Evaluation of DISSOLVE I/II Stopping Rules for Nanoencapsulated Sirolimus Plus Pegadricase (NASP) in Patients With Uncontrolled Gout

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CONCLUSIONS

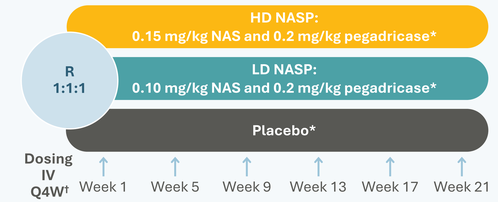
In this pooled *post hoc* analysis of the Phase 3 DISSOLVE I and II trials:

- The higher NAS dose resulted in fewer stopping-rule events; the protocol-defined stopping rule was met by twice as many LD versus HD NASP patients across the pooled 24-week main study period
- Regardless of dose, most stopping-rule events occurred early in treatment; almost half of HD NASP patients who met the rule did so after the first dose, and over half of LD NASP patients by the second dose
- The conservative stopping rule threshold of >1 mg/dL after the first dose of NASP resulted in 15 patients meeting the rule where only 7 (HD and LD) had an SU >6 mg/dL and the remainder had an SU between 1 to ≤6 mg/dL
- Although more patients on HD compared to LD NASP were ADA-negative when meeting the stopping rule, when present, anti-uricase antibodies were the most frequently detected ADA among patients meeting the stopping rule

INTRODUCTION

- Uricase therapies are highly effective at lowering serum urate (SU) in patients with uncontrolled gout (UG), but anti-drug antibodies (ADA) frequently develop, reducing urate-lowering efficacy and increasing the risk of infusion reactions[2,3]
- Nanoencapsulated sirolimus (NAS) plus pegadricase (P), NASP, is a novel, investigational, every 4-week, 2-component infusion therapy that reduces SU in patients with UG; the NAS component is a biodegradable, tolerogenic nanoparticle that encapsulates sirolimus, inducing antigen-specific regulatory T cells and mitigating ADAs to co-administered pegadricase, a pegylated uricase derived from *C. utilis*[3,4]
- In the Phase 3 DISSOLVE I and DISSOLVE II studies (NCT04513366, NCT04596540; **Figure 1**), NASP significantly reduced SU versus placebo (PBO) and was generally well tolerated.[4] Anti-uricase ADAs were more frequent compared to anti-PEG and anti-pegadricase ADAs, and associated with loss of SU control[3,4]
- Both trials required discontinuation of NASP as soon as SU control was lost, limiting continued exposure to minimize infusion reaction risk and avoid drug administration without benefit.[5] Patients were identified through a protocol-defined treatment-stopping rule[4]

Figure 1. DISSOLVE I and DISSOLVE II study design and objective of this analysis



DISSOLVE I and II inclusion criteria:
- Adults with uncontrolled gout (UG)
  - ≥3 gout flares within 18 months prior to screening, **OR** ≥1 tophus, **OR** current diagnosis of gouty arthritis‡
- Failure to normalize SU levels and control symptoms with XOIs (or contraindication to XOIs)
- Screening SU level ≥7 mg/dL

Primary endpoint:
- Percentage of patients with an SU response (SU levels <6 mg/dL for ≥80% of time during Weeks 21–24 of therapy)

Select secondary endpoints:
- SU reduction, change in number of tender and swollen joints, change in SF-36 physical component summary and HAQ-DI scores, assessed at baseline and Week 24
- Safety/tolerability

This *post hoc* analysis describes the frequency of stopping rule events and associated ADA status among patients receiving NASP in the pooled DISSOLVE I and II ITT population who met the stopping rule by Week 24

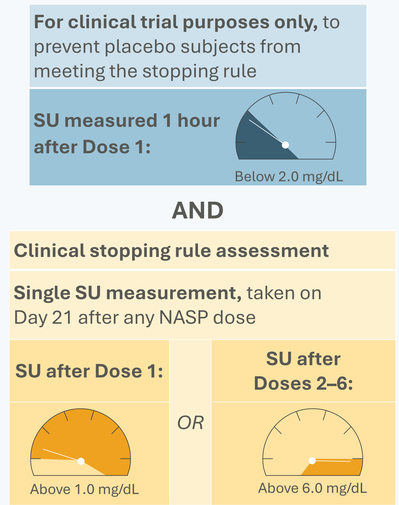
* Administered as sequential infusions; for patients who received NASP, pegadricase infusion began within 30 minutes of completion of NAS infusion. † Arrows indicate time of study drug administration. ‡ Signs or symptoms of persistent synovitis ascribed to gout as judged by the enrolling investigator.
Gout flare prophylaxis (colchicine and non-steroidal anti-inflammatory drugs) and premedication to mitigate occurrence of infusion reactions were provided to all patients unless contraindicated. ADA, anti-drug antibody; HAQ-DI, Health Assessment Questionnaire-Disability Index; HD, high dose; ITT, intent-to-treat; IV, intravenous; LD, low dose; NAS, nanoencapsulated sirolimus; NASP, nanoencapsulated sirolimus plus pegadricase; Q4W, every 4 weeks; R, randomization; SF-36, 36-Item Short Form Health Survey; SU, serum urate; UG, uncontrolled gout; XOI, xanthine oxidase inhibitor.

