Improvements in Patient-Reported Outcomes After Treatment with SEL-212 in Adults with Refractory Gout: Results from Two Randomized Phase 3 Trials

P0355

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CONCLUSIONS

- Patients treated with NASP (SEL-212) reported improvements in SF-36 physical components, HAQ-DI and pain VAS. Data appear to reflect a positive impact on several aspects of HRQoL for adults with refractory gout, including functional ability, physical functioning and pain
- Clinically meaningful changes in PROs were reported after three doses of NASP, which further improved after three additional doses, indicating patients reported an incremental HRQoL benefit with prolonged treatment duration
- Phase 3 data show that NASP improves clinical and HRQoL outcomes vs baseline, which is likely reflective of substantial urate lowering with this novel agent

INTRODUCTION

- Despite available therapies for gout, some patients suffer from refractory gout, leading to an impaired health-related quality of life (HRQoL) relating to acute or chronic inflammation from elevated serum uric acid (sUA) levels.[1,2] Patients with gout have reported experiencing pain, physical impairment and work productivity loss[3]
- Nanoencapsulated sirolimus plus pegadricase (NASP, also SEL-212) is a novel, once-monthly, two-component infusion therapy consisting of immune-tolerizing nanoparticles containing sirolimus (NAS, formerly SEL-110) and a pegylated uricase (pegadricase, also SEL-037), to reduce sUA[1]
- Results from the DISSOLVE I (US; NCT04513366) and II (global; NCT04596540) Phase 3 trials demonstrated that treatment with NASP significantly improved response rates (defined as sUA <6 mg/dL for ≥80% of treatment period [TP] 6) and reduced mean sUA levels vs placebo in patients with chronic refractory gout[1]
- Improvements in patient-reported outcome (PRO) scores may be associated with HRQoL and societal benefits such as increased work productivity and reduced healthcare utilization[4]

OBJECTIVE

- The aim of these *post hoc* analyses was to assess the effects of NASP on physical and mental functioning, daily activities and pain, in patients with chronic refractory gout. Analyses were performed using pooled data from DISSOLVE I and II in patients who received all doses of treatment at two assessment points: TP 4 Day 0 (D0), i.e. first three doses (F3D) subgroup; and TP6 D28, i.e. first six doses (F6D) subgroup

METHODS

- DISSOLVE I and II were randomized, double-blind, placebo-controlled trials of patients naïve to uricase-based therapy, with ≥3 gout flares within 18 months prior to screening or ≥1 tophus or a current diagnosis of gouty arthritis, in whom oral urate-lowering therapy failed to normalize sUA and control gout-related symptoms
- Patients received high- or low-dose (HD or LD) NASP (consisting of NASP [0.15 or 0.1 mg/kg] plus pegadricase [0.2 mg/kg]) or placebo on D0 for up to six 28-day TPs. Patients in all groups were allowed prophylaxis against infusion reactions and gout flares prior to study treatment
- PROs were assessed at baseline, TP4 D0 and TP6 D28: 36-item Short Form survey (SF-36), Health Assessment Questionnaire-Disability Index (HAQ-DI), and pain visual analogue scale (VAS)
- For the PRO scores, changes from baseline in the F3D and F6D subgroups were reported as least squares mean (standard error), where an improvement in SF-36 or HAQ-DI was represented by positive or negative change, respectively. The proportion of patients reporting scores greater than or equal to the minimum clinically important difference (MCID) in each PRO was also analyzed

RESULTS

Baseline characteristics

- A total of 192 and 144 patients received the F3D and F6D of treatment, respectively
- Baseline characteristics were similar in the overall intent-to-treat (not shown) and F3D/F6D populations, and across treatment arms for the F3D/F6D subgroups (**Table 1**)

Table 1: Baseline characteristics in patients receiving F3D or F6D of NASP (ITT)

