 (30.0)	5 (83.3)	9 (81.8)	9 (81.8)	7 (58.3)	10 (71.4)	9 (69.2)	13 (92.9)
Gout	3 (100)	0	2 (22.2)	2 (20.0)	2 (33.3)	1 (9.1)	2 (18.2)	2 (16.7)	6 (42.9)	3 (23.1)	2 (14.3)
Hypertriglyceridemia	0	0	0	0	1 (16.7)	1 (9.1)	1 (9.1)	0	2 (14.3)	2 (15.4)	1 (7.1)
Hypophosphatemia	0	0	4 (44.4)	0	0	0	0	0	0	1 (7.7)	0
Stomatitis	0	0	0	0	0	0	0	3 (25.0)	3 (21.4)	1 (7.7)	2 (14.3)
Headache	0	0	0	1 (10.0)	0	1 (9.1)	1 (9.1)	0	2 (14.3)	1 (7.7)	2 (14.3)
Dysgeusia	0	0	0	0	0	1 (9.1)	0	0	0	0	2 (14.3)
Anemia	0	0	0	0	2 (33.3)	3 (27.3)	1 (9.1)	3 (25.0)	3 (21.4)	1 (7.7)	3 (21.4)
Leukopenia	0	0	1 (11.1)	0	1 (16.7)	1 (9.1)	1 (9.1)	3 (25.0)	1 (7.1)	1 (7.7)	2 (14.3)

Table 3 continued

a

	Cohort										
	1 n = 3	**2** n = 3	**3** n = 9	**4** n = 10	**5** n = 6	**6** n = 11	**7** n = 11	**8** n = 12	**10** n = 14	**11** n = 13	**12** n = 14
Neutropenia	0	0	0	0	0	0	1 (9.1)	2 (16.7)	0	2 (15.4)	1 (7.1)
Infusion-related reaction	0	0	1 (11.1)	0	0	2 (18.2)	1 (9.1)	0	1 (7.1)	0	0

	Cohort			
	13 n = 23	**15** n = 11	**17** n = 12	**All cohorts** n = 152
Subjects with ≥ 1 TEAE, n (%)	21 (91.3)	9 (81.8)	12 (100)	141 (92.8)
Severe TEAE	3 (13.0)	2 (18.2)	2 (16.7)	22 (14.5)
Life-threatening TEAE	0	0	0	3 (2.0)
Drug-related TEAE	13 (56.5)	4 (36.4)	11 (91.7)	103 (67.8)
Serious TEAE	2 (8.7)	1 (9.1)	2 (16.7)	18 (11.8)
Drug-related serious TEAE	2 (8.7)	0	1 (8.3)	10 (6.6)
Fatal TEAE	0	0	0	0
TEAE leading to study discontinuation	2 (8.7)	2 (18.2)	4 (33.3)	23 (15.1)
Drug-related TEAEs in ≥ 5 subjects, n (%)	3 (13.0)	1 (9.1)	4 (33.3)	23 (15.1)
Gout	7 (30.4)	0	4 (33.3)	21 (13.8)
Hypertriglyceridemia	0	1 (9.1)	1 (8.3)	10 (66.7)
Hypophosphatemia	0	1 (9.1)	0	6 (3.9)
Stomatitis	0	1 (9.1)	0	10 (66.7)
Headache	1 (3.4)	1 (9.1)	1 (8.3)	11 (72.4)
Dysgeusia	2 (8.7)	0	0	5 (3.3)
Anemia	0	0	0	16 (10.5)

Table 3 continued

	Cohort 13 $n = 23$	Cohort 15 $n = 11$	Cohort 17 $n = 12$	All cohorts $n = 152$
Leukopenia	0	0	0	11 (72.4)
Neutropenia	0	0	0	6 (3.9)
Infusion-related reaction	0	0	1 (8.3)	6 (3.9)

b

	Cohort										
	1 $n = 3$	**2** $n = 3$	**3** $n = 9$	**4** $n = 10$	**5** $n = 6$	**6** $n = 11$	**7** $n = 11$	**8** $n = 12$	**10** $n = 14$	**11** $n = 13$	**12** $n = 14$
Subjects with ≥ 1											
TEAE, *n* (%)	0	0	1 (11.1)	1 (10.0)	3 (50.0)	2 (18.2)	4 (36.4)	4 (33.3)	5 (35.7)	5 (38.5)	2 (18.2)
Severe TEAE	0	0	1 (11.1)	0	1 (16.7)	0	0	1 (8.3)	0	0	0
Life-threatening TEAE	0	0	0	0	0	0	0	0	0	0	0
Drug-related TEAE	0	0	1 (11.1)	1 (10.0)	1 (16.7)	2 (18.2)	2 (18.2)	1 (8.3)	2 (14.3)	3 (23.1)	2 (18.2)
Serious TEAE	0	0	0	0	0	0	0	1 (8.3)	0	0	0
Drug-related serious TEAE	0	0	0	0	0	0	0	0	0	0	0
Fatal TEAE	0	0	0	0	0	0	0	0	0	0	0
TEAE leading study discontinuation	0	0	0	0	0	0	0	0	0	0	0
Drug-related TEAEs in ≥ 2 subjects, *n* (%)	0	0	1 (11.1)	1 (10.0)	1 (16.7)	2 (18.2)	2 (18.2)	1 (8.3)	2 (14.3)	3 (23.1)	2 (14.3)
Gout	0	0	0	0	0	1 (9.1)	0	0	1 (7.1)	2 (15.4)	1 (7.1)
Hypertriglyceridemia	0	0	0	0	0	0	0	0	0	1 (7.7)	0
Headache	0	0	0	0	0	0	1 (7.1)	0	1 (7.1)	0	0
Flushing	0	0	0	1 (10.0)	0	0	0	0	1 (7.1)	0	0
Lymphopenia	0	0	1 (11.1)	0	1 (16.7)	0	0	0	0	0	0

Table 3 continued

	Cohort 13 n = 23	15 n = 11	17 n = 12	All cohorts n = 152
Subjects with $\geq$ 1				
TEAE, n (%)	9 (39.1)	2 (18.2)	4 (33.3)	44 (28.9)
Severe TEAE	2 (8.7)	0	0	5 (3.3)
Life-Threatening TEAE	0	0	0	0
Drug-related TEAE	3 (13.0)	1 (9.1)	4 (33.3)	23 (15.1)
Serious TEAE	1 (4.3)	0	0	2 (1.3)
Drug-related serious TEAE	0	0	0	0
Fatal TEAE	0	0	0	0
TEAE leading to study discontinuation	1 (4.3)	0	0	1 (0.7)
Drug-related TEAEs in $\geq$ 2 subjects, n (%)	3 (13.0)	1 (9.1)	4 (33.3)	23 (45.1)
Gout	0	0	2 (16.7)	7 (4.6)
Hypertriglyceridemia	0	1 (9.1)	0	3 (2.0)
Headache	1 (4.3)	1 (9.1)	1 (8.3)	5 (3.3)
Flushing	2 (8.7)	0	2 (16.7)	3 (2.0)
Lymphopenia	0	0	0	2 (1.3)