RESULTS

Stopping rule events

- The stopping rule (SR) was defined as follows: (1) SU of <2.0 mg/dL measured 1 hour after infusion of the first dose of the study drug (to prevent placebo patients from meeting the stopping rule) and (2) SU of >1.0 mg/dL on Day 21 after the first dose of treatment or >6.0 mg/dL on Day 21 after any subsequent dose of treatment (**Figure 2**)
- The SR was met by 20 of 87 patients receiving HD NASP (23.0%) and 38 of 88 receiving LD NASP (43.2%) over the course of DISSOLVE I and II. Baseline demographics and disease characteristics were similar to those reported for the overall DISSOLVE I and II population[5] (**Table 1**)
  - 9 patients receiving HD NASP and 6 patients receiving LD NASP met the rule at Day 21 after Dose 1
  - 11 patients receiving HD NASP and 31 receiving LD NASP met the rule at Day 21 after subsequent doses

Figure 2. DISSOLVE I and II stopping rule



NASP, nanoencapsulated sirolimus plus pegadricase; SU, serum urate.

Table 1. Baseline characteristics in NASP-treated patients who met the stopping rule in DISSOLVE I and II

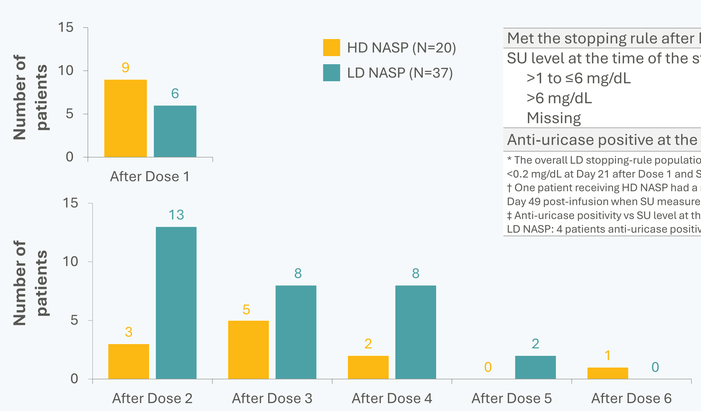
	HD NASP (N=20)	LD NASP (N=38)
Patient characteristics		
Age, years, mean (SD)	56.5 (11.8)	54.4 (11.2)
BMI, kg/m^2, mean (SD)	31.9 (6.0)	32.2 (7.1)
Gender, male, n (%)	19 (95.0)	38 (100)
Race, n (%)		
White	18 (90.0)	31 (81.6)
Black or African American	1 (5.0)	3 (7.9)
Other*	1 (5.0)	4 (10.5)
Disease characteristics		
Years since gout diagnosis, mean (SD)	15.7 (11.3)	11.5 (10.6)
eGFR, mL/min/1.73m^2, mean (SD)	72.9 (19.0)	74.5 (22.4)
SU at baseline, mg/dL, mean (SD)	8.7 (1.4)	8.5 (1.7)
Patients with tophi at baseline, n (%)	17 (85.0)	24 (63.2)

* Including Native Hawaiian or other Pacific Islander, HD NASP, n=1; LD NASP, n=1; Asian, LD NASP, n=2; other, LD NASP, n=1.
BMI, body mass index; eGFR, estimated glomerular filtration rate; HD, high-dose; LD, low-dose; NASP, nanoencapsulated sirolimus plus pegadricase; SD, standard deviation; SU, serum urate.