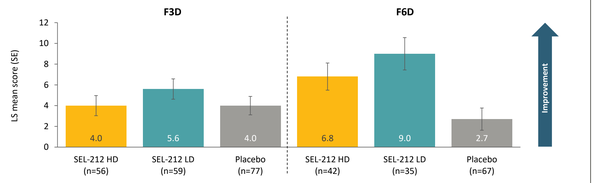
	F3D (n=192)			F6D (n=144)		
	NASP HD (n=56)	NASP LD (n=59)	Placebo (n=77)	NASP HD (n=42)	NASP LD (n=35)	Placebo (n=67)
Age, mean years (SD)	57.2 (9.1)	54.5 (10.3)	55.5 (10.4)	57.9 (8.7)	54.7 (9.9)	56.3 (9.9)
Male sex, n (%)	53 (94.6)	55 (93.2)	76 (98.7)	39 (92.9)	31 (88.6)	66 (98.5)
Mean time since gout diagnosis, years (SD)	12.9 (10.5)	12.6 (9.3)	11.1 (8.1)	13.3 (10.6)	12.1 (8.5)	11.7 (8.4)
Tophus present, n (%)	32 (57.1)	34 (57.6)	48 (62.3)	23 (54.8)	22 (62.9)	42 (62.7)
sUA, mg/dL, mean (SD)	8.7 (1.3)	8.4 (1.3)	8.6 (1.6)	8.5 (1.4)	8.5 (1.3)	8.7 (1.6)
	n=56	n=56	n=74	n=42	n=33	n=64
SF-36 PCS,[a] mean (SD)	37.9 (9.1)	36.9 (9.0)	35.9 (9.3)	39.3 (9.1)	36.7 (9.5)	36.3 (9.7)
	n=56	n=56	n=74	n=42	n=33	n=64
SF-36 MCS,[a] mean (SD)	47.0 (10.7)	47.7 (10.4)	45.9 (12.6)	47.2 (10.3)	51.0 (9.3)	45.7 (13.0)
	n=56	n=57	n=75	n=42	n=34	n=65
HAQ-DI score,[b] mean (SD)	1.0 (0.7)	1.0 (0.6)	1.0 (0.7)	0.9 (0.7)	1.0 (0.6)	1.0 (0.7)
	n=50	n=53	n=71	n=36	n=32	n=63
Pain VAS,[c] mean (SD)	38.9 (26.3)	45.6 (26.1)	44.2 (29.7)	38.3 (26.8)	45.5 (26.7)	42.9 (30.1)

[a]SF-36 is 36-item questionnaire with eight domains; each domain is scored on a scale of 0 (worst health) to 100 (best health); scores are also aggregated into PCS and MCS.[5] [b]HAQ-DI is a 20-item questionnaire, which assesses physical disability; each item is scored using a 4-point Likert scale of 0 (no disability) to 3 (completely disabled); HAQ-DI score is an average score.[6] [c]Pain VAS is scored from 0 (no pain) to 100 (extreme pain).[7]
F3D, first three doses; F6D, first six doses; HAQ-DI, Health Assessment Questionnaire-Disability Index; HD, high dose; ITT, intent-to-treat; LD, low dose; MCS, mental component summary; NASP, nanoencapsulated sirolimus plus pegadricase; PCS, physical component summary; SD, standard deviation; SF-36, 36-item Short Form survey; sUA, serum uric acid; VAS, visual analogue scale.

Change from baseline in SF-36

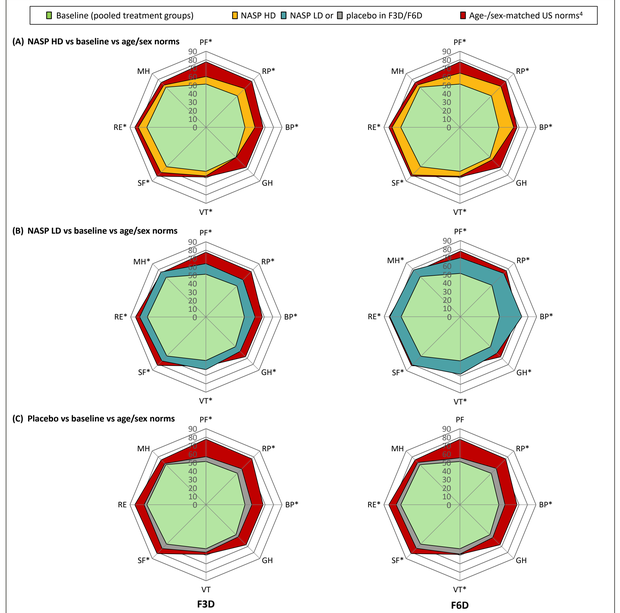
- Increases in SF-36 physical component summary (PCS) from baseline were reported with NASP HD and LD in the F3D subgroup, and further improved with NASP HD and LD in the F6D subgroup (**Figure 1**). In the placebo group, an initial improvement was observed in F3D, but then decreased with longer treatment in F6D
- The proportion of patients who reported scores ≥ MCID in SF-36 PCS with NASP HD or LD was 59%/66% in the F3D subgroup, which further improved to 67%/83% in the F6D subgroup. In the placebo group, a smaller proportion of patients reported scores ≥ MCID in the F3D subgroup (58%) compared with longer treatment in the F6D subgroup (54%)
- Increases in SF-36 mental component summary (MCS) from baseline were reported with NASP HD (2.9 [1.1]) and NASP LD (4.7 [1.1]) in the F3D subgroup, with consistent changes observed with NASP HD (2.4 [1.2]) and NASP LD (4.2 [1.5]) in the F6D subgroup. Increases in SF-36 MCS were reported with placebo in the F3D (1.6 [1.0]) and F6D (2.9 [1.0]) subgroups
- Improvements in SF-36 domain scores were reported with NASP in all domains except general health with NASP HD in the F3D subgroup (**Figure 2**). Scores ≥ MCIDs were consistently reported in the physical functioning, role physical, bodily pain, vitality, social functioning and role emotion domains. SF-36 scores met or exceeded US age-/sex-matched norms in several domains, including body pain and vitality in the F6D subgroup

