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Clinical science

The COMPARE head-to-head, randomized controlled trial of SEL-212 (pegadricase plus rapamycin-containing nanoparticle, ImmTOR™) versus pegloticase for refractory gout

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[†]The role with Arthrosi Therapeutics started after completion of the COMPARE trial.

Abstract

Objectives: Serum urate (SU) lowering with PEGylated uricases in gout can reduce flares and tophi. However, treatment-emergent anti-drug antibodies adversely affect safety and efficacy and the currently approved PEGylated uricase pegloticase requires twice-monthly infusions. Investigational SEL-212 therapy aims to promote uricase-specific tolerance via monthly sequential infusions of a proprietary rapamycin-containing nanoparticle (ImmTOR) and pegadricase.

Methods: COMPARE was a randomized, phase 2, open-label trial of SEL-212 vs pegloticase in adults with refractory gout. SEL-212 [ImmTOR (0.15 mg/kg) and pegadricase (0.2 mg/kg)] was infused monthly or pegloticase (8 mg) twice monthly for 6 months. The primary endpoint was the proportion of participants with SU <6 mg/dl for ≥80% of the time during 3 and 6 months. Secondary outcomes were mean SU, gout flares, number of tender and/or swollen joints and safety.

Results: During months 3 and 6 combined, numerically more participants achieved and maintained a SU <6 mg/dl for ≥80% of the time with SEL-212 *vs* pegloticase (53.0% *vs* 46.0%, $P=0.181$). The percentage reductions in SU levels were statistically greater during months 3 and 6 with SEL-212 *vs* pegloticase (−73.79% and −47.96%, $P=0.0161$). Reductions in gout flare incidence and number of tender and/or swollen joints were comparable between treatments. There were numerical differences between the most common treatment-related adverse events of interest with SEL-212 and pegloticase: gout flares (60.2% *vs* 50.6%), infections (25.3% *vs* 18.4%) and infusion-related reactions (15.7% *vs* 11.5%), respectively. Stomatitis (and related terms) was experienced by eight participants (9.6%) with SEL-212 and none with pegloticase. Stomatitis, a known event for rapamycin, was associated with ImmTOR only.

Conclusions: SEL-212 efficacy and tolerability were comparable to pegloticase in refractory gout. This was associated with a substantial reduction in treatment burden with SEL-212 due to decreased infusion frequency *vs* pegloticase.

Clinical trial registration: NCT03905512.

Keywords: gout, nanotechnology, pegadricase, pegloticase, SEL-212, rapamycin, serum urate, uricase

Rheumatology key messages

- SEL-212 is as effective as pegloticase, the only currently approved option for treating refractory gout.
- SEL-212 had a favourable safety profile; infusion reaction frequency was comparable between SEL-212 and pegloticase.
- Total exposure to pre-infusion glucocorticoids decreased due to the decreased frequency of SEL-212 *vs* pegloticase infusions.

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Introduction

Gout, affecting >9.2 million individuals, is the most common inflammatory arthritis in the USA [1]. Gout reflects sustained hyperuricaemia at levels exceeding urate solubility, which results in crystalline monosodium urate deposition in joints and soft tissues [2].

Once a pattern of recurrent gout flares (GFs) is established, treatment with sustained urate-lowering therapy (ULT) is required to resolve tophi and reverse the disease course [3]. At the extreme end of the clinical spectrum is chronic inflammatory arthritis, with disfiguring and sometimes draining tophaceous deposits, with or without bony destruction, deformity and profound functional disability, which may constitute ≈2% of all gout [4, 5]. Urate oxidase (uricase) is a peroxisomal enzyme that catalyses the oxidation of serum urate (SU) to allantoin during purine catabolism [6]. Not expressed in humans, uricase catalyses the reaction of urate with oxygen and water to form 5-hydroxy-isourate (HIU) [7, 8]. HIU undergoes further non-enzymatic hydrolysis and is decarboxylated to allantoin, which is easily excreted [7, 8]. Exogenous uricase treatment in refractory gout (RG) has resulted in reducing SU values to low/unmeasurable levels.

Two uricases are approved by the US Food and Drug Administration (FDA): pegloticase for RG and rasburicase for the prevention of tumour lysis syndrome [9, 10]. Pegloticase is a PEGylated chimeric recombinant mammalian urate oxidase with porcine + baboon genetic sequences [11, 12]. In two 6-month, phase 3 randomized controlled trials, biweekly pegloticase infusions met the primary endpoint of SU <6.0 mg/dl for ≥80% of the time in months 3 and 6 in 42% of participants *vs* 0% with placebo [11]. Secondary endpoints, including improvements in GF rates, tophus size, number of tender and swollen joints and health-related quality of life (HRQoL), were achieved in the pegloticase-responder group [11]. Nonetheless, >50% on active treatment were non-responders who failed to meet the primary endpoint [11].

This failure to achieve the primary endpoint resulted from pegloticase-induced immunogenicity and the generation of high-titre pegloticase anti-drug antibodies (ADAs), leading to a loss of SU lowering [11]. Further, 26% of pegloticase-treated participants experienced infusion-related adverse events inclusive of a 5% anaphylaxis rate [11]. Post hoc analyses of the phase 3 pegloticase data revealed that the risk of these events could be reduced by up to 90% by monitoring for loss of the SU lowering effect and discontinuing treatment if observed [13].

The loss of efficacy caused by pegloticase ADAs has led to studies examining the benefit of pre- and concurrent treatment with immunosuppressants [14–16]. Recently the FDA has updated the pegloticase label, recommending co-administration with MTX [9], which adds complexity (weekly MTX and daily folate for 1 month pretreatment and throughout therapy) and new MTX-associated risks.

