Health-related quality of life (HRQoL) and secondary clinical outcomes in adults with gout refractory to conventional therapy treated with SEL-212: Pooled 6-month data from the phase 3 DISSOLVE I & II clinical trials

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CONCLUSIONS

- Combined data from DISSOLVE I & II in patients with gout refractory to conventional oral urate-lowering therapies:
  - Demonstrated improvements in HRQoL, regardless of SEL-212 dose versus placebo.
  - Showed physical functioning and pain benefits as early as treatment period (TP) 4.
  - Both high- and low- doses significantly improved tender joint counts versus placebo.
- Treatment with HD and LD SEL-212 resulted in a marked reduction in the proportion of patients experiencing gout flares comparing treatment periods (TP) 1-3 and TP 4-6. In contrast, a similar percentage of patients experienced gout flares during TP 1-3 and TP 4-6 with placebo. This is indicative of a decline in the body's burden of urate in the two SEL-212 arms over time.
- SEL-212, an investigational, once-monthly, uricase-based therapy demonstrated improvement in patient-reported HRQoL, tender joints, and gout flares over 6-months in patients with gout refractory to conventional oral serum uric acid (sUA)-lowering therapies.

INTRODUCTION

- Sustained hyperuricaemia causes systemic deposition of monosodium urate crystals in joints and other tissues and may result in painful gout flares, chronic arthritis, and tophus formation, leading to poor health-related quality of life (HRQoL) outcomes and physical functioning.[1,2]
- Uricase-based therapies effectively lower sUA in patients with clinical manifestations of gout refractory to conventional oral sUA-lowering therapies; however, their use is limited by immunogenicity-related efficacy reductions and infusion reactions.[3,4]
- SEL-212 is a novel, once-monthly uricase-based therapy comprising sequential infusions of tolerogenic nanoparticles containing sirolimus (SEL-110) followed by a pegylated uricase (pegadricase; SEL-037).[5-10]
- Administration of SEL-110 followed by SEL-037 provided targeted immunomodulation that mitigated uricase immunogenicity, thereby enabling sustained sUA control without the need for broader immunosuppression.[6-10]

METHODS

- DISSOLVE I & II are placebo-controlled, double-blind, randomised, replicate-design phase 3 clinical trials evaluating the safety/efficacy of once-monthly SEL-212 (SEL-110 0.15 mg/kg [HD] or 0.1 mg/kg [LD] with SEL-037 [0.2 mg/kg]) in adults with sUA ≥7 mg/dL and inadequate symptom control despite medically appropriate doses of conventional oral gout therapies.
  - DISSOLVE I differed from DISSOLVE II as it included a 6-month double-blind extension period.
- Prespecified pooled analyses of data from DISSOLVE I & II evaluated key secondary clinical outcomes, including changes from baseline to TP 6 in patient-reported health outcome measures (Short Form-36 [SF-36]v2 physical component summary (PCS) score and total Health Assessment Questionnaire-Disability Index [HAQ-DI] score) and tender joints.
  - SF-36 and HAQ-DI were assessed at baseline, TP 4 Day 0, and TP6 Day 28.
- Incidence of gout flares per month was analysed for TP 1-3 and TP 4-6.
- SF-36 scores, HAQ-DI scores, and number of tender joints were analysed using a linear mixed model. Intercurrents events were addressed using a treatment policy.
- P-values ≤0.025 were considered statistically significant to account for the comparisons of the two doses with placebo.

RESULTS

Baseline characteristics

- Overall, 87, 88 and 90 patients in the combined DISSOLVE I & II intent-to-treat (ITT) set received HD SEL-212, LD SEL-212 and placebo, respectively. Of these, 60, 60 and 70, respectively, completed TP 6 (40, 39 and 68, respectively, while on treatment).
- Mean age was between 54 and 55 years across arms (median [range] 56.0 [28–77] for HD SEL-212, 55.0 [33–79] for LD SEL-212 and 54.5 [25–80] for placebo).
- Patients were predominantly male (94.3–98.9% across arms), with a body mass index of 32.9–33.5 kg/m^2, and >60% had ≥1 tophus at baseline. SF-36 and HAQ-DI scores suggested impaired HRQoL and physical function.
- Patients were White (73.3–85.1%), Black or African American (12.5–16.7%), Asian (0–4.4%), or Other (2.3–5.6%).
- Disease characteristics were similar across treatment arms (**Table 1**).