Figure 1: Change from baseline in LS mean SF-36 PCS



F3D, first three doses; F6D, first six doses; HD, high-dose; LD, low-dose; LS, least squares; NASP, nanoencapsulated sirolimus plus pegadricase; PCS, physical component summary; SE, standard error; SF-36, 36-item Short Form survey.

Figure 2: Mean SF-36 domain scores with NASP HD (A), NASP LD (B) and placebo (C) in the F3D and F6D subgroups compared to baseline and age-/sex-matched normative scores

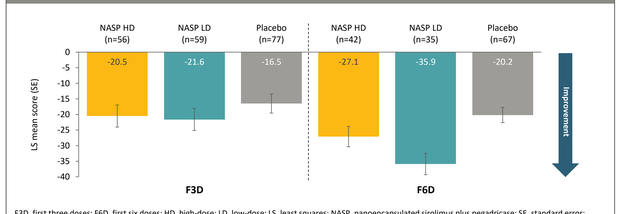


*Mean improvement sores ≥ MCID are marked with an asterisk. Domain scores are plotted from 0 (worst) at the center to 90 (best) at the outer edge. MCID is an increase of ≥5 points in mean score of any of the eight SF-36 domains at TP4 D0/TP6 D28; gridlines along axes represent changes of 10 points (equivalent to 2× MCID). Domain scores are connected by lines to facilitate recognition of patterns, and not to imply continuous scales. BP, pain; D, day; F3D, first three doses; F6D, first six doses; GH, general health; HD, high dose; LD, low dose; MCID, minimum clinically important difference; MH, mental health; NASP, nanoencapsulated sirolimus plus pegadricase; PF, physical functioning; RE, role emotion; RP, role physical; SF, social functioning; SF-36, 36-item Short Form survey; TP, treatment period; VT, vitality.

Change from baseline in HAQ-DI and pain VAS

- Reductions in HAQ-DI score (i.e. an improvement) from baseline were reported with NASP HD (−0.1 [0.1]) and NASP LD (−0.4 [0.1]) in the FD3 subgroup; HAQ-DI score further improved with continued treatment for NASP HD (−0.3 [0.1]) and remained consistent for NASP LD (−0.4 [0.1]) in the F6D subgroup. Reductions in HAQ-DI score in the placebo group were −0.1 (0.1) and −0.2 (0.1) in the F3D and F6D subgroups, respectively
- The proportions of patients who reported scores ≥ MCID in HAQ-DI (i.e. reduction of ≥0.22 points) with NASP HD or LD were 28%/42% in the F3D subgroup, which improved to 37%/51% in the F6D subgroup; scores ≥ MCID were reported in 29% of patients treated with placebo in both the F3D and F6D subgroups
  - HAQ-DI appears to capture the impact of gout on the upper extremities (vs lower extremities) and may be more relevant to patients with specific forms of gout[8]
- Similar data were reported for pain VAS score, with a trend for reduced pain with longer treatment in the F6D vs FD3 subgroup (**Figure 3**)
- The proportions of patients who reported scores ≥ MCID in pain VAS with NASP HD or LD were greater in the F6D subgroup (62%/64%) than the F3D subgroup (50%/53%); scores ≥ MCID were reported in 46% and 43% of patients treated with placebo in the F6D and F3D subgroups, respectively

Figure 3: Change from baseline in LS mean pain VAS score



F3D, first three doses; F6D, first six doses; HD, high-dose; LD, low-dose; LS, least squares; NASP, nanoencapsulated sirolimus plus pegadricase; SE, standard error; VAS, visual analogue scale.

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