SEL-212 is a two-component drug product designed to provide antigen-specific immune tolerance to a uricase biologic therapy through the induction of regulatory T cells that skew the immune response towards tolerance rather than stimulation [17]. Induction of antigen-specific tolerance should improve the efficacy, safety and tolerability of uricase treatment in participants who require long-term treatment to manage symptoms and progression of RG, while potentially avoiding infection risks associated with less-targeted immunosuppression [18].

SEL-212 is delivered as a two i.v. infusion sequence on a single day repeated at 4-week intervals [19]. The first component of this infusion sequence is ImmTOR, a proprietary rapamycin (also known as sirolimus)-containing nanoparticle [18]. ImmTOR is a platform technology that has been developed to provide antigen-specific tolerance to co-administered biologic therapies [18]. After 15 minutes, the second infusion component, pegadricase, a yeast-derived, PEGylated recombinant uricase [17], is administered.

In preclinical studies, SEL-212 prevented ADA formation and prolonged uricase activity in uricase-deficient mice and wild-type non-human primates, resulting in sustained SU control [20]. In phase I studies, a single infusion of pegadricase 0.1–1.2 mg/kg and/or ImmTOR ≤0.3 mg/kg was well tolerated in healthy adults with baseline SU ≥6 mg/dl [17]. Moreover, a single co-administration of pegadricase 0.4 mg/kg with ImmTOR 0.03–0.3 mg/kg rapidly reduced SU to <0.1 mg/dl and dose-dependently reduced/prevented ADA formation up to 60 days post-treatment. These studies identified the respective doses of ImmTOR (0.15 mg/kg) and pegadricase (0.2 mg/kg) to move forward into larger-scale clinical trials.

The COMPARE study examined the efficacy of SEL-212 [ImmTOR (0.15 mg/kg) and pegadricase (0.2 mg/kg)] monthly *vs* pegloticase biweekly to maintain lowered SU (<6 mg/dl) during a 6-month period. Safety and secondary laboratory and clinical endpoints, including the mean reduction in SU, the number of GFs and the number of tender and/or swollen joints were compared.

Methods

Trial design

COMPARE was a 1:1 randomized, 6-month, phase 2, open-label, parallel-arm safety and efficacy study of SEL-212 and pegloticase. It was divided into three periods: screening (≤45 days), treatment (24 weeks) and safety follow-up (30–34 days after the last infusion). It was conducted in accordance with the Declaration of Helsinki and/or all relevant federal regulations as set forth in the US Code of Federal Regulations and in compliance with International Council for Harmonisation good clinical practice guidelines. Written informed consent was provided by all participants. Institutional review board approval was obtained (Copernicus Group IRB, Cary, NC, USA).

Participants

Males and females of non-childbearing potential, ages 21–80 years inclusive, with a history of symptomatic gout (as assessed by the investigator/treating physician) were included. Symptomatic gout was defined as three or more GFs within 18 months of screening, or the presence of one or more tophus or a current diagnosis of gouty arthritis. Participants had a screening SU ≥7 mg/dl with RG, defined as failure to normalize SU and inadequate control of gout signs and symptoms with xanthine oxidase inhibitor (XOI) at the medically appropriate dose or XOI being contraindicated (full criteria are available in Supplementary Materials, available at *Rheumatology* online).

Key exclusion criteria included prior exposure to any experimental/marketed uricase, history of anaphylaxis/severe allergic reactions to medications, history of any PEGylated product allergy, use of a known moderate/severe cytochrome

P450 family 3 subfamily A (CYP3A4) inhibitors or inducers or drugs known to interact with ImmTOR. Those with a GF during screening that resolved <1 week prior to the first study drug treatment (exclusive of synovitis/arthritis) were excluded unless they had a history of interflare intervals of <1 week (full criteria in Supplementary Materials, available at *Rheumatology* online).

Interventions

Participants stopped prior ULT ≥7 days before study drug administration. Pre-infusion, participants were medicated with oral prednisone (40 mg) ≈24 h, oral fexofenadine (180 mg) ≈12 and 2 h and i.v. methylprednisolone (40 mg) ≈1 h prior to dosing to reduce infusion reactions (IRs) (see Supplementary Methods, available at *Rheumatology* online for full pre-medication regimen). Participants were randomized to SEL-212 [ImmTOR (0.15 mg/kg) and pegadricase (0.2 mg/kg)] or pegloticase (8 mg). SEL-212 was administered on day 0 of each of the six treatment months. ImmTOR was infused intravenously at 3.0 ml/h for the first 30 min, then at a rate adequate to deliver the remaining dose volume over a period of 60 min concurrently with 125 ml of normal saline. Pegadricase infusion was started within 15 min of completion of the ImmTOR and infused over a period ≥120 min. Pegloticase was administered on days 0 and 14 of each month by i.v. infusion according to the US labelling. The study was open label, so participants and study staff were unblinded to treatment allocation.

Outcomes

Primary

The primary outcome was the percentage of participants in the SEL-212 *vs* pegloticase arms who achieved and maintained a reduction of SU <6 mg/dl for ≥80% of the time during study months 3 and 6 combined.

