Once-monthly SEL-212 demonstrates efficacy and safety for up to 6-months in gout refractory to conventional therapy: Combined data from the DISSOLVE I & II Phase 3, double-blind, placebo-controlled clinical trials

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CONCLUSIONS

- Combined DISSOLVE I & II data confirm that SEL-212 significantly lowered serum uric acid (sUA) and significantly increased sUA response in a population with gout refractory to conventional uric acid lowering therapy (RG).
- The observed sUA-lowering in this difficult-to-treat population has the potential to have a beneficial impact on the clinical manifestations of gout.
- The safety and tolerability profile of SEL-212 was favourable.
- There was a low rate of infusion reactions, which all occurred within the first three infusions.
- Overall, investigational once-monthly SEL-212 has potential as a well-tolerated and effective uricase-based urate-lowering therapy for patients with RG.

INTRODUCTION

- Sustained hyperuricemia is a known risk factor for recurrent gout flares and progression of tophaceous burden in patients with RG.[1]
- Uricase-based therapy can effectively reverse these outcomes but is limited by immunogenicity, which impairs efficacy and increases the risk of infusion reactions.[2]
- SEL-212 is an investigational, once-monthly, two-component infusion therapy consisting of nanoparticles containing sirolimus with immune-tolerising effects (SEL-110) and pegadricase (a pegylated uricase, SEL-037).[3-6]
- DISSOLVE I & II were US and global clinical trials, respectively, that evaluated efficacy and safety of SEL-212 in adults with RG.[7,8]
  - In DISSOLVE, RG was defined as sUA ≥7 mg/dL and inadequate control of clinical manifestations despite medically appropriate doses of conventional oral gout therapies.
- Individual study data from DISSOLVE I & II have been presented previously,[9] this poster presents combined data from the DISSOLVE I and II main study periods.

METHODS

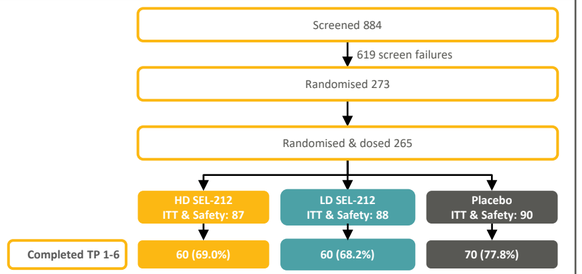
- DISSOLVE I & II were placebo-controlled, double-blind, randomised, replicate-design phase 3 trials that evaluated once-monthly sequential administration of SEL-110 at either 0.15 mg/kg [HD] or 0.1 mg/kg [LD] followed by SEL-037 (0.2 mg/kg) for the main study period (6 treatment periods [TP]).
  - DISSOLVE I differed from DISSOLVE II as it included a 6-month double-blind extension period.
- The intent-to-treat (ITT) set included all randomized and treated patients.
- The safety set included all patients who were administered any amount of study drug.
- Treatment was discontinued if the **stopping rule** was met: sUA <2.0 mg/dL 1-h after infusion of the second component of the study drug during TP1 **AND** >1.0 mg/dL at Day 21 of TP1 **OR** >6.0 mg/dL at Day 21 of TP 2-6.
- Pre-specified analyses of combined outcomes included the primary endpoint (response rate, RR), defined as sUA levels <6mg/dL for ≥80% of the time during TP6, sUA reduction, and safety.

RESULTS

Patient disposition, baseline characteristics

- The combined ITT population included 87, 88, and 90 patients in the HD, LD, and placebo arms, respectively (**Figure 1**).
- Key reasons for study drug discontinuation (n [%]) in the HD, LD, and placebo arms, respectively, included meeting the stopping rule (20 [23.0%], 38 [43.2%], 1 [1.1%]), withdrawal of consent (9 [10.3%], 7 [8.0%], 8 [8.9%]), adverse events (12 [13.8%], 6 [6.8%], 2 [2.2%], loss to follow-up (2 [2.3%], 0 [0%], 4 [4.4%]), COVID-19 (0 [0%], 1 [1.1%], 1 [1.1%]), and 'Other' (3 [3.4%], 1 [1.1%], 7 [7.8%]).
  - Patients who discontinued study drug continued study visits.
- Twenty-seven (31.0%), 28 (31.8%) and 20 (22.2%) patients in the HD, LD, and placebo arms, respectively, discontinued the study.

