Impact of Anti-drug Antibodies on the Efficacy of SEL-212 in Patients with Chronic Gout Refractory to Conventional Therapy

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CONCLUSIONS

- In the DISSOLVE studies, nanoparticles containing sirolimus (NAS) mitigated anti-drug antibody (ADA) formation for up to 12 months of treatment, allowing for serum uric acid (sUA) control in patients with chronic gout refractory to conventional therapy treated with nanoencapsulated sirolimus plus pegadricase (NASP).
- High-dose (HD) NAS appeared to be more effective at preventing the formation of ADAs compared to low-dose (LD) NAS.
- Anti-uricase ADAs were the most common ADAs formed, as previously reported.[1] These appeared to be the most relevant for loss of sUA control.
- Infusion reactions (IRs) were few and generally correlated with the presence of anti-uricase ADAs.
- The immunogenicity data from DISSOLVE supports NASP as a promising treatment option for patients with chronic refractory gout.
- Further analysis exploring the relationship of anti-uricase titer and efficacy are ongoing.

INTRODUCTION

- NASP (also referred to as SEL-212) is a novel once-monthly, investigational, two-component infusion therapy consisting of pegadricase (formerly SEL-037, a pegylated uricase) and targeted immune-tolerizing NAS (formerly SEL-110), for the treatment of patients with chronic gout refractory to conventional therapy.
- Uricases are an effective treatment option in gout,[2] but their use is limited. This is partly due to development of ADAs, which can restrict the sUA response to therapy and can predispose patients to IRs.[3] Hence, mitigation of ADAs is a key step in maintaining patients on treatment.
- The nanoparticles in NASP deliver sirolimus in a targeted manner to antigen-presenting cells (APCs), which inhibits the mammalian target of rapamycin (mTOR) pathway, to induce a tolerogenic phenotype. Infusing pegadricase after NAS allows pegadricase antigen presentation in the context of APCs with a tolerogenic phenotype, which promotes the induction of antigen-specific regulatory T cells and inhibits ADA formation.[4]
- Mitigation of ADA formation by NAS has been demonstrated in a Phase 2 study with NASP. The most commonly detected ADAs in the study were anti-uricase ADAs, and maintaining low anti-uricase titers enabled sustained sUA control.[1]

OBJECTIVES

- This investigation aims to describe ADAs formed in response to NASP treatment in the DISSOLVE Phase 3 trials and their associations with IRs and treatment outcomes.

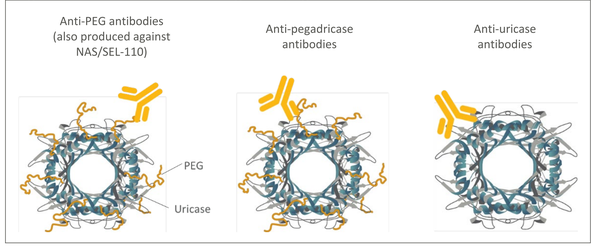
METHODS

- The DISSOLVE I (NCT04513366) and DISSOLVE II (NCT04596540) Phase 3 trials investigated efficacy and safety of NASP.
- In both studies, participants were randomized 1:1:1 between high-dose (HD) NASP (sequential infusions of 0.15 mg/kg NAS and 0.2 mg/kg pegadricase), low-dose (LD) NASP (sequential infusions of 0.10 mg/kg NAS and 0.2 mg/kg pegadricase), and placebo.
- NASP or placebo were administered every 28 days for up to 6 treatment periods (TPs) in DISSOLVE II, or up to 12 TPs in DISSOLVE I.
- For the pooled DISSOLVE population, data up to TP6 from both studies were combined. For data up to TP12, results from DISSOLVE I were analyzed separately.
- Patients were considered treatment ADA-positive if they were (1) ADA-negative at baseline and became ADA-positive at any time post-baseline or, (2) ADA-positive at baseline with a post-baseline titer greater or equal to (a) 4-fold the baseline titer for anti-PEG or anti-pegadricase antibodies, or (b) 9-fold the baseline titer for anti-uricase antibodies.

METHODS (cont'd)

- Titers of ADAs against polyethylene glycol (PEG), uricase, and pegadricase, i.e. ADAs recognizing specifically the PEGylated uricase, were measured using immunoassays at baseline (BL) and during each TP (Figure 1).
- Relationships of ADAs with sUA were analyzed from BL to TP6 for the pooled DISSOLVE population who received NASP; possible associations with ADAs were investigated for all IRs.
- Infusion reactions were defined as a study drug-related adverse event that occurred during or after completion of study drug infusion (Rheumatology Common Criteria, V2.0). The observation time was defined as 1 h following the completion of the pegadricase infusion.