Secondary

The secondary endpoints included the percentage who achieved/maintained an SU reduction <6 mg/dl for ≥80% or 100% of the time during months 3 and 6 separately, the percentage with pre-dose SU >6 mg/dl during months 2–6 and the absolute/percentage reduction of mean SU during months 3 and 6 combined and month 6 alone. The incidence and frequency of GFs per 3-month period (months 1–3 and 4–6) were assessed by treatment-emergent adverse events (TEAEs). The change from baseline to month 6 in the number of tender or swollen joints was also examined. HRQoL outcomes [Health Assessment Questionnaire–Disability Index (HAQ-DI), 36-item Short Form Health Survey (SF-36) and physician global assessment of disease activity (PhGA)] were assessed at baseline, day 0 month 4 and day 28 month 6 (see Supplementary Methods, available at *Rheumatology* online). A post hoc analysis examined mean SU over time in the overall population and the responder/non-responder subgroups. Subgroup analysis stratified by participants with/without tophi was performed for the primary and key secondary endpoints.

Safety

Adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESIs), deaths and discontinuations due to AEs were recorded. AESIs monitored included GFs, infections, viral infections, interstitial lung disease, stomatitis and related terms, infusion-related reactions, malignancies, renal failure and clinically significant laboratory findings. Anaphylaxis was assessed based on the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network Symposium criteria [21]. Additional safety assessments included laboratory tests and physical examination.

Stopping rule

Participants in the SEL-212 arm were withdrawn if they recorded SU >1.0 mg/dl at the day 21 visit of month 1 or SU >6.0 mg/dl at the day 21 visit of months 2, 3, 4 or 5. In the pegloticase arm, participants were withdrawn if SU >6.0 mg/dl was measured on two consecutive pre-dose measurements.

Sample size

Assuming primary outcome responses of 65% with SEL-212 and 44% with pegloticase, 69 participants would be required per treatment group based on χ^2 testing with a one-sided α of 5% and a statistical power of 80%.

Statistical analysis

Analysis populations

The intention-to-treat (ITT) analysis included all randomized participants. The per protocol (PP) analysis included participants who received any amount of study medication, had no major protocol deviations and either completed ≥65% of study dosing visits (with or without receiving study drug) or completed <65% of study dosing visits because of early termination or withdrawal due to stopping rules, AEs or an investigator decision. The safety analysis included all those who were randomized and received any amount of study medication.

Primary endpoint

The SU concentration time curve was used to estimate the proportion of time that the SU was <6 mg/dl during months 3 and 6. Missing scheduled SU assessments were imputed (see Supplementary Material, available at *Rheumatology* online for imputation methodology). Cochran–Mantel–Haenszel (CMH) testing was performed to calculate the overall treatment difference between SEL-212 and pegloticase treatment with a one-sided type 1 error rate α of 5% and considering the randomization stratum of tophus presence (yes/no) (see Supplementary Material, available at *Rheumatology* online for additional statistical methodology).

Secondary endpoints

There was no hierarchical ordering of the secondary endpoints (see Supplementary Material, available at *Rheumatology* online for additional statistical methodology relating to the secondary endpoints). SAS version 9.4 or higher (SAS Institute, Cary, NC, USA) was used for all statistical analyses and tabulations.

Results

Participant flow

Of 426 screened patients, 170 were randomized, 132 (77.6%) completed the trial and 38 discontinued (Fig. 1). Withdrawal