Drug-related TEAEs included any TEAE possibly related to or related to the study drug. Cohort 1 = SEL-037 0.2 mg/kg; cohort 2 = SEL-037 0.4 mg/kg; cohort 3 = SEL-037 0.2 mg/kg + SEL-110 0.05 mg/kg; cohort 4 = SEL-037 0.4 mg/kg + SEL-110 0.05 mg/kg; cohort 5 = SEL-037 0.2 mg/kg + SEL-110 0.08 mg/kg; cohort 6 = SEL-037 0.4 mg/kg + SEL-110 0.08 mg/kg; cohort 7 = SEL-037 0.2 mg/kg + SEL-110 0.1 mg/kg; cohort 8 = SEL-037 0.4 mg/kg + SEL-110 0.1 mg/kg; cohort 10 = SEL-037 0.4 mg/kg + SEL-110 0.125 mg/kg; cohort 11 = SEL-037 0.2 mg/kg + SEL-110 0.15 mg/kg; cohort 12 = SEL-037 0.4 mg/kg + SEL-110 0.15 mg/kg; cohort 13 = SEL-037 0.2 mg/kg + SEL-110 0.15 mg/kg; cohort 15 = SEL-037 0.2 mg/kg + SEL-110 0.15 (0.10) mg/kg; cohort 17 = SEL-037 0.2 mg/kg + SEL-110 0.1 mg/kg

n number of subjects, *N* total number of subjects, *TEAE* treatment-emergent adverse event

21 of each TP, antibody blood draws on days 7, 14 and 21 and safety blood draws on day 14 (cohorts 1–2) or days 7, 14, and 21 (cohorts 3–17). An End-of-Study (EOS) visit was performed on TP5, day 30 ± 1 and (for participants with sUA < 6 mg/dl on day 21 of TP5) at 60 ± 1 days after TP5. Participants were initially withdrawn from the study for meeting the following stopping rule: Weekly sUA levels ≥ 6 mg/dl or > 50% of baseline on day 21 of any TP in cohorts 1 and 2. To reduce the risk of infusion reactions and improve safety, stopping criteria were later adjusted to include sUA > 1.0 mg/dl at day 21 of any TP in cohorts 3–17. Subjects meeting the stopping criteria were assessed in an EOS visit 30 ± 2 days after their last study drug dose. Dual-energy computed tomography (DECT) scans were performed as exploratory measures for select participants in cohorts 10–17 at baseline, between days 21 and 28 (inclusive) of TP3 and between days 21 and 30 of TP5 or at early termination (ET).

Safety and tolerability were determined by frequencies of serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), and TEAEs leading to study discontinuation. Physical examinations, clinical laboratory tests, vital signs and concomitant medications were assessed up to 30 days after the last study drug administration. Laboratory testing and sUA measurements were performed at a central laboratory (ACM Medical Laboratory). Levels of serum SEL-037 and whole blood sirolimus were determined at Sannova Analytical Inc., uricase activity at SGS Health Science, and ADAs (anti-uricase, anti-PEG and anti-SEL-037 antibodies) at TGA and Charles River Laboratories. DECT scans were performed at individual sites using Siemens SOMATOM Definition scanners and read by an independent central reader at Arthritis Research, Canada using a Syngo Via DECT software package. Bioanalytical methods are further described in the Supplementary Material.

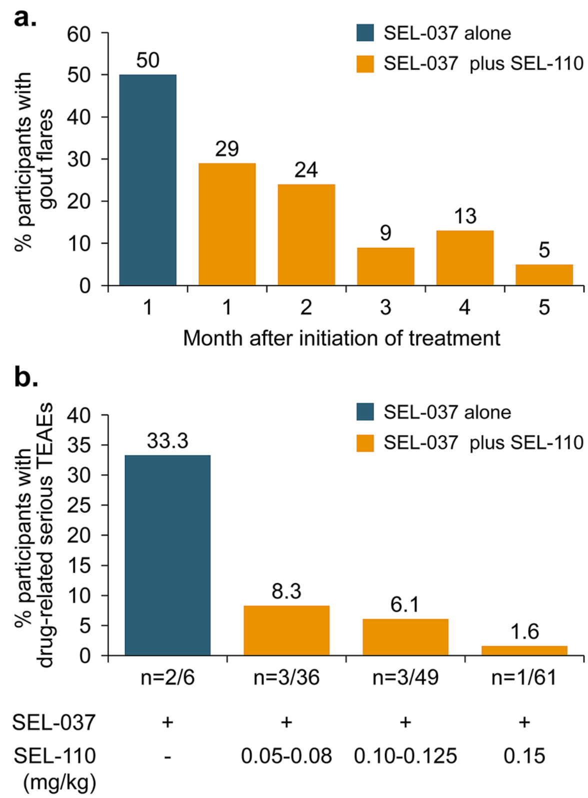
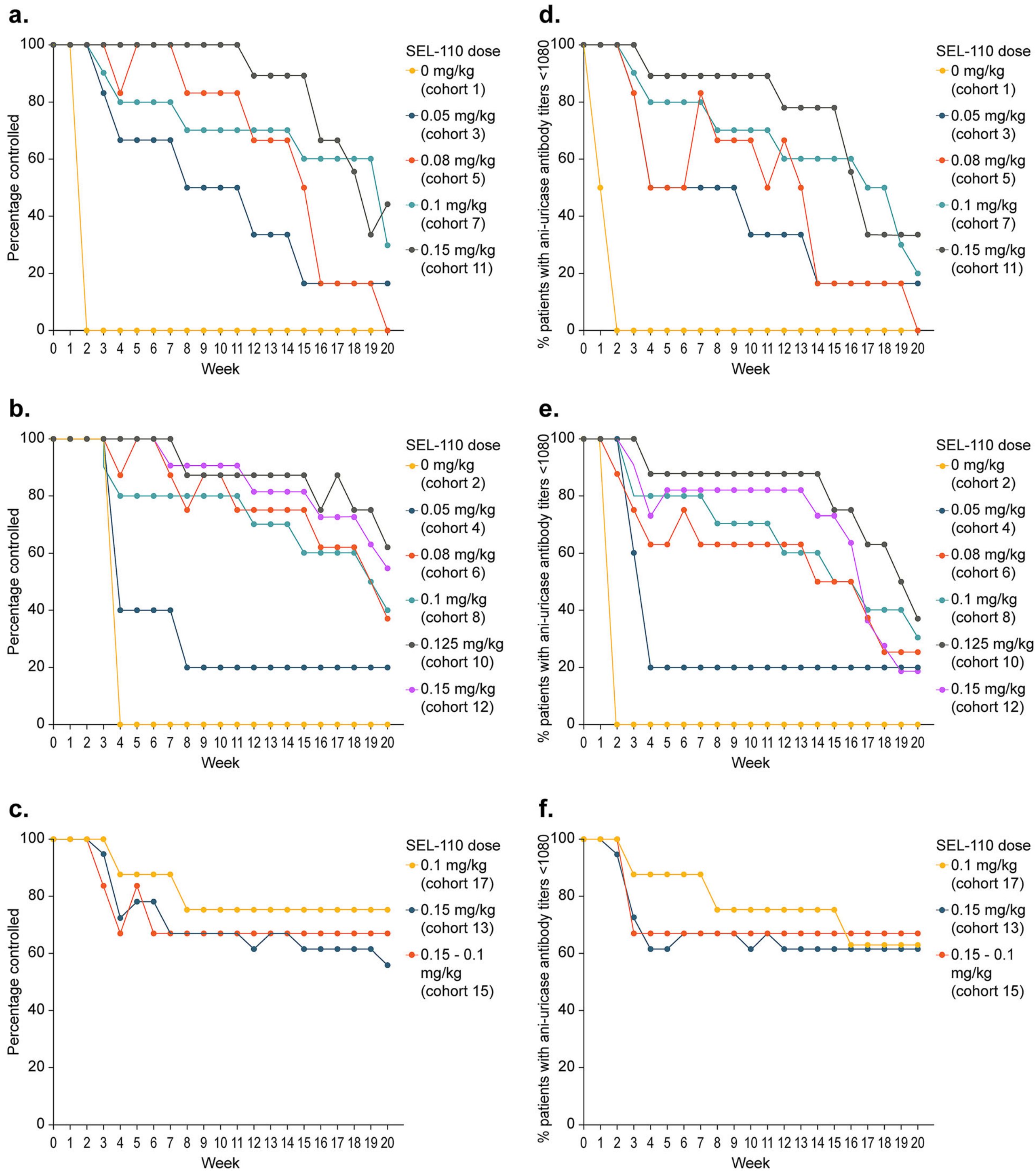