Figure 1. Patient flow



HD, high-dose; ITT, intent-to-treat; LD, low-dose; TP, treatment period.

- Baseline demographics and disease characteristics (**Table 1**) were largely similar across groups.
  - Mean age was 54.2–55.3 years and those aged ≥50 years comprised 65.9–71.3% of patients across treatment groups.
  - Most patients (94.3–98.9%) were male and mean BMI was approximately 33 kg/m^2.
  - DISSOLVE included White (73.3–85.1%), Black and African American (12.5–16.7%), Asian (2.3–4.4%), and 'Other' (2.3–5.6%) patients.

Table 1. Combined DISSOLVE I and II disease characteristics (ITT set)

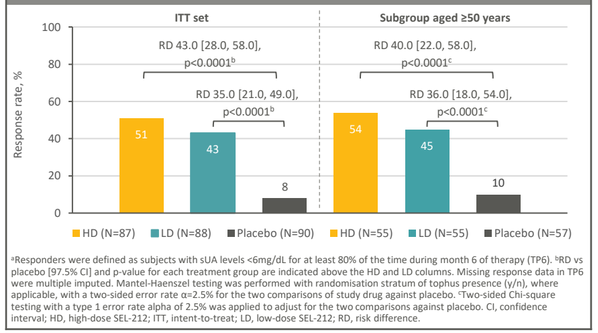
	Combined data: DISSOLVE I and II		
	High dose (N=87)	Low dose (N=88)	Placebo (N=90)
Time since gout diagnosis, years, mean (SD)	12.3 (9.7)	11.7 (9.3)	11.3 (8.5)
Common comorbidities,[a] n (%)			
Hypertension	55 (63.2)	51 (58.0)	57 (63.3)
Hyperlipidaemia	29 (33.3)	22 (25.0)	26 (28.9)
Dyslipidaemia	13 (14.9)	15 (17.0)	10 (11.1)
Obesity	14 (16.1)	12 (13.6)	9 (10.0)
Chronic kidney disease stage, n (%)			
Stage 1 (eGFR ≥ 90 mL/min/1.73 m^2)	22 (25.3)	21 (23.9)	20 (22.2)
Stage 2 (60 ≤ eGFR < 90 mL/min/1.73 m^2)	45 (51.7)	49 (55.7)	47 (52.2)
Stage 3a (45 ≤ eGFR < 60 mL/min/1.73 m^2)	15 (17.2)	13 (14.8)	19 (21.1)
Stage 3b (30 ≤ eGFR < 45 mL/min/1.73 m^2)	5 (5.7)	5 (5.7)	4 (4.4)
sUA level[b], mg/dL, mean (SD)	8.6 (1.3)	8.6 (1.4)	8.7 (1.6)
Use of ULT at screening, n (%)			
Allopurinol	57 (65.5)	61 (69.3)	48 (53.3)
Febuxostat	14 (16.1)	11 (12.5)	14 (15.6)
Benzbromarone	0	0	1 (1.1)
Missing	2 (2.3)	0	1 (1.1)
Participants with tophi at screening, n (%)	55 (63.2)	55 (62.5)	57 (63.3)
Tender joints, n	85	82	86
Mean (SD)	7.5 (10.4)	8.0 (11.3)	7.5 (11.5)
Swollen joints, n	84	82	86
Mean (SD)	4.8 (8.7)	4.1 (7.8)	4.7 (7.9)

[a]Affecting ≥15% of patients in any treatment group (excludes gout and gouty arthritis); [b]At baseline. BMI, body mass index; eGFR, estimated glomerular filtration rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; ITT, intent-to-treat; n, number; SD, standard deviation; SF-36, Short Form-36; sUA, serum uric acid; ULT, urate lowering therapy.