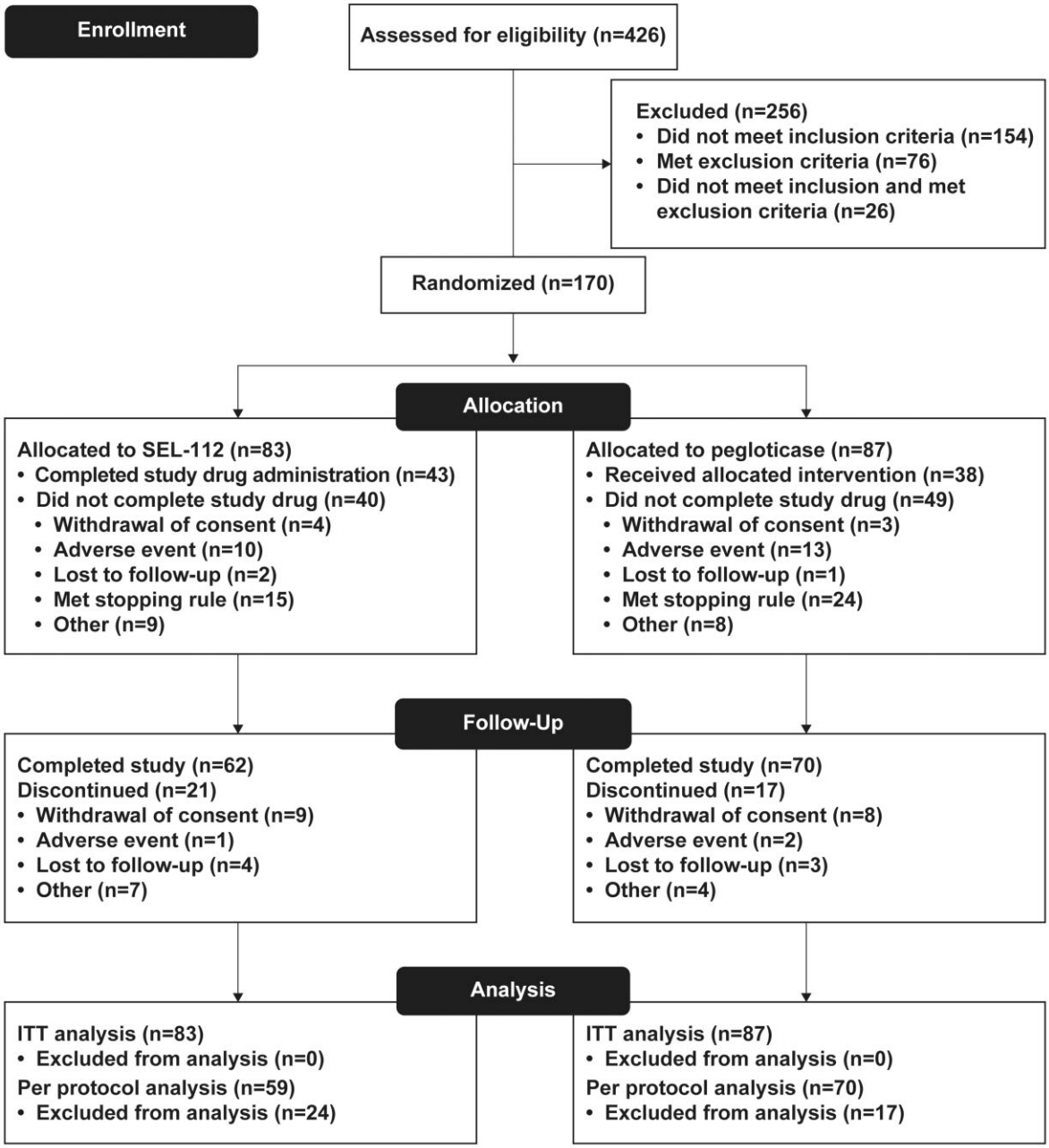

Figure 1. Participant disposition

of consent was the most common reason for discontinuation ($n = 17$). The ITT population included all randomized participants in the SEL-212 ($n = 83$) and pegloticase ($n = 87$) arms. The PP population included 59 and 70 participants in the SEL-212 and pegloticase arms, respectively.

Recruitment

The study took place at 44 US sites between May 2019 and August 2020.

Baseline data

Most participants were male (95.9%), White (77.1%) or Black/African American (18.4%) and 29–79 years of age (Table 1). Sixty-nine participants (40.6%) had visible tophi. The median body mass index was 34.6 kg/m^2. All participants had received, or were still receiving, one or more prior or concomitant medication. At screening, the most commonly administered ULT was allopurinol [$n = 26$ (15.3%)]. The most common concomitant medications were the protocol-required infusion pre-medications fexofenadine [$n = 168$ (98.8%)], methylprednisolone [$n = 125$ (73.5%)] or methylprednisolone sodium succinate [$n = 75$ (44.1%)] and the GF prophylaxis medications colchicine [$n = 133$ (78.2%)] or indomethacin [$n = 31$ (18.2%)].

Impact of coronavirus disease 2019 (COVID-19)

One participant in the pegloticase arm had a confirmed COVID-19 infection that led to discontinuation. There were 25 missing clinic visits related to COVID-19 (SEL-212: 13 visits, 4 participants; pegloticase: 12 visits, 5 participants;

Table 1. Baseline demographics (ITT population)

Parameter	Statistics	Treatment group		
		SEL-212 ($n=83$)	Krystexxa ($n=87$)	Total ($N=170$)
Age (years)	Mean (S.D.)	52.6 (11.5)	52.0 (10.4)	52.3 (10.9)
	Median (min, max)	51.0 (31, 79)	52.0 (29, 79)	51.5 (29, 79)
SU (mg/dl)	Mean (S.D.)	9.2 (1.3)	8.6 (2.1)	8.9 (1.7)
	Median (minimum– maximum)	9.1 (5.9–13.1)	8.9 (0.2–11.8)	9 (0.2–13.1)
Tophus presence				
Yes	n (%)	35 (42.2)	34 (39.1)	69 (40.6)
No	n (%)	48 (57.8)	53 (60.9)	101 (59.4)
Gender				
Male	n (%)	78 (94.0)	85 (97.7)	163 (95.9)
Female	n (%)	5 (6.0)	2 (2.3)	7 (4.1)
Race				
American Indian or Alaska Native	n (%)	0	0	0
Asian	n (%)	3 (3.6)	1 (1.1)	4 (2.4)
Black or African American	n (%)	16 (19.3)	16 (18.4)	32 (18.8)
Native Hawaiian or other Pacific Islander	n (%)	0	1 (1.1)	1 (0.6)
White	n (%)	62 (74.7)	69 (9.3)	131 (77.1)
Other	n (%)	2 (2.4)	0	2 (1.2)
Ethnicity				
Hispanic or Latino	n (%)	15 (18.1)	21 (24.1)	36 (21.2)
Not Hispanic or Latino	n (%)	68 (81.9)	66 (75.9)	134 (78.8)
BMI (kg/m^2)	Mean (S.D.)	34.8 (6.7)	35.4 (7.2)	35.1 (7.0)
	Median (minimum–maximum)	33.4 (24–57)	36.0 (23–53)	34.6 (23–57)
Comorbidities				
Hypertension	n (%)	41 (49.3)	46 (52.8)	87 (51.1)
Dyslipidaemia	n (%)	34 (40.9)	36 (41.3)	70 (41.1)
Diabetes mellitus	n (%)	15 (18.0)	10 (11.4)	35 (20.5)
Cardiac arrhythmia	n (%)	2 (2.4)	0	2 (1.1)
Coronary artery disease	n (%)	3 (3.6)	5 (5.7)	8 (4.7)
Cardiac failure	n (%)	2 (2.4)	0	2 (1.1)
Peripheral vascular disease	n (%)	0	1 (1.1)	1 (0.5)

Supplementary Table S1, available at *Rheumatology* online). During the study, two and one participant from the SEL-212 and pegloticase arms, respectively, discontinued treatment due to COVID-19. In addition, one participant (pegloticase arm) withdrew consent due to COVID-19 and another participant (pegloticase arm) had to discontinue the study due to a COVID-19-related SAE.