Fig. 1 Percentage of participants with **a** gout flares by month and **b** serious drug-related TEAEs following monthly IV infusions of SEL-037 0.2–0.4 mg/kg co-administered with and without increasing doses of SEL-110. *TEAE* treatment-emergent adverse event, *IV* intravenous. Drug-related TEAE, any TEAE resulting from study drug treatment

Study Objectives

The primary objective was to assess the safety and tolerability of monthly IV infusions of SEL-037 0.2–0.4 mg/kg administered with and without SEL-110 0.05–0.15 mg/kg up to 6 months after initial treatment. Secondary objectives were to assess changes over time in the PD, PK, and immunogenicity of SEL-037 with and without SEL-110 and the PK of sirolimus after SEL-110 co-administration with SEL-037. Changes over time in total body urate deposits and/or tophi at specific body sites were assessed as an exploratory objective in a subset of patients.


a.
Percentage controlled
Week
SEL-110 dose
0 mg/kg (cohort 1)
0.05 mg/kg (cohort 3)
0.08 mg/kg (cohort 5)
0.1 mg/kg (cohort 7)
0.15 mg/kg (cohort 11)
b.
Percentage controlled
Week
SEL-110 dose
0 mg/kg (cohort 2)
0.05 mg/kg (cohort 4)
0.08 mg/kg (cohort 6)
0.1 mg/kg (cohort 8)
0.125 mg/kg (cohort 10)
0.15 mg/kg (cohort 12)
c.
Percentage controlled
Week
SEL-110 dose
0.1 mg/kg (cohort 17)
0.15 mg/kg (cohort 13)
0.15 - 0.1 mg/kg (cohort 15)
d.
% patients with ani-uricase antibody titers <1080
Week
SEL-110 dose
0 mg/kg (cohort 1)
0.05 mg/kg (cohort 3)
0.08 mg/kg (cohort 5)
0.1 mg/kg (cohort 7)
0.15 mg/kg (cohort 11)
e.
% patients with ani-uricase antibody titers <1080
Week
SEL-110 dose
0 mg/kg (cohort 2)
0.05 mg/kg (cohort 4)
0.08 mg/kg (cohort 6)
0.1 mg/kg (cohort 8)
0.125 mg/kg (cohort 10)
0.15 mg/kg (cohort 12)
f.
% patients with ani-uricase antibody titers <1080
Week
SEL-110 dose
0.1 mg/kg (cohort 17)
0.15 mg/kg (cohort 13)
0.15 - 0.1 mg/kg (cohort 15)

◀**Fig. 2** Changes over time in the percentage of evaluable participants achieving sUA control (sUA < 6 mg/dl) treated with **a** SEL-037 0.2 mg/kg + SEL-110 0–0.15 mg/kg (cohorts 1, 3, 5, 7, 11; Parts A and B), **b** SEL-037 0.4 mg/kg + SEL-110 0–0.15 mg/kg (cohorts 2, 4, 6, 8, 10, 12; Parts A and B) and **c** SEL-037 0.2 mg/kg + SEL-110 0.1–0.15 mg/kg (cohorts 13, 15, 17; Part C). Changes over time in the percentage of participants with maximum anti-uricase antibody titers < 1080 treated with **d** SEL-037 0.2 mg/kg + SEL-110 0–0.15 mg/kg (cohorts 1, 3, 5, 7, 11; Parts A and B), **e** SEL-037 0.4 mg/kg + SEL-110 0–0.15 mg/kg (cohorts 2, 4, 6, 8, 10, 12; Parts A and B) and **f** SEL-037 0.2 mg/kg + SEL-110 0.1–0.15 mg/kg (cohorts 13, 15, 17; Part C). Results are shown as percentage of evaluable participants (participants who received a full first dose and did not discontinue study treatments due to any measure other than drug effectiveness or drug-related safety). *sUA* serum uric acid

Statistical Analysis

The Safety Analysis Set (SAS) included all participants who were randomized and received ≥ 1 dose of SEL-037 and/or SEL-110. PD and PK were analyzed for all participants in the SAS who had ≥ 1 post-baseline assessment and no protocol deviations that could significantly affect PD/PK evaluations. Descriptive statistics were used to summarize safety, PD, PK, radiology results (by cohort and overall), and the frequency and titers of ADAs by study day, cohort, time of onset, and time of resolution. Statistical analyses were performed using SAS for Windows version 9.3 (SAS Institute Inc., Cary, NC, USA). PK parameters were derived using Phoenix WinNonLin 6.4 or higher. PK parameters were then analyzed using linear mixed effects models. The last non-missing value before the start of infusion of any study drug in TP1 was used as baseline. The PK and PD relationship was explored using Spearman correlation analysis. Full details of the statistical analyses can be found in the Supplementary Material.