Figure 1: Antibodies formed against pegadricase (SEL-037)



RESULTS

Patient demographics and baseline characteristics

- In the pooled DISSOLVE intention-to-treat population, 87 patients received HD NASP, 88 received LD NASP, and 90 received placebo.
- The baseline patient demographics and disease characteristics for patients who received NASP are outlined in Table 1.

Table 1: Baseline patient demographics and disease characteristics.

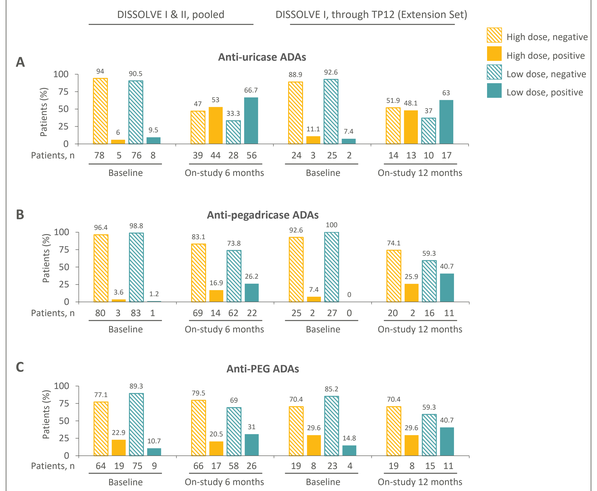
	High dose (N=87)	Low dose (N=88)
Age, years, mean (SD)	55.2 (10.8)	54.2 (10.6)
Age ≥50 years, n (%)	62 (71.3)	58 (65.9)
BMI, kg/m^2, mean (SD)	33.5 (5.8)	32.9 (6.8)
Gender, male, n (%)	82 (94.3)	84 (95.5)
Race, white, n (%)	74 (85.1)	73 (83.0)
Time since gout diagnosis, years, mean (SD)	12.3 (9.7)	11.7 (9.3)
eGFR, mL/min/1.73 m^2, mean (SD)	72.5 (17.3)	76.0 (21.6)
sUA level at screening, mg/dL, mean (SD)	8.9 (1.3)	8.9 (1.3)
Participants with tophi at baseline, n (%)	55 (63.2)	55 (62.5)
Any comorbidity at baseline, n (%)	87 (100)	88 (100)
Hypertension	55 (63.2)	51 (58.0)
Hyperlipidemia	29 (33.3)	22 (25.0)
Obesity	14 (16.1)	12 (13.6)
Dyslipidemia	13 (14.9)	15 (17.0)

BMI, body mass index; eGFR, estimated glomerular filtration rate; n, number; SD, standard deviation; sUA, serum uric acid.

Incidence of ADA formation

- In the pooled DISSOLVE population, fewer patients in the HD group developed ADAs compared to the LD group (Figure 2).
- Consistent with previous findings, anti-uricase ADAs were the most frequent ADAs observed after 6 months on study in the pooled population, and after 12 months on study in DISSOLVE I (Figure 2A). However, formation of anti-uricase ADAs did not prevent response to therapy, as 51% and 43% of patients in the HD and LD groups, respectively, met the primary endpoint,[5] despite some of these patients developing anti-uricase ADAs.

Figure 2: Cumulative percent of patients on-treatment positive or negative for (A) anti-uricase ADAs, (B) anti-pegadricase ADAs, or (C) anti-PEG ADAs.

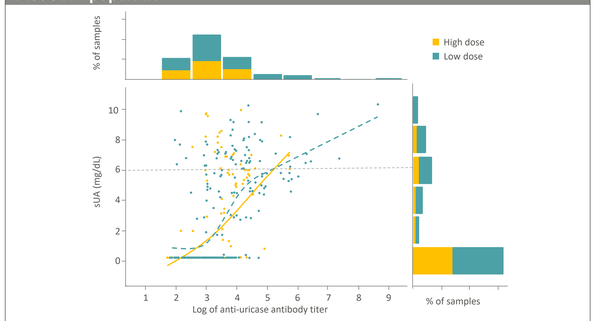


All patients with a non-missing baseline and at least 1 non-missing post-baseline assessment were considered at risk of developing ADAs. The baseline data show the proportion of patients who were negative versus positive for the respective ADA. Within the patients at risk of developing ADAs, patients were considered ADA-positive on-study up to 6 months if (1) ADA-negative at baseline and became ADA-positive at any time post-baseline or, (2) ADA-positive at baseline and with a post-baseline titer greater or equal to (a) 4-fold the baseline titer for anti-PEG or anti-pegadricase antibodies, or (b) 9-fold the baseline titer for anti-uricase antibodies. Patients who did not meet any of the criteria above were considered treatment ADA-negative. Patients in DISSOLVE I who completed TP6 were eligible to enter the 6-month blinded extension phase (TP7-12) on the same treatment for up to an additional 6 months (Extension Set).
ADA, anti-drug antibody; PEG, polyethylene glycol; TP, treatment period.

