Safety and Efficacy of SEL-212 in the US and ex-US Subgroups: Results from the Phase 3 DISSOLVE Studies

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CONCLUSIONS

- Response rates were statistically significantly higher in patients treated with nanoencapsulated sirolimus plus pegadricase (NASP, also referred to as SEL-212) compared to placebo in both dose groups
- Treatment with NASP for up to 6 months resulted in rapid and sustained serum uric acid (sUA) control in responding patients at TP6 with 98% and 96% reductions in sUA in responders starting at TP1 in US and ex-US, respectively.
- NASP was generally well tolerated with gout flares similar in NASP and placebo and infusion reactions were rare with no hospitalizations.
- The results support NASP as a potential novel, once-monthly treatment option that can alleviate the disease burden in patients with chronic gout refractory to conventional therapy.

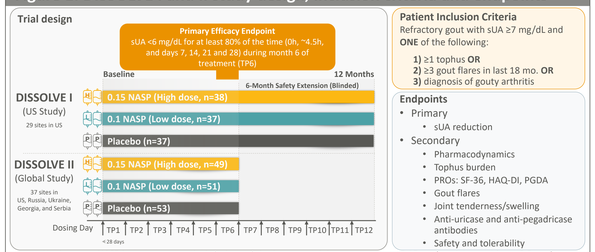
INTRODUCTION AND OBJECTIVES

- Uricase-based therapies may substantially lower sUA levels in people with gout refractory to conventional treatments also known as chronic refractory gout (CRG). However, their use is limited by immunogenicity-related efficacy reductions and infusion reactions.[1]
- NASP (also referred to as SEL-212) is a novel, once-monthly, two-component therapy consisting of pegadricase (a pegylated uricase, also SEL-037), which converts uric acid to soluble allantoin resulting in reduced serum uric acid, and nanoencapsulated sirolimus (NAS, also SEL-110), an mTOR inhibitor which provides targeted antigen-specific immune tolerance to pegadricase through the induction of regulatory T cells.[2]
- Administration of NAS followed by pegadricase mitigates uricase immunogenicity in clinical studies, thereby enabling rapid, sustained, and clinically meaningful sUA control without the need for additional broad immunosuppression.[3-5]
- The Phase 3 DISSOLVE study program investigated the efficacy and safety of NASP in patients with chronic refractory gout enrolling patients in two parallel studies.[2]
- This analysis aims to describe the pooled data and outcomes from US participants with those of other participants from Eastern Europe (ex-US) enrolled across the DISSOLVE studies.

METHODS

- In DISSOLVE I and II (Figure 1), participants were randomized 1:1:1 between two doses of NASP (high-dose [HD]: sequential infusions of 0.15 mg/kg NAS and 0.2 mg/kg pegadricase; low-dose [LD]: sequential infusions of 0.10 mg/kg NAS and 0.2 mg/kg pegadricase) and placebo.
- For the analysis of the pre-specified US and ex-US subgroups, pooled data from TP1–6 were evaluated for primary and secondary endpoints and safety outcomes.
- Patients who discontinued study drug were still followed for the efficacy endpoint and included in the intent-to-treat population.

Figure 1: DISSOLVE I and II study design, inclusion criteria and endpoints[2]



h, hour; H, high-dose NASP included sequential infusions of sirolimus-containing nanoparticles 0.15 mg/kg and pegadricase 0.2 mg/kg; HAQ-DI, Health Assessment Questionnaire-Disability Index; IV, intravenous; L, low-dose NASP included sequential infusions of sirolimus-containing nanoparticles 0.1 mg/kg and pegadricase 0.2 mg/kg; mo., months; NASP, nanoencapsulated sirolimus plus pegadricase; PGDA, Provider Global Assessment of Disease Activity; PRO, patient-reported outcome; sUA, serum uric acid; SF-36, Short-form 36; TP, treatment period.

RESULTS

Patient disposition and baseline characteristics

- Among 265 patients in DISSOLVE I and II, 168 patients were from the US (Table 1).
- sUA level, participants with tophi, and tender joints were similar between treatment groups at enrollment.
- Common comorbidities at baseline are presented in Table 2.

Table 1: Baseline demographics and disease characteristics in US subgroup

Intent-to-treat set	High dose (N=52)	Low dose (N=55)	Placebo (N=61)
Age, years, mean (SD)	54.2 (10.9)	54.6 (10.2)	53.9 (10.1)
Age ≥50 years, n (%)	35 (67.3)	38 (69.1)	38 (62.3)
BMI, kg/m^2, mean (SD)	35.1 (6.4)	34.6 (7.5)	33.6 (6.3)
Gender, male, n (%)	48 (92.3)	51 (92.7)	61 (100.0)
Race, n (%)			
White	39 (75.0)	40 (72.7)	37 (60.7)
Black or African American	11 (21.2)	11 (20.0)	15 (24.6)
Asian	0	2 (3.6)	4 (6.6)
Native Hawaiian or other Pacific Islander	2 (3.8)	1 (1.8)	0
Other	0	1 (1.8)	5 (8.2)
Time since gout diagnosis, years, mean (SD)	14.2 (10.6)	13.4 (10.0)	12.4 (8.9)
eGFR, mL/min/1.73 m^2, mean (SD)	69.4 (17.3)	75.7 (19.0)	74.0 (17.4)
sUA level at screening, mg/dL, mean (SD)	9.0 (1.4)	8.6 (1.0)	8.8 (1.3)
Participants with tophi at baseline, n (%)	31 (59.6)	32 (58.2)	39 (63.9)
Tender joints, n	50	49	57
Mean (SD)	2.9 (6.2)	4.0 (8.5)	3.0 (8.9)
Swollen joints, n	49	49	57
Mean (SD)	2.0 (4.0)	2.7 (6.3)	1.4 (3.5)