RESULTS

Participant Flow

Of the 443 individuals screened, 167 were enrolled (119 in Parts A and B; 48 in Part C), and 152 received ≥ 1 dose of study drug (Supplementary Material Figure S1). Overall, 63/167 randomized subjects (37.7%) completed the study. The most common reasons for study discontinuation were stopping criteria (21.0%) and TEAEs (13.2%); other reasons for discontinuation are listed in Supplementary Material Fig. S1. All subjects had ≥ 1 post-baseline assessment of sUA and 152 dosed subjects were included in the PD/PK analysis sets. All subjects in cohorts 1 and 2 ($n = 3$ per cohort) received SEL-037 in TP1. Of these, three (two in cohort 1; one in cohort 2) received SEL-037 in TP2 and none received SEL-037 in TPs 3–5. Six subjects (one in each of cohorts 6, 8, 10, and 11; two in cohort 17) received SEL-110 in TP1 but did not receive SEL-037 due to TEAEs.

Baseline Characteristics

Of the 152 dosed subjects, 90.8% were male, 67.8% were white, and 93.4% were non-Hispanic or Latino (Table 2). Mean body mass index (BMI) (34.78 kg/m^2; range 24.8–68.2 kg/m^2) was similar across cohorts. Mean duration of gout was 8 years and mean sUA was 7.76 mg/dl and 9 subjects (5.9%) had tophi at baseline. Those with uncontrolled diabetes (HbA_{1c} ≥ 64 mmol/mol [≥ 8%]) were excluded. Metabolism and nutrition disorders were present in 98.7% of randomized participants, however, and 20 participants (13.2%) had diabetes at baseline. In total, 68.4% had undergone previous surgical or medical procedures, 61.2% had musculoskeletal and connective tissue disorders and 59.9% had vascular disorders. All participants received ≥ 1 prior or concomitant medication, most commonly fexofenadine (100%), methylprednisolone (78.9%), colchicine (78.3%), ibuprofen (51.3%), allopurinol (35.5%), and lisinopril (23.0%).

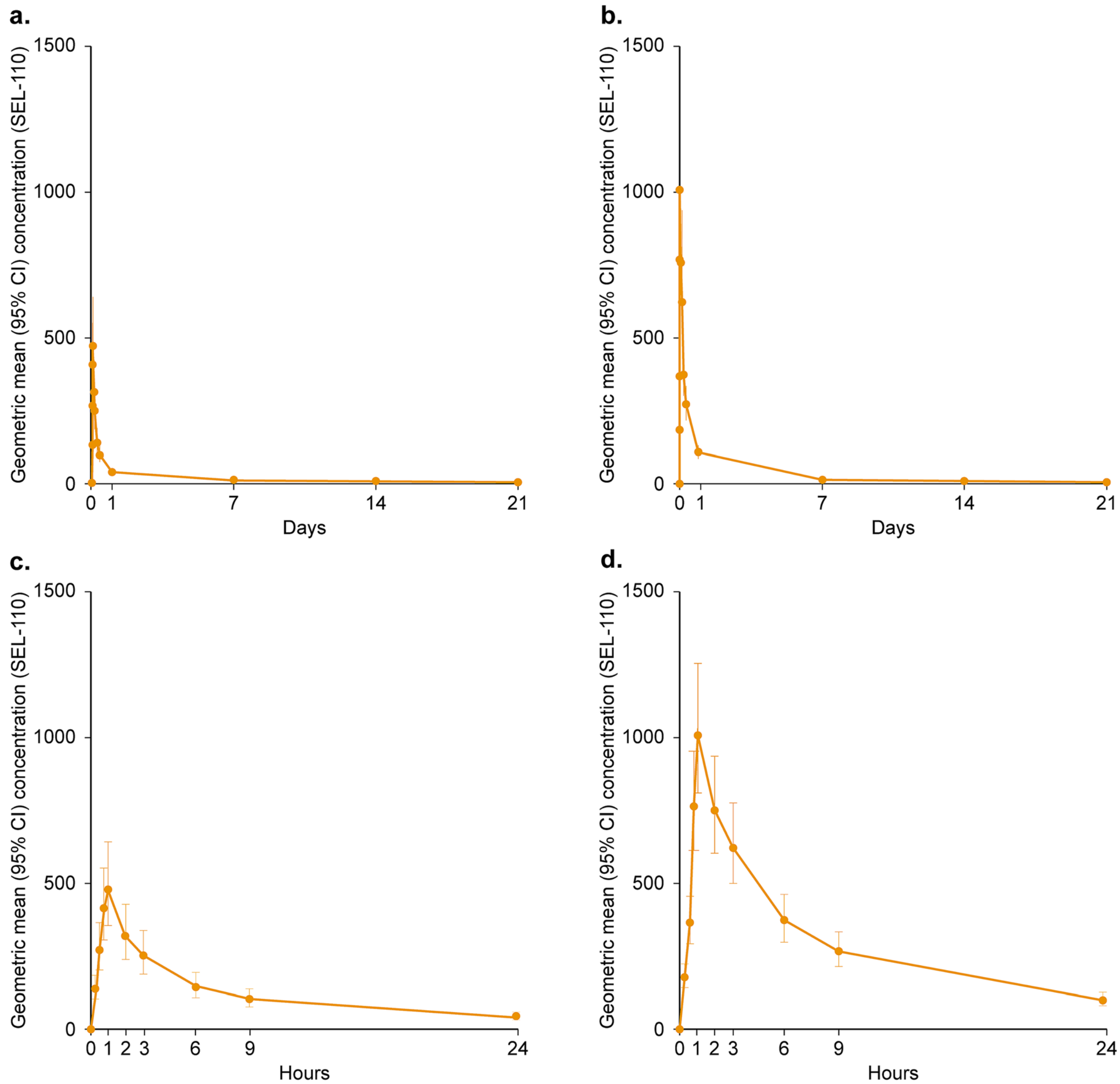


Fig. 3 Whole blood SEL-110 (sirolimus) concentrations over the entire 504 h (21 days) of sampling for cohorts receiving SEL-037 0.2 mg/kg in combination with **a** SEL-110 0.1 mg/kg and **b** SEL-110 0.15 mg/kg, respectively. SEL-110 (sirolimus) concentrations over the first 24 h of sampling for cohorts receiving SEL-037 0.2 mg/kg in combination with **c**. SEL-110 0.1 mg/kg and **d**. SEL-110 0.15 mg/kg, respectively. Results are shown as geometric mean (ng/ml) ± 95% CI. *CI* confidence interval, *SD* standard deviation. *Upper bound*: exp(mean[$_{\log}$(concentration)] + SD[$_{\log}$(concentration)]). *Lower bound*: exp(mean[$_{\log}$(concentration)] – SD[$_{\log}$(concentration)])