Table 1. Baseline disease characteristics for the DISSOLVE I & II trials (combined ITT set)[a]

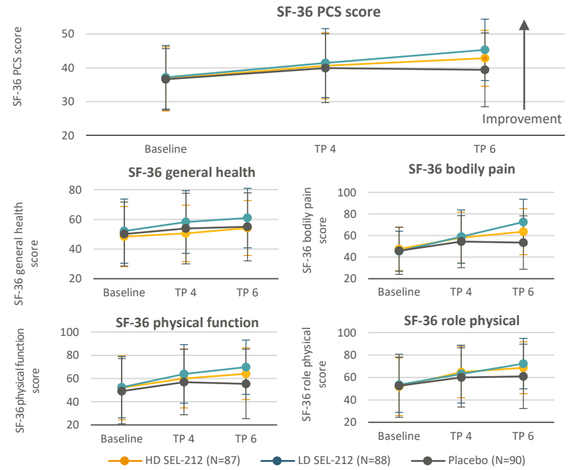
	Combined data: DISSOLVE I and II		
	High-dose SEL-212 (N=87)	Low-dose SEL-212 (N=88)	Placebo (N=90)
Disease characteristics			
Time since gout diagnosis, years, mean (SD)	12.3 (9.7)	11.7 (9.3)	11.3 (8.5)
Participants with tophi at screening, n (%)	55 (63.2)	55 (62.5)	57 (63.3)
Tender joints	n = 85	n = 82	n = 86
Mean (SD)	7.5 (10.4)	8.0 (11.3)	7.5 (11.5)
Median (range)	2.0 (0–58)	4.5 (0–60)	1.0 (0–56)
Swollen joints	n = 84	n = 82	n = 86
Mean (SD)	4.8 (8.7)	4.1 (7.8)	4.7 (7.9)
Median (range)	1.5 (0–58)	1.0 (0–40)	1.0 (0–34)
SF-36 PCS score[b]	n = 86	n = 84	n = 87
Mean (SD)	36.7 (9.5)	37.2 (9.4)	36.6 (9.2)
Median (range)	36.0 (14.0–58.7)	36.1 (18.7–58.4)	34.1 (23.1–56.3)
HAQ-DI score, n[c]	n = 85	n = 85	n = 88
Mean (SD)	1.0 (0.7)	1.0 (0.6)	1.0 (0.7)
Median (range)	1.0 (0–2.5)	1.0 (0–2.5)	1.1 (0–2.3)

[a]Or screening for presence of tophi; [b]SF-36 is scored on a scale from 0 (lowest HRQoL) to 100 (highest HRQoL); [c]HAQ-DI is scored on a scale of 0 (no disability) to 3 (maximum disability), with a MCID of 0.22. The ITT population included all randomised patients who were dosed. BMI, body mass index; HAQ-DI, Health Assessment Questionnaire-Disability Index; ITT, intent-to-treat; MCID, minimum clinically important difference; PCS, Physical Component summary; SD, standard deviation; SF-36, Short Form Health Survey.

HRQoL (SF-36) and physical functioning (HAQ-DI)

- For SEL-212 LD, patients reported improvements in SF-36 as early as TP 4, which continued through TP6. Mean improvement in SF-36 PCS score from baseline to TP 6 was significantly better (9.10) versus placebo (3.40) in the overall combined DISSOLVE I & II population (LS mean difference [97.5% confidence interval (CI)] 5.70 [2.31, 9.08], p<0.001).
- SF-36 PCS scores improved with SEL-212 HD (36.70 baseline and 42.80 TP 6) and placebo (36.60 baseline and 39.40). Mean improvement 6.70 and 3.40, respectively; LS mean difference [97.5% CI] 3.30 [0.03, 6.57], p=0.026).
- Mean SF-36 PCS scores and sub-domains (General health, Bodily Pain, Physical function, and Role Physical) increased numerically from baseline to TP4 and TP6 with SEL-212 HD, LD and placebo (**Figure 1**).
  - The numerical increases in mean SF-36 PCS scores between baseline, TP4 and TP6 were generally higher with SEL-212 HD and LD compared with placebo.

Figure 1. SF-36[a] PCS score and related subdomains (combined ITT set)

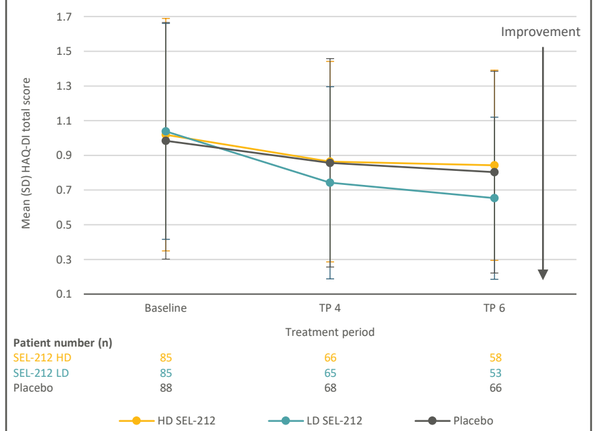


Data are mean (SD). [a]SF-36 is scored on a scale from 0 (lowest HRQoL) to 100 (lowest HRQoL). SD, standard deviation; SF-36, Short Form Health Survey; TP, treatment period.