BMI, body mass index; eGFR, estimated glomerular filtration rate; SD, standard deviation.

Table 2: Baseline comorbidities in the US subgroup

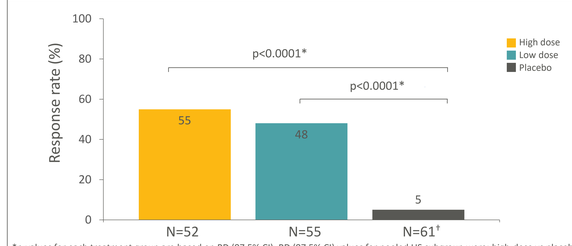
	High dose (N=52)	Low dose (N=55)	Placebo (N=61)
Any comorbidity at baseline*	52 (100)	55 (100)	61 (100)
Hypertension	32 (61.5)	33 (60.0)	40 (65.6)
Hyperlipidemia	21 (40.4)	15 (57.3)	20 (32.8)
Sleep apnea syndrome	11 (21.2)	2 (3.6)	4 (6.6)
Obesity	8 (15.4)	11 (20.0)	6 (9.8)
Diabetes mellitus†	8 (15.3)	6 (10.9)	4 (6.5)
Dyslipidemia	5 (9.6)	4 (7.3)	2 (3.3)
Hypertriglyceridemia	2 (3.8)	5 (9.1)	3 (4.9)

*Comorbidities in ≥20% in at least one subgroup. Patients may have more than one comorbidity recorded.
† Includes diabetes mellitus and diabetes mellitus type 2.

Response to treatment (primary endpoint)

- Response rates were statistically significantly higher in patients treated with NASP compared to placebo in both dose groups in US patients (Figure 2).

Figure 2: Response rate in the US in DISSOLVE

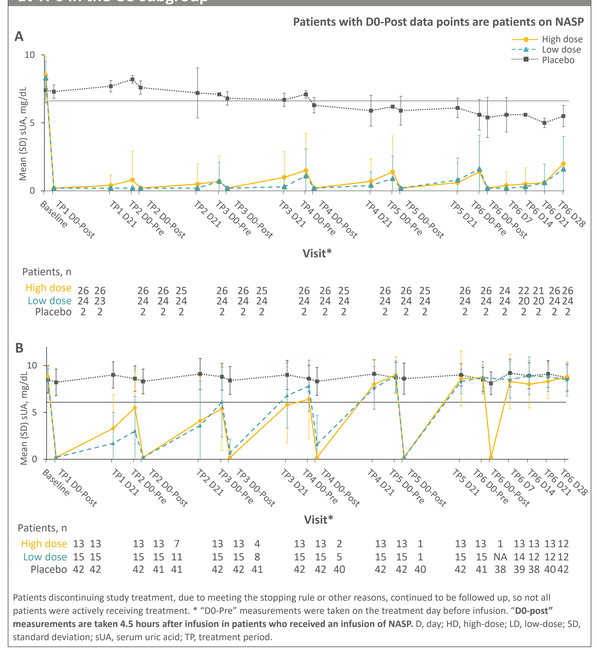


*p-values for each treatment group are based on RD (97.5% CI); RD (97.5% CI) values for pooled US subgroup were: high-dose vs placebo: 49% (31%, 67%); low-dose vs placebo: 42% (25%, 60%). Missing response data in TP6 were multiple imputed. †Several studies have investigated differences in placebo response rates and have found that geographical setting of clinical studies impacts rates of placebo response.[6-8] One study identified a significant negative association between placebo response and gross national product of the recruiting country, and which may be explained by more limited access to healthcare and innovative therapies.[6] CI, confidence interval; RD, risk difference; TP, treatment period.