Efficacy

Achievement/maintenance of SU <6 mg/dl for ≥80% of the time during months 3 and 6 (ITT population)

Of 170 ITT participants, 44 (53.0%) in the SEL-212 arm and 40 (46.0%) in the pegloticase arm achieved and maintained a reduction of SU <6 mg/dl for ≥80% of the time during months 3 and 6 [treatment difference 7.0 percentage points (90% CI −5.6, 19.6; $P=0.181$) (Table 2). In the PP population there was a trend towards better achievement of SU <6 mg/dl with SEL-212 *vs* pegloticase, with a 13.6 percentage points treatment difference (90% CI −0.8, 28.0), however, statistical significance was missed by a narrow margin ($P=0.056$). A total of 86 participants (50.6%) were non-responders: 39 (47.0%) in the SEL-212 arm and 47 (54.0%) in the pegloticase arm. The mean percentage changes in SU from baseline were larger and more consistent on each dosing day with SEL-212 *vs* pegloticase (Fig. 2).

Achievement/maintenance of SU <6 mg/dl for ≥80% of the time during months 3 or 6 (ITT population)

During month 3, significantly more participants in the SEL-212 arm [$n=58$ (69.9%)] *vs* the pegloticase arm [$n=47$ (54.0%)] achieved and maintained reductions of SU <6 mg/dl for ≥80% of the time, a treatment difference of 15.9 percentage points (90% CI 3.8, 27.9; $P=0.017$). This finding was confirmed by the sensitivity analyses in which withdrawals before month 3 were considered as non-responders [treatment difference 15.7 percentage points for SEL-212 *vs* pegloticase (90% CI 3.5, 28.0; $P=0.017$)]. A numerical difference in responders favouring SEL-212 (54.2%) *vs* pegloticase (47.1%) was observed in month 6 but did not achieve statistical significance [treatment difference 7.1 percentage points (90% CI −5.5, 19.7), $P=0.179$].

Achievement/maintenance of SU <6 mg/dl for 100% of the time during month 6 (ITT population)

During month 6, 38 (45.8%) in the SEL-212 arm *vs* 36 (41.4%) in the pegloticase arm achieved and maintained a reduction of SU <6 mg/dl for 100% of the time. However, this did not achieve statistical significance [treatment difference 4.4 percentage points (90% CI −8.1, 16.9); $P=0.282$].

Mean and percentage reduction in SU (ITT population)

The mean SU levels were significantly lower with SEL-212 *vs* pegloticase for the overall time period ($P=0.006$), although as the study progressed the difference between the arms decreased (Fig. 3A). SU levels were very low in responders in both the SEL-212 and pegloticase populations (Fig. 3B). In the non-responder population, SU reductions were greater with SEL-212 *vs* pegloticase through week 20 ($P=0.006$), however, since responses were based on the 3- and 6-month timepoints, up to week 12 the 'non-responder population'

Table 2. Achievement and maintenance of SU <6 mg/dl for ≥80% of the time during months 3 and 6 (ITT and PP population)

Variable	ITT dataset			PP dataset		
	SEL-212 ($n=83$)	Pegloticase ($n=87$)	Treatment difference (SEL-212 – pegloticase)	SEL-212 ($n=59$)	Pegloticase ($n=70$)	Treatment difference (SEL-212 – pegloticase)
Participants with SU responder assessment, *n*	83	87		59	70	
Responder						
Participants, *n* (%)	44 (53.0)	40 (46.0)	7.0%	35 (59.3)	32 (45.7)	13.6%
90% CI of percentage	(44.0, 62.0)	(37.2, 54.8)	(−5.6, 19.6)	(48.8, 69.8)	(35.9, 55.5)	(−0.8, 28.0)
One-sided *p*-value (SEL-212 > pegloticase)			0.181			0.056
Non-responder, *n* (%)	39 (47.0)	47 (54.0)		24 (40.7)	38 (54.3)	

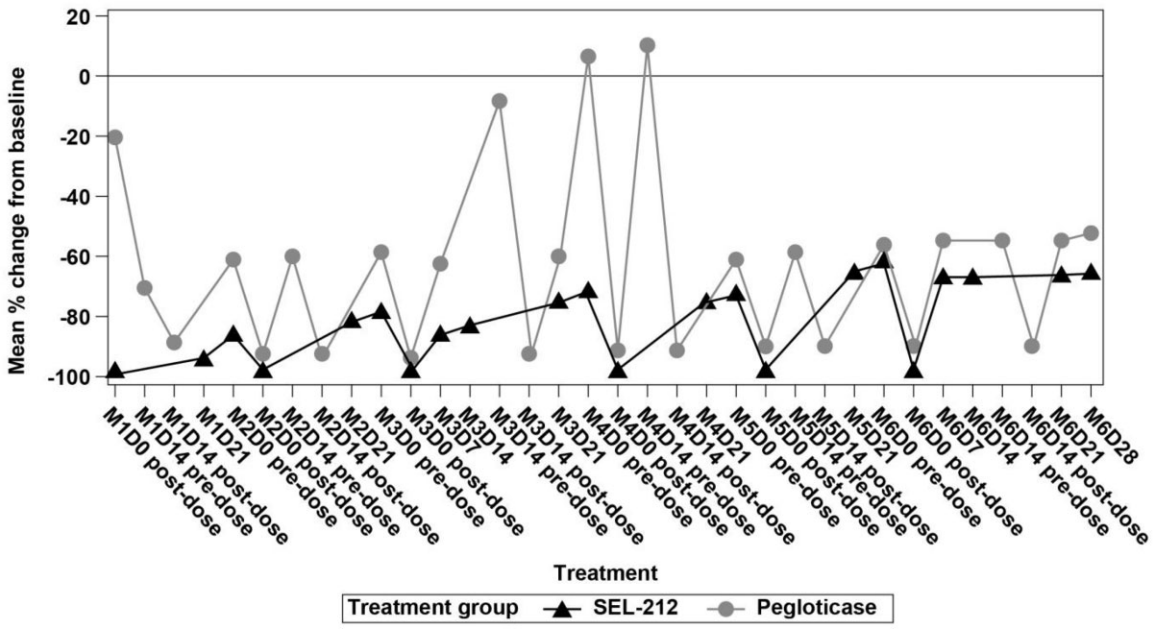

Figure 2. Mean percentage change in SU with SEL-212 and pegloticase from baseline (ITT population).
D: day; M: month