HAQ-DI

- Mean change in HAQ-DI total score from baseline to TP 6 for the SEL-212 LD (-0.40) versus placebo (-0.20) indicated statistical significantly-improved physical functioning (LS mean difference [97.5% CI] -0.20 [-0.35, -0.03], p=0.007), which exceeded the MCID of 0.22.
- The LS mean change in HAQ-DI total score from baseline to TP 6 with SEL-212 HD (-0.20) and placebo (-0.20) did not achieve statistical significance (LS mean difference [97.5% CI] 0.00 [-0.15, 0.17], p=0.893).
- Mean (SD) HAD-QI scores over time are shown in **Figure 2**.

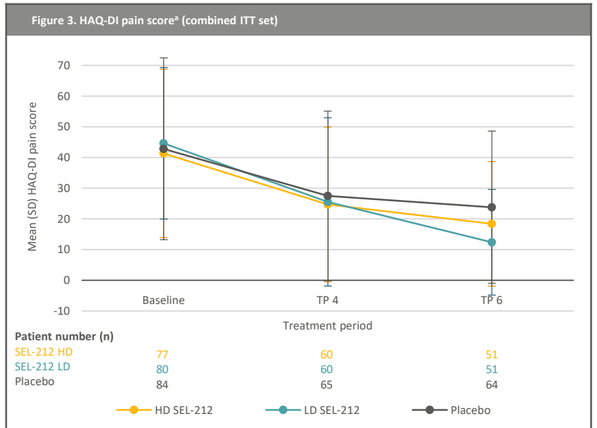
Figure 2. HAQ-DI[a] total score (combined ITT set)



Error bars indicate SD. [a]HAQ-DI is scored on a scale of 0 (no disability) to 3 (maximum disability), with a MCID of 0.22. HAQ-DI, HAQ-DI, Health Assessment Questionnaire-Disability Index; HD, high-dose SEL-212; ITT, intent-to-treat, LD, low-dose SEL-212; MCID, minimal clinically important difference; SD, standard deviation; TP, treatment period.

- Patient reported mean (SD) HAQ-DI pain scores were reduced by TP4 with further reductions by TP6 (**Figure 3**).

Figure 3. HAQ-DI pain score[a] (combined ITT set)



Error bars indicate SD. [a]HAQ-DI pain is scored 0 (no pain) to 100 (severe pain). HAQ-DI, Health Assessment Questionnaire-Disability Index; HD, high-dose SEL-212; ITT, intent-to-treat, LD, low-dose SEL-212; SD, standard deviation; TP, treatment period.

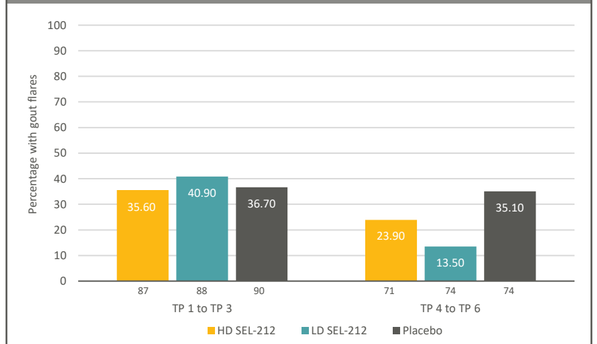
Tender joints

- The reduction in mean number of tender joints from baseline to TP 6 was significantly greater with SEL-212 HD (reduction of 5.50 joints, LS mean difference [97.5% CI] versus placebo -2.40 [-4.06, -0.65], p=0.002) and LD (reduction of 6.60 joints, LS mean difference [97.5% CI] versus placebo -3.50 [-5.20, -1.72], p<0.001) compared with placebo (3.10 joints).

Gout flares

- The proportion of patients with gout flares was numerically decreased with HD and LD SEL-212 but not with placebo between TP 1-3 and TP 4-6 (**Figure 4**).

Figure 4. Percentage of patients with gout flares, TP 1 to 3, and TP 4 to 6 (combined ITT set)



Percentages are based on the number of patients who started the corresponding treatment period. HD, high-dose SEL-212; ITT, intent-to-treat; LD, low-dose SEL-212; TP, treatment period.

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