Stopping-rule stringency and anti-uricase antibody status

- Compared with HD NASP, twice as many patients receiving LD NASP met the SR, with most events occurring early in the treatment course in both treatment arms (**Figure 3**)
- Among the patients who met the SR after Dose 1, SU levels were as follows:
  - SU >1 to ≤6 mg/dL: 5/9 HD (55.6%) representing 5.7% of all HD NASP (n=87) and 2/6 LD patients (33.3%) representing 2.3% of all LD NASP (n=88) patients
  - SU >6 mg/dL: 3/9 HD (33.3%) representing 3.4% of all HD NASP (n=87) and 4/6 LD patients (66.7%) representing 4.5% of all LD NASP (n=88) patients
- Among patients who met the SR, anti-uricase antibodies were observed in 73.7% of patients, compared with anti-PEG (19.6%) and anti-pegadricase antibodies (5.4%). This pattern was consistent across both dose groups
  - However, SR events did not uniformly coincide with anti-uricase antibody positivity at the stopping-rule assessment: after Dose 1, 3/9 HD (33.3%) and 2/6 LD patients (33.3%) were anti-uricase negative while after Doses 2–6, 5/11 HD (45.5%) and 5/31 LD patients (16.1%) were anti-uricase negative (1 LD patient had a missing anti-uricase measurement)
  - In those patients who met the SR and were anti-uricase antibody negative, neither anti-PEG nor anti-pegadricase antibodies were detected

Figure 3. Temporal distribution of patients meeting the SR and anti-uricase antibody status at the time of meeting the SR in DISSOLVE I and II



	HD NASP	LD NASP
Met the stopping rule after Dose 1, n	9	6*
SU level at the time of the stopping rule, n (%)		
>1 to ≤6 mg/dL	5 (55.6)	2 (33.3)
>6 mg/dL	3 (33.3)	4 (66.7)
Missing	1 (11.1)†	0
Anti-uricase positive at the time of meeting the stopping rule, n (%)‡	6/9 (66.7)	4/6 (66.7)

* The overall LD stopping-rule population (n=38) includes one additional patient who is not included in the dose-specific summaries (n=37). This patient had SU <0.2 mg/dL at Day 21 after Dose 1 and SU 8.2 mg/dL at a later assessment, without receiving Dose 2. The study records classified this event as occurring after Dose 1.
† One patient receiving HD NASP had a missing SU assessment at the Day 21 visit after Dose 1 but was judged to meet the stopping rule after an unscheduled visit Day 49 post-infusion when SU measured 7.3 mg/dL.
‡ Anti-uricase positivity vs SU level at the time of meeting the stopping rule: HD NASP: 6 patients anti-uricase positive, 4/6 with SU >1 to ≤6, 2/6 with SU >6; LD NASP: 4 patients anti-uricase positive, 2/4 with SU >1 to ≤6, 2/4 with SU >6.

	HD NASP	LD NASP
Met the stopping rule after Dose 2–6, n	11	31*
Anti-uricase positive at the time of meeting the stopping rule, n (%)	6/11 (54.5)	26/31 (83.9)

* The overall LD stopping-rule population (n=38) includes one additional patient who is not included in the dose-specific summaries (n=37). This patient had SU <0.2 mg/dL at Day 21 after Dose 1 and SU 8.2 mg/dL at a later assessment, without receiving Dose 2. The study records classified this event as occurring after Dose 1.

HD, high-dose NASP; LD, low-dose NASP; NASP, nanoencapsulated sirolimus plus pegadricase; SR, stopping rule; SU, serum urate.

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Disclosures

P.P. Khanna: Grant/research: Arthrosi, Crystalys; Consultant: Amgen, Sobi. **A. Kivitz:** Consultant or speaker/honoraria: AbbVie; Stock options or bond holdings: Amgen; Consultant: EcoR1, Grünenthal, Innovaderm, SynAct; Advisor/review panel member or consultant: Fresenius Kabi, Takeda, UCB; Scientific expert: Genzyme; Consultant or stocks/bonds: Gilead; Speaker/honoraria: Sanofi/Regeneron; Advisor/review panel member or stocks/bonds: Novartis; Speaker/honoraria or stocks/bonds: Pfizer; Educational: Prime. **P. Parsa:** Employee and/or shareholder: Sobi. **B. Peace:** Contractor: Employee of Veramed contracted to Sobi. **B. Desai:** Employee and/or shareholder: Sobi. **R. Azeem:** Stock options or bond holdings in a for-profit corporation or self-directed pension plan: Sobi; Employee and/or shareholder: Sobi. **S. Leung:** Employee and/or shareholder: Sobi. **H.S.B. Baraf:** Consultant: Sobi, Olatec, Pacira.

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