included a mix of responders and non-responders (Fig. 3C). During months 3 and 6 combined, the mean reduction in SU was 6.8 mg/dl (S.D. 3.4) with SEL-212 and 4.8 mg/dl (S.D. 3.9) with pegloticase ($P=0.003$). Similarly, percentage SU reductions during months 3 and 6 combined were significantly better with SEL-212 (73.8%) *vs* pegloticase (48.0%; $P=0.016$; Supplementary Table S2, available at *Rheumatology* online). Significantly better percentage reductions in SU were also observed with SEL-212 *vs* pegloticase for month 3 (79.2% and 43.7%; $P=0.02$), but not for month 6 (65.6% and 51.4%; $P=0.09$).

GFs and the number of tender or swollen joints

The incidence of GFs (Supplementary Table S3, available at *Rheumatology* online), maximum GFs and reductions in swollen joints and/or tender joints were not significantly reduced with SEL-212 *vs* pegloticase. In both treatment arms, however, there was a trend for GF incidence and frequency to decrease during months 4–6 compared with months 1–3 (Supplementary Table S3, available at *Rheumatology* online).

There was a decrease in number of tender joints over the course of the study (from baseline to month 6 day 28) from 5.2 to 2.4 in the SEL-212 arm and from 4.1 to 0.9 in the pegloticase arm, but there was no statistical difference (Supplementary Table S4, available at *Rheumatology* online). Based on two-sided *P*-values, treatment with pegloticase was statistically significantly better than SEL-212 in decreasing the number of swollen joints at month 4 day 0 [change from baseline −2.3 (S.D. 4.9) *vs* −0.6 (4.0), respectively; $P=0.005$] but no difference between SEL-212 and pegloticase at month 6 day 28 (Supplementary Table S4, available at *Rheumatology* online).

Effect of SEL-212 in participants with and without tophi

The percentage of participants who achieved/maintained a reduction of SU <6 mg/dl for ≥80% of the time on study drug was statistically significantly higher for SEL-212 (70.8%) *vs* pegloticase (54.7%) in participants without tophi during month 3 [treatment difference 16.1 percentage points (95% CI 0.5, 31.7); $P=0.048$; Supplementary Table S5, available