Comparison between ADA titers and sUA levels

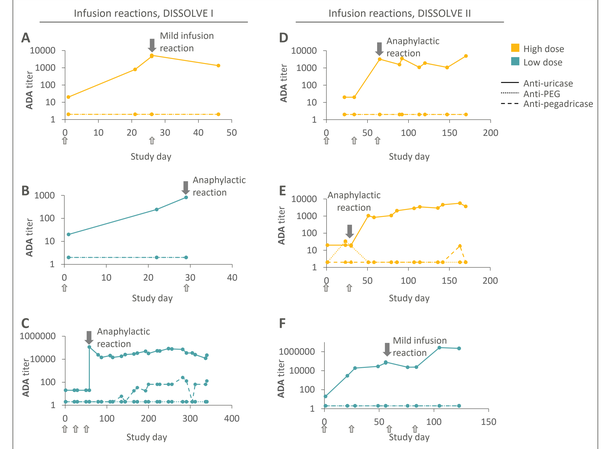
- In general, low anti-uricase titers did not impact sUA control as evidenced by the data points in Figure 3. However, high anti-uricase titers were associated with an observed loss of sUA control.
- Anti-PEG and anti-pegadricase antibodies were less frequent as these antibodies appeared to be transient in nature. In addition, the majority of the positive antibody samples coincided with the presence of anti-uricase antibodies and were often detected after the induction of anti-uricase antibodies.
- Consistent with previous findings, anti-uricase titers appeared to be the most relevant for loss of sUA control.[1]

Figure 3: On-treatment anti-uricase ADA titers and sUA levels in the pooled DISSOLVE population.



All on-treatment assessments are included. Histograms depict the number of assessments from patients in the HD (yellow) and LD (green) groups at a given sUA or anti-uricase titer level. Solid yellow and dashed green curves represent smoothing curves fitted by local regression (LOESS) within the HD and LD treatment arms, respectively. Dashed grey line represents 6 mg/dL reference line. Multiple assessments with low titer/low sUA measurements are included.
ADA, anti-drug antibody; sUA, serum uric acid; TP, treatment period.

Figure 4: Titer of ADAs during the study period and time of infusion reactions observed within 1 hour of pegadricase infusion in (A–C) DISSOLVE I and (D–F) DISSOLVE II.



Titer of ADAs during the study period is shown by the lines, time of infusion reactions by the dark grey arrows with infusion reaction severity listed next to the arrow, and time of NASP infusions by the light grey arrows below the graphs. Baseline value for anti-uricase ADA titers is 1:20; baseline values for anti-PEG and anti-pegadricase ADA titers are 1:2. Treatment for anaphylactic reactions were as follows: The patient in (B) recovered with epinephrine, intravenous (IV) diphenhydramine, methylprednisolone and fluids, and neither hospitalization nor resuscitation were required. The patient in (C) recovered with methylprednisolone, acetaminophen, and diphenhydramine. The patient in (D) recovered with IV diphenhydramine, acetaminophen, and methylprednisolone. The patient in (E) recovered with diphenhydramine, prednisone, IV ondansetron, and IV methylprednisolone. The mild IR in Patient in (F) resolved after treatment with diphenhydramine. ADA, anti-drug antibody; PEG, polyethylene glycol.

Relationship between ADA titers and the incidence of infusion reactions

- In the pooled DISSOLVE population, while 53% and 67% of patients on HD and LD NASP were positive for anti-uricase ADAs after 6 months, respectively (Figure 2), only seven patients experienced IRs meeting hypersensitivity and allergic reaction criteria (Figure 4).
- All IRs occurred within the first three infusions.
- Three patients in each group had IRs within an hour of pegadricase administration, which coincided with increases in anti-uricase titers in all except for one patient (Figure 4E). No increases in anti-PEG or anti-pegadricase ADA titers were detected at the time of the IRs (Figure 4A-F).
- One patient had an IR to the NAS component which occurred during the patient's first exposure (data not shown).

References

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