EFFICACY

- For the primary endpoint, 51%, 43%, and 8% in HD SEL-212-, LD SEL-212-, and placebo-treated arms, respectively, achieved sUA responses (**Figure 2**).
  - Similar sUA responses were observed in the subgroup aged ≥50 years old.
- In the subgroup with tophi at screening, sUA responses were achieved by 43%, 43%, and 8% in HD SEL-212-, LD SEL-212-, and placebo-treated arms, respectively.

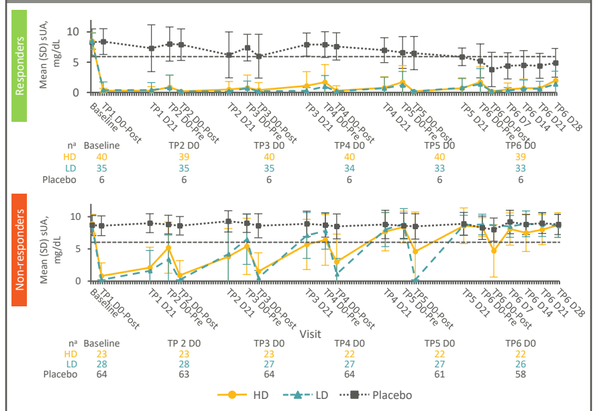
Figure 2. Response rates[a] with SEL-212 versus placebo (combined DISSOLVE I & II ITT and subgroup aged ≥50 years)



[a]Responders were defined as subjects with sUA levels <6mg/dL for at least 80% of the time during month 6 of therapy (TP6). [b]RD vs placebo [97.5% CI] and p-value for each treatment group are indicated above the HD and LD columns. Missing response data in TP6 were multiple imputed. Mantel-Haenszel testing was performed with randomisation stratum of tophus presence (y/n), where applicable, with a two-sided error rate α=2.5% for the two comparisons of study drug against placebo. [c]Two-sided Chi-square testing with a type 1 error rate alpha of 2.5% was applied to adjust for the two comparisons against placebo. CI, confidence interval; HD, high-dose SEL-212; ITT, intent-to-treat; LD, low-dose SEL-212; RD, risk difference.

- Mean absolute (percentage) sUA reductions from baseline were 5.3 mg/dL (60.8%) for HD, 4.5 mg/dL (52.2%) for LD, and 0.3 mg/dL (2.1%) for placebo (p<0.001 for both HD and LD SEL-212 vs placebo).
- In the responder population, sUA remained well below 6 mg/dL throughout the 6-month study period in the SEL-212 HD and LD arms, while in the placebo arm sUA remained >6 mg/dL close to TP 6 and then fell to just below 6 mg/dL during TP 6 (**Figure 3**).
- In the non-responder population, mean sUA was reduced during the first 2 TPs with HD and LD. From TP 4, the mean sUA value at the end of each treatment cycle was comparable to that of placebo-treated patients.

Figure 3. Mean sUA (SD) values over time in responders vs. non-responders (combined DISSOLVE I & II ITT set)



The dashed horizontal line on the figure represents the 6 mg/dL sUA level. **Patients discontinuing study treatment, due to meeting the stopping rule or other reasons, continued to be followed up, so not all patients were actively receiving treatment**. Responder assessment was performed at TP6 [a]Number of patients on day 0 (pre-dose) of each treatment period shown. D, day; HD, high-dose SEL-212; ITT, intent to treat; LD, low-dose SEL-212; SD, standard deviation; sUA, serum uric acid; TP, treatment period.

SAFETY

- Most patients (72.4%, 70.5%, and 63.3% in the HD, LD, and placebo arms) experienced ≥1 treatment emergent adverse event (TEAE); with most being mild/moderate in severity.
- Adverse events of special interest (AESI) affecting >5% of patients included gout flares, COVID-19 infection, hypertriglyceridaemia, and stomatitis (**Table 2**).
- Mild to moderate adverse events of stomatitis, oral ulcer, and aphthous ulcers did not lead to any withdrawals.