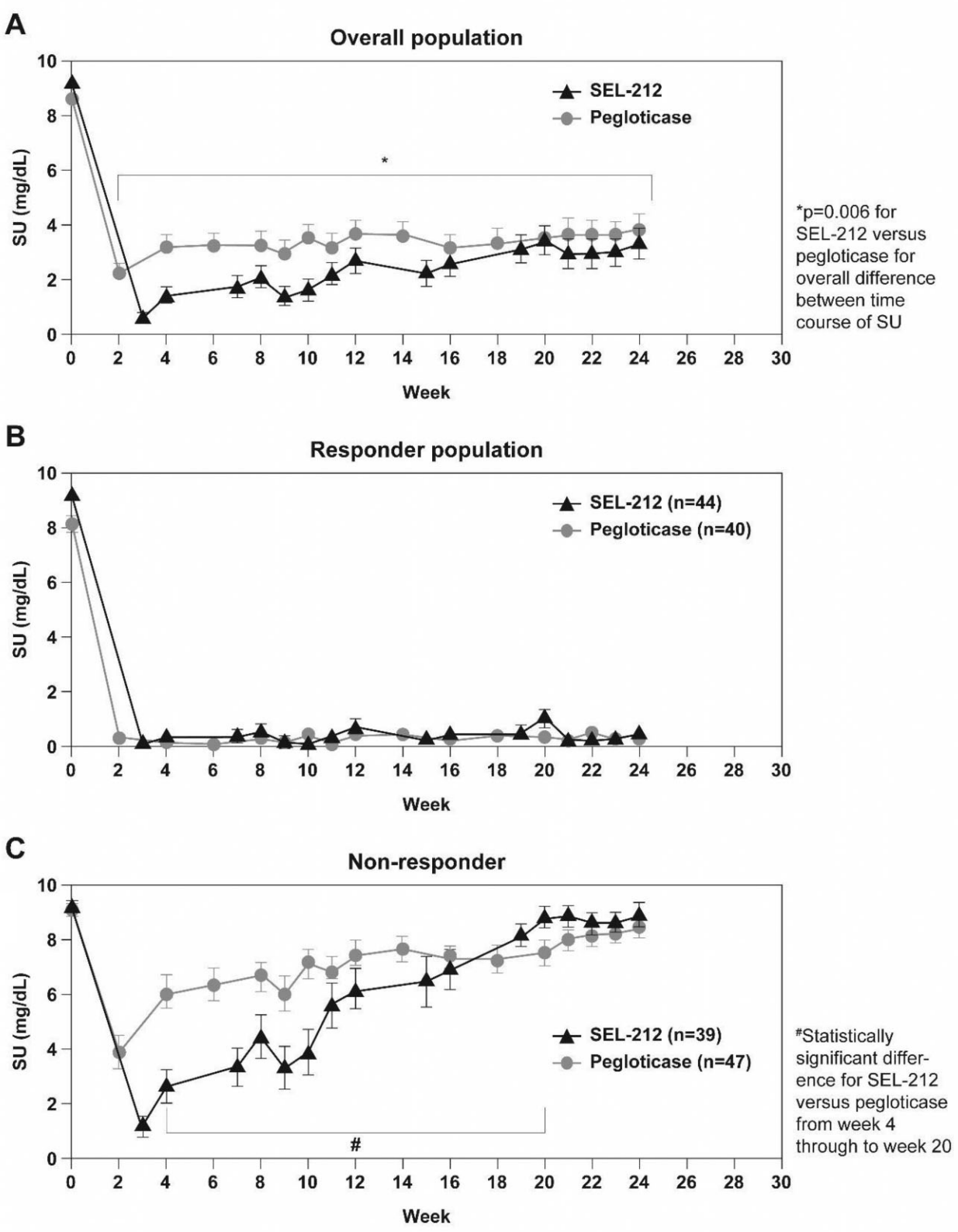

Figure 3. Mean SU levels over time by overall, responder and non-responder populations (ITT population).
Data are means and S.D.S.

at *Rheumatology* online]. Similarly, mean SU reductions were significantly higher for SEL-212 *vs* pegloticase (−7.32 and −4.89 mg/dl, respectively; $P = 0.0185$) in participants with tophi during months 3 and 6 combined, but narrowly missed achieving significance in those without tophi (Supplementary Table S6, available at *Rheumatology* online). There were no differences in mean SU levels over time in the responder and non-responder populations stratified by the presence of tophi

(Supplementary Figs S1A and B, available at *Rheumatology* online).

HRQoL

HAQ-DI, SF-36 and PhGA outcomes were comparable for SEL-212 and pegloticase (see supplementary results section and Supplementary Table S7, available at *Rheumatology* online).

Safety

In total, 89.2% (74/83) of SEL-212 participants and 78.2% (68/87) of pegloticase participants experienced one or more TEAEs (Table 3), with the majority classified as mild or moderate. Of the TEAEs, 54.2% and 39.1% in the SEL-212 and pegloticase arms, respectively, were considered treatment related (Table 3). The most common treatment-related adverse events (TRAEs) reported in the SEL-212 and pegloticase arms were GFs (32.5% and 23.0%, respectively), infusion-related reactions (15.7% and 11.5%) and headache (4.8% and 0%). Treatment-related SAEs were observed in 2.4% ($n=2$) with SEL-212 (infusion-related anaphylaxis and infusion reactions) and 3.4% ($n=3$) with pegloticase (infusion-related anaphylaxis, infusion reactions and hypotensive emergency), respectively. All treatment-related SAEs resolved without sequelae.

TEAEs leading to study drug withdrawal occurred in 12.0% ($n=10$) and 17.2% ($n=15$) of participants with SEL-212 and pegloticase, respectively. The largest number of withdrawals in both arms resulted from infusion-related reactions (4.8% with SEL-212 and 8.0% with pegloticase). Other reasons for withdrawal included lower gastrointestinal haemorrhage, anaphylactic reaction, abscesses, investigations for haemoglobin or hepatic enzyme increase, GFs, pulmonary embolism and deep vein thrombosis (DVT) with SEL-212. For pegloticase, other reasons for withdrawal included thrombocytopenia, peripheral oedema, anaphylactic reaction, drug hypersensitivity, cellulitis, coronavirus, GFs and a hypertensive emergency.

There were no deaths during the study. GFs (60.2% and 50.6% with SEL-212 and pegloticase, respectively) and infusion-related reactions (15.7% and 11.5% with SEL-212 and pegloticase, respectively) were the most commonly reported AESIs. Stomatitis (and related terms, aphthous ulcer, cheilitis, mouth ulceration, oral mucosal blistering, tongue ulceration, mucosal inflammation, mucosal ulceration and nasal ulcer) was experienced by 8 (9.6%) patients on SEL-212 and none with pegloticase. Two participants in the SEL-212 group experienced DVT with pulmonary embolism and one experienced DVT, while no thrombotic events were reported in the pegloticase group. The three DVTs were all assessed by the investigators as unlikely to be related to SEL-212. One participant in each treatment group experienced an AESI of anaphylaxis.

For changes in vital signs, electrocardiograms and laboratory values, please see the Supplementary results section, available at *Rheumatology* online.

Discussion

This is the first published head-to-head study of uricase treatment for RG. SEL-212 showed a numerically better response in terms of the proportion who achieved and maintained SU <6 mg/dl for ≥80% of the time (months 3 and 6 combined) but did not meet the primary endpoint of statistical superiority over pegloticase. For the secondary endpoint (month 3 only), SEL-212 showed a statistically significantly higher response rate *vs* pegloticase. Absolute and percentage SU reductions in months 3 and 6 were also significantly better with SEL-212 *vs* pegloticase. These improvements in mean SU reflected the higher proportion of responders in the SEL-212 *vs* pegloticase arms. In the subgroup of participants with tophi at baseline, indicative of more severe gout, the mean reduction in SU was significantly higher for SEL-212 *vs* pegloticase. In the subgroup without tophi, however, the reduction in SU narrowly missed statistical significance. In agreement with previous data from two phase 3 trials with pegloticase [11], both SEL-212 and pegloticase treatment resulted in reductions in GF incidence and frequency in months 4–6 *vs* months 1–3 and reductions in the number of swollen and/or tender joints. While a single dose of pegadricase alone may be more immunogenic than pegloticase, the immunogenicity of both uricases has not been tested in a head-to-head trial. However, with co-administration as SEL-212, pegadricase with rapamycin-containing nanoparticles