Safety Results

Overall, 92.8% of the 152 evaluable participants in TPs 1–3 and 28.9% in TPs 4–5 reported ≥ 1 TEAE (Table 3), most of which were mild (30.9%) or moderate (46.7%). The most commonly reported TEAEs were gout flare (33.6% in TPs 1–3; 7.2% in TPs 4–5) and headache (13.2% and 5.3%, respectively). Of these, 97% of gout flares and 100% of headaches were mild or moderate. Rates of gout flares were lower among participants treated with SEL-037 co-administered with vs. without SEL-110 and the number of cases decreased over time (Fig. 1a). One subject (0.7%; cohort 3) had a life-threatening infusion-related reaction following SEL-037 administration in TP2, and two subjects (1.3%; one in each of cohorts 7 and 8) had life-threatening anaphylactic reactions, one of which was attributed to a dosing error. Overall, 24 participants discontinued the study due to TEAEs (23 in TPs 1–3; one in TPs 4–5) including six with infusion-related reactions and six with anaphylactic reactions or shock. One third of the drug-related serious TEAEs were associated with the six patients who received SEL-037 alone, and the incidence of drug-related serious TEAEs decreased with increasing doses of SEL-110 (Fig. 1b). The most frequently reported TEAEs related or possibly related to study drug were gout flares (23.6%), anemia (10.5%), headache (7.2%), leukopenia (7.2%), hypertriglyceridemia (6.6%), and stomatitis (6.6%) in TPs 1–3 (Table 3a), and gout (4.6%) and headache (3.3%) in TPs 4–5 (Table 3b).

Overall, 20 participants (13.2%) reported $\geq$ 1 SAE during the study, all of which resolved/were successfully treated. Of these, one SAE was possibly related to treatment (pyelonephritis; cohort 13) and nine were related to treatment (five cases of anaphylaxis [cohorts 1, 3, 7, 8, and 13], three infusion reactions [cohorts 3, 6, and 17]), and one anaphylactic shock in a patient receiving SEL-037 without SEL-110 [cohort 2]). The risk of treatment-related SAEs decreased with increasing doses of SEL-110 (Table 3; Fig. 1b). No SAEs were assessed as possibly related/related to treatment during TPs 4–5. No deaths occurred, the majority of clinical laboratory results were within normal ranges, and no safety concerns were reported relating to vital signs or ECGs.

Pharmacodynamic Results

Administration of SEL-037 0.2 and 0.4 mg/kg with and without SEL-110 resulted in rapid reductions in sUA below the limit of quantification (BLQ) within 1.5 h of treatment for all cohorts. The minimum observed sUA change from baseline (%CFB_{min}) reached 100% in all cohorts (with a few exceptions in single TPs), suggesting a total suppression of sUA shortly after dosing. Comparisons of sUA levels between different cohorts showed geometric mean ratios > 100% for sUA with 90% CIs above the equivalence range (80–125%), showing high variability, and high, non-significant *p* values. Spearman correlation analysis did not show a strong linear relationship between PK and PD parameters.

The proportion of participants achieving sUA control (sUA < 6 mg/dl) 12 weeks after SEL-037 administration (the end of TP3) increased with increasing doses of SEL-110, ranging from 20.0–33.3% for cohorts 3 and 4 (SEL-110 0.05 mg/dl) to 66.1–88.9% for cohorts 5–17 (SEL-110 $\geq$ 0.08 mg/dl) (Fig. 2a-c). Only 17% of participants receiving SEL-037 alone (cohorts 1 and 2) achieved sUA control at TP1 (week 4), and none achieved sUA control at TP3. However, none of these participants received SEL-037 after TP2 because of lack of tolerability and concern for immunologic adverse events. sUA control at TP3 was achieved by 61.1–88.9% of evaluable participants receiving SEL-037 0.2 mg/kg + SEL-110 0.1–0.15 mg/kg in TPs 1–3 (cohorts 7, 11, 13, 15 and 17). Overall, 21/32 evaluable participants (66%) receiving SEL-037 0.2 mg/kg + SEL-110 $\geq$ 0.1 mg/kg in all 5 TPs (cohorts 13–17) maintained sUA control at TP5 (week 20), compared with 8/31 (26%) participants who discontinued SEL-110 at TP3 (cohorts 3, 5, 7, and 11). All 21 evaluable participants in cohorts 13–17 who achieved sUA control at TP3 maintained control at TP5. Mean sUA reductions and anti-uricase antibody titers are shown in Supplementary Material Figure S2. In cohorts 1 and 2, who did not receive SEL-110 in TPs 1–5, sUA < 6 mg/dl was not maintained until week 12. In contrast, in cohorts 13, 15 and 17 where SEL-037 0.2 mg/kg and SEL-110 0.1–0.15 mg/kg were both administered in TPs 1–5 between 61.1 and 75.0% maintained sUA < 6 mg/dl to week 20.

Pharmacokinetic Results for SEL-110 Co-administered with SEL-037

Whole blood sirolimus, the active agent in SEL-110, demonstrated a concentration vs. time profile typical for an IV infusion with dose proportional differences for each SEL-110 dose. PK data were similar for cohorts receiving the