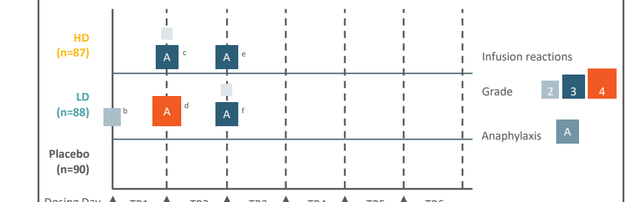
Table 2. Summary of adverse events of special interest[a,b]

	Combined data: DISSOLVE I and II		
Safety Set, patients, n (%)	High dose (N=87)	Low dose (N=88)	Placebo (N=90)
≥1 Treatment-emergent AESI	56 (64.4)	59 (67.0)	49 (54.4)
Gout	37 (42.5)	39 (44.3)	39 (43.3)
Infections (including viral)	20 (23.0)	16 (18.2)	15 (16.7)
COVID-19[c]	5 (5.7)	5 (5.7)	6 (6.7)
Infusion-related AEs (24h)	7 (8.0)	6 (6.8)	2 (2.2)
Infusion reactions (1h) incl. anaphylaxis[d]	3 (3.4)	4 (4.5)	0 (0)
Hypertriglyceridaemia[e]	6 (6.9)	4 (4.5)	6 (6.7)
Stomatitis[f]	8 (9.2)	3 (3.4)	0 (0)
Renal and urinary disorders[g]	1 (1.1)	2 (2.3)	3 (3.3)
Pulmonary embolism	0 (0)	1 (1.1)	0 (0)
Leukopenia	0 (0)	2 (2.3)	0 (0)

[a]Safety data shown are during the first 6 treatment periods during DISSOLVE I and DISSOLVE II. Events occurring during the extension phase of the DISSOLVE I study are excluded. [b]AESIs included in protocol as agreed with FDA; No other TEAEs ≥5%. [c]There were no other individual infections >2%. [d]IRs (1h) are included in the Infusion-related AEs (24h). [e]Dyslipidaemia/hypertriglyceridaemia/hyperlipidaemia. [f]Stomatitis/oral ulcer/aphthous ulcer; 67% mild, 33% moderate; [g]Includes microalbuminuria and renal impairment. AE, adverse event; AESI, adverse event of special interest; FDA, Food & Drug Administration; IR, infusion reaction; LDL, low-density lipoprotein; TEAE; treatment-emergent adverse event.

- All infusion-related reactions (≤1h) occurred within the first three infusions (**Figure 4**).
  - All events were reported during the infusion and completely resolved upon cessation of the infusion and administration of symptomatic treatment.
- COVID-19 infections affected 5 (5.7%) in each of the SEL-212 arms and 6 (6.7%) in the placebo arm.
- No TEAEs resulted in death.

Figure 4. Incidence of infusion reactions (combined DISSOLVE I & II Safety set)[a]



[a]Infusion reactions defined as a study drug-related AE that occurs during or after completion of study drug infusion (Rheumatology Common Criteria, ver. 2.0). The observation time was defined as 1 h following the completion of the pegadricase infusion. [b]Infusion reaction in the low-dose group occurred during the infusion of SEL-110; pegadricase not administered. All the other infusion reactions occurred during the pegadricase infusion. [c]Patient recovered with diphenhydramine, prednisone, IV ondansetron, and IV methylprednisolone. [d]Patient recovered with epinephrine, IV diphenhydramine, methylprednisolone and fluids. [e]Patient recovered with IV diphenhydramine, acetaminophen, and methylprednisolone. [f]Patient recovered with methylprednisolone, acetaminophen, and diphenhydramine. IR, infusion reaction; IV, intravenous; TP, treatment period.

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