Table 3. Summary of TEAEs and treatment-related TEAEs in ≥2% of participants (safety population)

	SEL-212 ($n=83$), *n* (%)	Pegloticase ($n=87$), *n* (%)
Participants with ≥1 TEAE		
TEAE	74 (89.2)	68 (78.2)
Treatment-related TEAE	45 (54.2)	34 (39.1)
Serious TEAE	7 (8.4)	8 (9.2)
Treatment-related serious TEAE	2 (2.4)	3 (3.4)
TEAE of special interest	63 (75.9)	59 (67.8)
TEAE leading to study drug withdrawal	10 (12.0)	15 (17.2)
TEAE leading to death	0	0
TEAE of infusion reaction	15 (18.1)	15 (17.2)
Treatment-related TEAEs in ≥2% of participants		
Participants with ≥1 related TEAEs	45 (54.2)	34 (39.1)
Gout flare	27 (32.5)	20 (23.0)
Infusion-related reaction	13 (15.7)	10 (11.5)
Headache	4 (4.8)	0
Hypertriglyceridemia	3 (3.6)	2 (2.3)
Aphthous ulcer	2 (2.4)	0
Hyperglycaemia	2 (2.4)	1 (1.1)
Hypophosphatemia	2 (2.4)	0
Back pain	2 (2.4)	0

inhibited ADA formation in a dose-dependent manner in a phase 1 trial [17].

A higher proportion of participants experienced TRAEs with SEL-212 *vs* pegloticase, however, most events were assessed as mild or moderate in severity. TEAEs leading to study drug withdrawal were higher in the pegloticase *vs* SEL-212 arm (17.2% *vs* 12.0%, respectively). The proportion of participants with SAEs, treatment-related SAEs and infusion-related reactions were similar between SEL-212 and pegloticase. Stomatitis was observed with SEL-212 but not pegloticase, possibly reflecting the rapamycin component of SEL-212, as rapamycin-induced stomatitis has been reported [22]. Pegloticase has been studied and on the market for a combined 15-year period without safety concerns relating to profound/prolonged hypouricaemia being identified, although monitoring in participants with congestive heart failure is recommended [23].

SEL-212 is infused monthly, whereas pegloticase is biweekly. The pegloticase summary of product characteristics recommends that infusions be administered in a clinical setting that can manage potential anaphylactic responses/infusion reactions and that pre-infusion infusion reaction prophylaxis, including antihistamines and glucocorticoids, should be administered [24]. In addition, clinical monitoring is required during the infusion and for 2 h post-treatment [24]. Therefore, reducing the frequency of uricase infusion from biweekly to monthly could ease the treatment burden and total glucocorticoid dose for the person with gout and the healthcare utilisation burden for the treatment centre. In this study, participants in the pegloticase arm received 26% more pre-infusion glucocorticoids *vs* those in the SEL-212 arm. Thus SEL-212 achieved similar or improved efficacy outcomes compared with pegloticase, despite reduced glucocorticoid use. COVID-19 had an impact on the study. There were 25 missing data points and a number of withdrawals, discontinuations and early terminations due to pandemic restrictions. In addition, COVID-19 infections resulted in eight major protocol deviations in seven participants that affected the efficacy evaluation. Thus it is possible that COVID-19-related missing data and protocol deviations had an impact in terms of meeting the study endpoints.

Study strengths include that it was a well-designed head-to-head study that was appropriately powered for the primary endpoint. A potential weakness was the reduction in the number of evaluable participants caused by the stopping rule and the unforeseeable impact of COVID-19. For SEL-212, treatment was withdrawn if SU was >1.0 mg/dl on the day 21 visit of month 1 or >6.0 mg/dl at the day 21 visit of months 2, 3, 4 or 5, based on clinical development experience. For pegloticase, treatment was withdrawn if SU was >6.0 mg/dl on two consecutive pre-dose measurements, based on the pegloticase label [23]. While the stopping rule was implemented as part of a safety focus in the trial, such rules were not utilized in the original pegloticase phase 3 trials [11]. Given the rule resulted in study drug withdrawal in 18.1% of participants in the SEL-212 group and 27.6% in the pegloticase group, it decreased the number of on-treatment participants evaluated. The COVID-19 pandemic affected the powering of the trial by reducing the number of evaluable participants and causing missed visits. Additionally, as the study was open label, self-reported endpoints were potentially open to bias, as participants were aware of what treatment they were receiving. Finally, while the current study was a comparison between SEL-212 and pegloticase monotherapy, a co-administration of pegloticase and MTX was recently approved in the USA [25]. We are confident that these results remain clinically relevant, particularly for participants who are intolerant of or otherwise not candidates for MTX and/or pegloticase.

In conclusion, this head-to-head study demonstrated that SEL-212 was as effective as pegloticase for the treatment of RG. The study did not demonstrate statistical superiority for SEL-212 *vs* pegloticase for the primary endpoint, which may, in part, reflect COVID-19-related disruptions. Overall, SEL-212 demonstrated a favourable safety profile and the proportion experiencing infusions reactions was comparable between SEL-212 and pegloticase. By reducing infusion frequency from biweekly to monthly, SEL-212 may offer a substantial reduction in treatment burden and associated healthcare utilisation for participants with RG.

Supplementary data

Supplementary data are available at *Rheumatology* online.

Data availability

The data underlying this article will be shared upon reasonable request to medinfo@selectabio.com.

Authors' contributions

All authors contributed to the study design, data collection, study analysis, interpretation of results and reviewed and revised the manuscript for content.

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