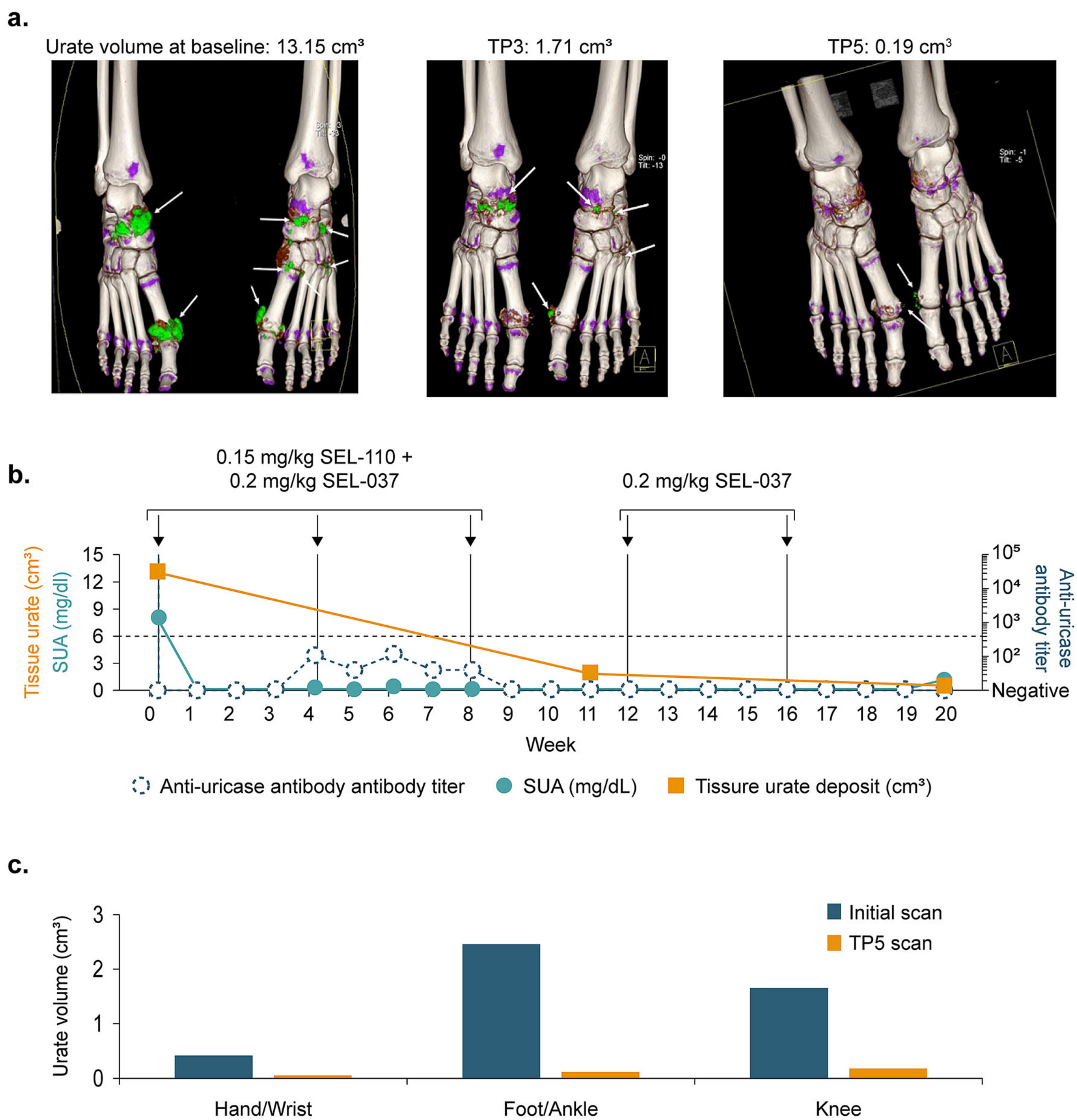


Fig. 4 Changes over time in **a**. Localized urate volume in the foot/ankle at baseline and at TPs 3 and 5 (DECT scans), and **b**. Tissue urate levels, sUA and anti-uricase titers in a representative patient from cohort 11 receiving SEL-037 0.2 mg/kg + SEL-110 0.15 mg/kg in TPs 1–3 and SEL-037 0.2 mg/kg in TPs 4–5. c. Total urate levels in the hand/wrist, foot/ankle and knee at baseline and at TP5 in a representative patient from cohort 12 receiving SEL-037 0.4 mg/kg + SEL-110 0.15 mg/kg in TPs 1–3 and SEL-037 0.4 mg/kg in TPs 4–5. *DECT* dual-energy computed tomography, *sUA* serum uric acid, *TP* treatment period. DECT scans were performed as an exploratory measure at individual sites using Siemens SOMATOM 2nd/3rd generation Dual-Source CT scanners, Forchheim, Germany and read by an independent central reader with over 15 years of experience with DECT imaging at Arthritis Research, Canada using Syngo Via VB 20 software, Forkeim, Germany, with a specific validated urate algorithm based on the differential attenuation and digital separation of uric acid and calcium at low and high energy levels. For panel **a**: *Green*, uric acid; *blue*, cortical bone; *purple*, trabecular

same dose of SEL-110 with little difference between SEL-037 doses or TPs (Supplementary Material Table S1). Consequently, PK data for each of the SEL-110 doses administered with SEL-037 0.2 mg/kg or SEL-037 0.4 mg/kg during TPs 1–5 were combined (Supplementary Material Table S2). Based on the PD/PK analysis and in consultation with the FDA, the doses of SEL-212 chosen for further study in the phase 3 studies (NCT04513366 and NCT04596540) were SEL-037 0.2 mg/kg in combination with SEL-110 0.1 mg/kg and 0.15 mg/kg. Figure 3 shows SEL-110 (sirolimus) PK data for cohorts 7 and 17 (SEL-037 0.2 mg/kg + SEL-110 0.1 mg/kg), 11 and 13 (SEL-037 0.2 mg/kg + 0.15 mg/kg) and 15 (SEL-037 0.2 mg/kg + 0.15–0.1 mg/kg), all of which received SEL-110 throughout the trial (TPs 1–5). Changes in whole blood levels of sirolimus over time demonstrate peak sirolimus levels 1 h after infusion (median 1 h; range 0.3 to 3 h), with rapid reductions in the first 24 h (Supplementary Material Table S2; Fig. 3). These rapid reductions were expected and are likely related to the clearance of nanoparticles from the blood. This is because the assay used to measure sirolimus in whole blood does not distinguish between nanoparticle-encapsulated sirolimus and cell-associated or free sirolimus.

Pharmacokinetic Results for SEL-037 Following Co-administration with and without SEL-110

Median T_{max} for SEL-037 during TP1 was 2 h for cohort 1 (SEL-037 0.2 mg/kg) and 1 h for cohort 2 (SEL-037 0.4 mg/kg) vs. 22–23 h for most cohorts receiving SEL-037 + SEL-110 (Supplementary Material Table S3). Maximum uricase activity was observed approximately 24 h post-infusion in all cohorts, with drug elimination occurring after 24 h. Based on serum SEL-037 concentrations, geometric mean $T_{1/2}$ for SEL-037 0.4 mg/kg (cohort 2) was 112.2 h (coefficient of variation [CV] not applicable). $T_{1/2}$ for SEL-037 0.2 mg/kg (cohort 1) was not available. Based on uricase activity, geometric mean (CV) $T_{1/2}$ for SEL-037 following co-administration with SEL-110 was similar across all cohorts, ranging from 88.12 (NA) h to 226.4 (NA) h. The addition of SEL-110 increased the exposure of SEL-037. As observed for T_{max}, AUC from drug administration to the time of last quantifiable concentration ($AUC_{0\text{-last}}$) based on serum SEL-037 concentrations in TP1 was larger when SEL-037 was co-administered with SEL-110 $\geq$ 0.1 mg/kg (cohorts 7–17) than when SEL-037 was administered alone (cohorts 1 and 2) or with SEL-110 < 0.1 mg/kg, while C_{max} was similar across cohorts (Supplementary Material Table S3). A similar trend was observed for parameters based on uricase activity (data not shown). No participants in cohorts 1 and 2 were dosed beyond TP2; consequently, PK comparisons could not be made for SEL-037 co-administered with vs. without SEL-110 for later TPs. Significant differences ($p < 0.001$) were observed between most cohorts when comparing SEL-037 0.2 mg/kg vs. 0.4 mg/kg with regards to C_{max}/Dose and $AUC_{0\text{-last}}$/Dose, indicating dose proportionality for SEL-037.