sUA control

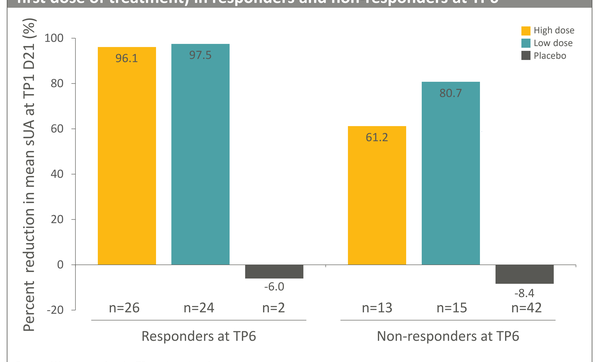
- NASP treatment resulted in rapid and sustained sUA control in patients who were responders at TP6, starting with the first dose (TP1) of NASP (Figures 3A,B).
- Immediately following the first dose of NASP (TP1 D0-Post) mean (SD) sUA levels decreased to 0.2 (0) mg/dL in the HD and LD for both, responders and non-responders at TP6. In the placebo group, mean (SD) sUA following the first dose (TP1 D0-Post) remained similar to baseline for placebo responders (7.3 [0.49] mg/dL) and for placebo in non-responders (8.4 [1.42] mg/dL) (Figure 3A, B).
- After the first month of therapy (TP1 D21), mean sUA (SD) was reduced by 96.1% (7.65) from baseline to TP1 D21 in HD and by 97.5% (0.41) in LD in responders at TP6, and these reductions were maintained through TP6 (Figure 4).
- In patients who were non-responders at TP6, sUA initially decreased to a similar degree as responders at TP6 (Figures 3B, 4). As patients came off NASP an increase in sUA was observed.

Figure 3: Mean (SD) sUA over time in responders (A) and non-responders (B) at TP6 in the US subgroup



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. * "D0-Pre" measurements were taken on the treatment day before infusion. "**D0-post" measurements are taken 4.5 hours after infusion in patients who received an infusion of NASP.** D, day; HD, high-dose; LD, low-dose; SD, standard deviation; sUA, serum uric acid; TP, treatment period.

Figure 4: Percent reduction from baseline mean sUA levels to TP1 D21 (after first dose of treatment) in responders and non-responders at TP6



D, day; sUA, serum uric acid; TP, treatment period.

Safety

- Most patients (82.7%, 74.5%, and 68.9% 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, hypertriglyceridemia, and stomatitis (Table 3). Mild to moderate adverse events of stomatitis, oral ulcer, and aphthous ulcers did not lead to any withdrawals.
- Gout flares were similar among patients receiving high-dose NASP compared to those receiving placebo.

Table 3: AESI affecting ≥5% in at least one group in the US subgroup

Safety Set, patients, n (%)	High dose (N=52)	Low dose (N=55)	Placebo (N=61)
≥1 AESI*	40 (76.9)	40 (72.7)	35 (57.4)
Gout flare	29 (55.8)	29 (52.7)	32 (52.5)
Infections (including viral)	16 (30.8)	12 (21.8)	11 (18.0)
COVID-19	5 (9.6)	3 (5.5)	3 (4.9)
Infusion-related reaction (24h)	8 (15.4)	6 (10.9)	2 (3.3)
IR (1h) incl. Anaphylaxis†	3 (5.8)	2 (3.6)	0
Anaphylaxis	2 (3.8)	2 (3.6)	0
Stomatitis‡	7 (13.5)	3 (5.5)	0
Hypertriglyceridemia	3 (5.8)	1 (1.8)	1 (1.6)

*AESIs in at least 5% in any treatment arm of the US subgroup. AESIs included gout flares, infections, malignancies, viral infections, interstitial lung disease, stomatitis, infusion-related reactions including anaphylaxis, thrombosis, and the following laboratory tests, if deemed clinically significant by the investigator: hyperlipidemia, worsening of renal function tests, proteinuria, and leukopenia. †IRs within 1h were also included in IRs within 24h. ‡ Stomatitis includes events of mouth ulceration and aphtous ulcer.
AE, adverse event; AESI, adverse event of special interest; IR, infusion reaction; TEAE, treatment-emergent adverse event.

Summary of results in ex-US patients

- The ex-US subgroup included 97 treated patients, including 35, 33, and 29 patients in the HD, LD and placebo arms, respectively.
- Age, proportion of male patients and sUA concentrations in the ex-US subgroup were similar to US subgroup at enrollment. The proportion of non-white patients and BMI were lower in the ex-US subgroup compared to the US subgroup.
- Response rates were 45% in HD, 36% in LD, and 15% in the placebo arm.
- Results for changes in sUA over time in responders and non-responders for the ex-US subgroup were similar to those for the US subgroup.
- Similar sUA reductions in responder patients were seen as in the US subgroup, with a 96.3% (5.0) mean (SD) reduction from baseline to TP1 D21 in HD, and 88.9% (29.5) in LD.
- Upon study entry, patients in the ex-US subgroup had mean (SD) 14.1 (11.8) tender joints in HD (n=35), 14.0 in LD (33), and 16.5 in placebo (n=29). At TP4 this was reduced to 5.4 (6.9) in HD, 5.0 (4.3) in LD and 10.2 (7.3) in placebo. At TP6, the mean (SD) number of tender joints was 5.1 (5.4), 3.2 (3.4), and 10.4 (10.5) in HD, LD, and placebo, respectively.
- Overall, the safety profile of NASP was similar in ex-US patients as in US patients, with 1 (2.9%) of patients in HD and 2 (6.1%) in LD reporting infusion-related AEs within 24 hours of treatment.

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