Immunogenicity Results

Dosing with SEL-037 alone (cohorts 1 and 2) resulted in a robust immune response with 100% of participants testing positive for anti-PEG, anti-SEL-037 and anti-uricase antibodies in TP2 (Supplementary Material Fig. S3). The addition of low-dose SEL-110 (< 0.1 mg/kg) (cohorts 3–6) reduced the frequency of anti-PEG positive participants to below 20% throughout the trial. Anti-SEL-037 antibody formation was likewise controlled until TP3, day 21, when the frequency of anti-SEL-037 positive participants began to rise, reaching a maximum of 46.2% at TP4, day 14. Anti-uricase antibody formation was less well controlled, with 78.3% of participants testing positive for anti-uricase antibodies at TP2, day 0. The maximum frequency of anti-uricase antibodies for participants receiving SEL-037 in combination with low-dose SEL-110 was 87.5% (TP 5, day 0).

Co-administration of higher doses of SEL-110 ($\geq$ 0.1 mg/kg) with SEL-037 (cohorts 7–12) further controlled antibody formation, with anti-PEG antibodies remaining low (< 10%) throughout the study (Supplementary Material Fig. S3). Anti-SEL-037 antibody formation was well controlled (< 10%) when SEL-037 was co-administered with SEL-110 during TPs 1–3, but the maximum incidence of anti-SEL-037 antibodies increased to 21.1% and 51.5% when SEL-110 was withdrawn in TPs 4 and 5, respectively. These results compare favorability to the approximate 85% and 100% of patients in cohorts 1 and 2 who developed anti-SEL-037 antibodies after one or two doses of SEL-037 alone. Anti-uricase antibody control improved with higher doses of SEL-110 with 41.7% of participants testing positive in TP2, day 0. The level of anti-uricase positive participants remained roughly steady until TP4, day 14, after which levels rose until the end of the study, peaking at 87.5%. The increase in antibodies coincided with TP4 and TP5 when SEL-037 was dosed without SEL-110.

The co-administration of SEL-110 with SEL-037 in TP4 and TP5 (cohorts 13–15) resulted in the strongest mitigation of antibody formation (Supplementary Material Fig. S3). The proportion of participants with anti-PEG and anti-SEL-037 antibodies remained low throughout the study (less than 15% and 10%, respectively). Improved control of anti-uricase antibody formation was also observed, with a maximum frequency of 40% at TP5, day 14.

The maximum anti-uricase titers observed in responding TPs (TPs in which sUA control was achieved at all times during the 28-day dosing cycle or sUA was ≤ 1 mg/dl on day 21) suggest that titers < 1080 can be used to distinguish responding from non-responding participants. For cohorts receiving SEL-037 + SEL-110 ≥ 0.1 mg/kg in all five TPs (cohorts 13–17), maximum anti-uricase titers were < 1080 in 94.9% (112/118) of responding TPs whereas titers were ≥ 1080 in all 11 non-responding TPs (TPs with sUA ≥ 6 mg/dl at any time during the dosing cycle). Maximum anti-uricase titers for non-responding TPs decreased during successive TPs with no participants in cohorts 13–17 having titers ≥ 1080 in TPs 4–5. Mean uricase activity AUC for cohorts 13–17 was 8864 mU/dl/week for TPs with antibody titers < 1080 vs. 6993 mU/dl/week for TPs with titers ≥ 1080 (p = 0.0112). The comparable value for cohorts 1 and 2 receiving SEL-037 alone was 3437 mU/dl/week. In general, co-administration of SEL-037 with increasing doses of SEL-110 enabled a greater proportion of participants to achieve anti-uricase titers < 1080 (Fig. 2d–f).

Radiology Results

DECT scans were available for 34 participants across six cohorts at baseline (cohorts 10–13, 15 and 17), all of which received SEL-037 with higher doses of SEL-110 (≥ 0.1 mg/kg). Of these, 27 had ≥ 1 follow-up scan at the end of TP3 and/or TP5/EOS. Total body urate volumes and urate volumes at each joint decreased from baseline to TP3 and correlated with reductions in sUA and ADAs (Fig. 4). Further decreases in urate volumes were observed from TP3 to TP5/EOS in all participants.

DISCUSSION

Monthly IV infusions of SEL-037 0.2–0.4 mg/kg with or without SEL-110 0.05–0.15 mg/kg were generally well tolerated in people with symptomatic gout and chronic hyperuricemia, with no safety concerns relating to vital signs, ECG, or clinical laboratory results. Drug-related TEAEs were generally mild or moderate in severity and were consistent with results from phase I studies for SEL-037 0.1–1.2 mg/kg and SEL-110 ≤ 0.3 mg/kg [25], and the known safety profile for sirolimus [27–29]. Nine participants reported a serious TEAE related to study drug(s), including six with anaphylactic reaction/shock and three with infusion-related reactions. Two of these events occurred among the six subjects receiving SEL-037 alone and the frequency of events in the remaining cohorts decreased with increasing doses of SEL-110. Overall, the risk of serious infusion-related reactions and anaphylaxis reported for subjects treated with SEL-212 (SEL-037 + SEL-110) in this study (2.0% and 2.6%, respectively) was lower than that previously reported for pegloticase (29% [18, 30] and 4.8–6.5% [15]). This is likely because infusion reactions and hypersensitivity (including anaphylaxis) are related to ADAs [15], the formation of which is largely mitigated by the SEL-110 component of SEL-212.

The PD/PK profiles for SEL-037 and SEL-110 following multiple monthly IV infusions were well characterized. Both SEL-037 0.2 and 0.4 mg/kg resulted in rapid reductions in sUA (BLQ) within 1.5 h of treatment when administered with and without SEL-110. sUA levels rapidly rebounded within 4 weeks in five of the six participants treated with SEL-037 alone, due to the formation of anti-uricase antibodies with titers $\geq$ 1080 and the loss of serum uricase activity. Results are consistent with those from a phase I study in which 4/5 participants treated with a single infusion of SEL-037 0.4 mg/kg showed an immediate decrease in sUA (BLQ) that returned to baseline 30 days post-treatment due to the formation of anti-uricase antibody titers > 1000 [25]. The fifth participant in this phase I cohort developed a low anti-uricase titer (120) and maintained sUA control (< 6 mg/dl) for at least 30 days. A similar relationship between anti-uricase antibodies and sUA control has been reported in pegloticase studies [17, 18].

Previous studies found that a single infusion of SEL-110 (0.03, 0.1, 0.15 or 0.3 mg/kg) co-administered with SEL-037 0.4 mg/kg dose-dependently reduced ADA titers, with SEL-110 0.15 mg/kg reducing anti-uricase titers to $\leq$ 1000 in 4 of 5 subjects, thereby providing durable sUA control for at least 30 days [25]. Results from the present study found that the dose-dependent reductions in ADA titers with SEL-110 were considerably greater for SEL-110 doses $\geq$ 0.1 mg/kg than for lower doses. Moreover, monthly co-administrations of SEL-110 $\geq$ 0.1 mg/kg with SEL-037 increased serum concentrations of SEL-037 and uricase activity relative to SEL-037 alone, with significantly higher uricase activity AUC observed in TPs with anti-uricase antibody titers < 1080. Sustained sUA control was observed throughout each 28-days TP in the majority of TPs with anti-uricase titers < 1080 whereas sUA control was not achieved throughout the 28-days dosing period in any of the TPs with titers $\geq$ 1080. This suggests that maintaining anti-uricase titers < 1080 using higher doses of SEL-110 ($\geq$ 0.1 mg/kg) prolongs uricase activity in patients receiving SEL-037 enabling sustained sUA control from once-monthly dosing. Importantly, SEL-110 treatment was also effective at inhibiting anti-PEG antibody responses, most of which were transient (Supplementary Material Fig. S4).

The proportion of participants maintaining sUA control at TP5 increased with increasing doses of SEL-110 and decreased if SEL-110 was withdrawn after TP3. Of the evaluable participants receiving SEL-037 0.2 mg/kg + SEL-110 $\geq$ 0.1 mg/kg, 66% of those continuing combination treatment in all 5 TPs maintained sUA control at TP5 compared with 26% of those who withdrew SEL-110 treatment after TP3. These results compare favorably to subjects in cohorts 1 and 2 in which only 17% (1/6) of subjects maintained sUA control after a single injection of SEL-037 without SEL-110. Extending the dosing of SEL-110 beyond TP3 reduced the number of participants with anti-uricase and anti-PEG antibodies at TP5, reinforcing the need for continued SEL-110 dosing alongside SEL-037. Compared to other dosing combinations, the greatest degree of sUA control and the lowest ADAs at TP3 were achieved using SEL-037 0.2 mg/kg + SEL-110 0.15 mg/kg.

Across the cohorts in which DECT scans were performed, notable decreases in tophi from baseline to TP3 were observed in the majority of participants, with levels of urate deposits in joints correlating with both sUA levels and ADAs, and continuous reductions in tophi from TP3 to TP5 or ET. Although urate levels were assessed at multiple joints, results should be treated with caution due to the small number of participants with available data. However, preliminary results suggest that monthly co-administrations of SEL-037 with SEL-110 in people with symptomatic gout and hyperuricemia can reduce tophi by inhibiting the formation of ADAs, prolonging uricase activity, and enabling sustained sUA control.

Results from this study demonstrate that a once monthly co-administration of SEL-110 with SEL-037 mitigates the formation of ADAs against a highly immunogenic enzyme in people with gout that is refractory to standard treatment. Overall, sUA control was achieved by 66% of evaluable participants after 5 months of SEL-212 treatment with limited ADA formation. Previous studies show that only 42% of participants maintain sUA control after 3–-6 months of pegloticase treatment due to the formation of ADAs [11, 17]. Although the co-administration of pegloticase with an immunosuppressant (e.g., methotrexate) reduces the risk of ADAs and improves responder rates [20, 31], patients require a month long run-in with methotrexate prior to the first dose of pegloticase [15, 32, 33]. A large clinical trial in patients with cardiovascular disease found that 19% (1372/6158) of patients failed a similar run-in of low-dose methotrexate due to AEs or abnormal laboratory findings [34]. This suggests that the co-administration of methotrexate with pegloticase limits the number of patients suitable for treatment. Another limitation for methotrexate co-therapy is the requirement for a complex dosing regimen involving weekly methotrexate maintenance doses and daily doses of folate in a patient population that, historically, has shown compliance rates as low as 10–46% in real world settings [32]. Moreover, chronic dosing of methotrexate can lead to global immunosuppression and may be contraindicated in patients with comorbidities that are frequently observed in patients with uncontrolled gout, such as chronic liver disease, Type 2 diabetes, hyperlipidemia, renal impairment, and excessive alcohol consumption [35–37]. Unlike immunosuppressants, SEL-110 induces antigen-specific immune tolerance without suppressing the entire immune system [21, 24]. Compared to pegloticase, which requires bimonthly administration, monthly administration of SEL-212 has the potential to improve dosing convenience, which may have a beneficial impact on long-term sUA control by improving treatment compliance.

A number of points should be taken into consideration when assessing these data. Firstly, the study was 6 months long, so it would be of great interest to examine longer-term follow up in future clinical trials. The BMI range in this study (median 30–47 kg/m^2) indicated that the majority of participants were obese. While it is possible that this could have biased results, it is consistent with the mean BMI range of 31–35 kg/m^2 reported in a previous phase 3 trial of pegloticase [18]. As stated above, PEGylated uricases are generally infused following premedication with an immunosuppressant, such as a glucocorticoid, to reduce the risk of IRs. In this study, IV methylprednisolone was used. Therefore, while we are unable to separate out any potential impact of methylprednisolone on clinical outcomes, this use reflects how the drug would be administered in clinical practice following approval. Finally, as this was a dose-finding study, the number of adverse events would be expected to be higher than normal. For example, SEL-110 reduces ADAs to SEL-037 and high-titer ADAs are associated with an increased risk of infusion reactions [25]. Therefore, sub-therapeutic SEL-110 doses, below the 0.1–0.15 mg/kg dose range selected for the ongoing clinical trial program, may have increased the risk of serious infusion reactions in some cohorts. Additionally, some participants received supra-therapeutic doses of SEL-037 (0.4 mg/kg), above the 0.2 mg/kg dose that was selected for the ongoing clinical trial program.

CONCLUSIONS

Results from this phase 2 dose-finding study demonstrate that co-administration of SEL-110 with SEL-037 dose-dependently reduced ADA formation, prolonged uricase activity, and reduced levels of sUA in adults with symptomatic gout and hyperuricemia. SEL-110 doses $\geq$ 0.1 mg/kg provided sustained sUA control (sUA < 6 mg/dl) at 20 weeks in 66% of evaluable participants after five-monthly infusions, with 100% of participants achieving sUA control at TP3 maintaining control at TP5. Benefits were attenuated when SEL-110 was withdrawn, suggesting the need to continue SEL-110 dosing alongside SEL-037. Both SEL-037 and SEL-110 were well-tolerated with no safety concerns; however, safety profiles improved with increasing doses of SEL-110. Compared to other doses, SEL-037 0.2 mg/kg + SEL-110 0.15 mg/kg achieved the most effective sUA and ADA control at week 12 and was associated with a low risk of TEAEs. Overall, results provide continued support for the use of multiple monthly co-administrations of SEL-037 0.2 mg/kg + SEL-110 0.1–0.15 mg/kg in the ongoing phase 3 clinical trials for SEL-212 (NCT04596540 and NCT04513366) and the COMPARE trial (NCT03905512).

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Data Availability. The majority of data generated or analyzed during this study are included in this published article and as supplementary information files. Any additional data underlying this article will be shared on reasonable request to the following email address: medinfo@selectabio.com.

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