Pooled Results From the Phase 3 Trials of Nanoencapsulated Sirolimus Plus Pegadricase in Uncontrolled Gout: Characterization of Adverse Events of Special Interest

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CONCLUSIONS

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

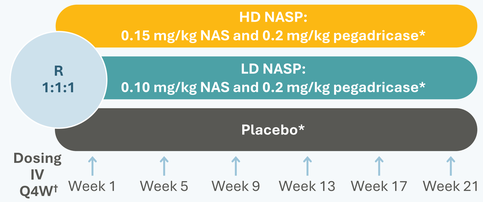
- Gout flares occurred at similar rates across treatment arms and were mostly mild or moderate with over 50% of patients being flare-free for the entire study period
- Infections were predominantly mild to moderate and viral or bacterial in origin, and the majority were assessed as unrelated to study drug. No mycobacterial, fungal or herpes zoster infections were observed
- Sirolimus-associated events, including stomatitis, anemia and rash, occurred at lower rates than published oral sirolimus data
- Stomatitis occurred in patients treated with NASP, but most were not assessed as related to study drug per the investigator and none led to study drug discontinuation

These findings support NASP as a novel, generally well-tolerated treatment option for patients with uncontrolled gout

INTRODUCTION

- Gout is the most common form of inflammatory arthritis[1] and is caused by monosodium urate crystal deposition in joints and soft tissues when serum urate (SU) exceeds the saturation threshold,[2] that can lead to systemic chronic inflammation, progressive joint damage, and impaired physical functioning[2,3]
- Persistent SU elevation ≥6 mg/dL despite oral urate-lowering therapy is associated with significant impacts on quality of life and increased healthcare resource utilization[4,5]
- Nanoencapsulated sirolimus (NAS) plus pegadricase (P), NASP, is a novel, investigational, every 4-week, 2-component infusion therapy that consists of targeted immunomodulating NAS co-administered with pegadricase (a pegylated uricase), which converts uric acid to soluble allantoin, resulting in profoundly reduced SU[6]
- In the Phase 3 DISSOLVE I and DISSOLVE II studies (**Figure 1**), NASP significantly reduced SU versus placebo in participants with uncontrolled gout (UG) and was generally well tolerated[6]
- The most common adverse events of special interest (AESI) (reported in >5% of treated patients) were gout flares, infections, stomatitis, and infusion-related adverse events (AEs) within 24 hours.[6] Previous analyses have described patient narratives for infusion reactions[7]

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 reports outcomes in patients from the pooled DISSOLVE I and II ITT population who received ≥1 dose of treatment:
- 3 AESIs (gout flares, infections and stomatitis)
- Other AEs associated with sirolimus evaluated and classified according to RCTC, v2.0[8]

* 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. AE, adverse event; AESI, adverse event of special interest; 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; RCTC, Rheumatology Common Toxicity Criteria; SF-36, 36-Item Short Form Health Survey; SU, serum urate; UG, uncontrolled gout; XOI, xanthine oxidase inhibitor.

RESULTS

Gout flares

- Gout flares were the most common AESI and occurred at similar rates across the NASP and placebo (PBO) arms (**Table 1**). Most flares were mild or moderate (**Figure 2**)
- Severe flares occurred in 3 patients receiving HD NASP, 4 receiving LD NASP, and 1 patient on PBO (**Figure 2**). Of these, 1 in each NASP arm was considered related to study drug; the remaining severe flares were possibly related or not considered study drug-related

Table 1. Select AESIs (pooled Safety Set, N=265)

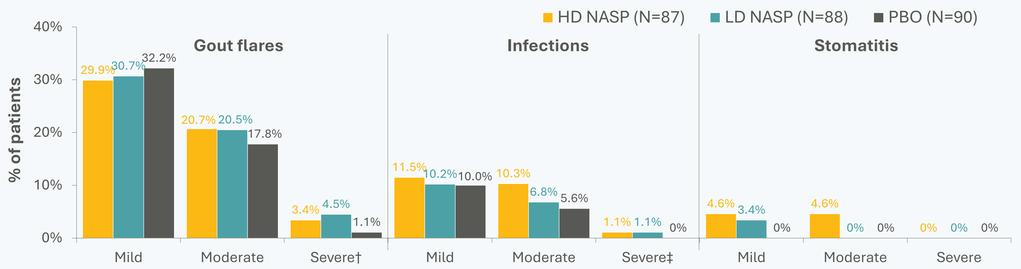
AESIs, n (%)	HD NASP (N=87)	LD NASP (N=88)	PBO (N=90)
Patients with gout flares	37 (42.5)	39 (44.3)	39 (43.3)
Infections and infestations*	20 (23.0)	16 (18.2)	15 (16.7)
COVID-19	5 (5.7)	5 (5.7)	6 (6.7)
Urinary tract infection	2 (2.3)	3 (3.4)	0
Upper respiratory tract infection	2 (2.3)	2 (2.3)	1 (1.1)
Pharyngitis streptococcal	2 (2.3)	1 (1.1)	0
Nasopharyngitis	2 (2.3)	0	3 (3.3)
Folliculitis	2 (2.3)	0	0
Cellulitis	1 (1.1)	1 (1.1)	2 (2.2)
Pneumonia	0	2 (2.3)	0
Stomatitis†	8 (9.2)	3 (3.4)	0

* Coded as per MedDRA V25.1. Most frequent infections are listed by Preferred Term for infections reported as AESIs in >2% of patients in any treatment arm. 2 cases of Clostridium difficile (HD NASP, n=1; LD NASP, n=1) and 2 cases of staphylococcal infections (LD NASP, staphylococcal sepsis, determined not study drug-related; PBO, staphylococcal septic olecranon bursitis) occurred.
† Including events of stomatitis, mouth ulceration, and aphthous ulcer.
AESI, adverse events of special interest; HD, high dose; LD, low dose; NASP, nanoencapsulated sirolimus plus pegadricase; PBO, placebo.

Infections

- Infections were reported more frequently with HD NASP than with LD NASP or PBO, and were predominantly viral or bacterial, and mild to moderate in severity (**Table 1**, **Figure 2**)
- Severe infections occurred in 1 patient in each NASP arm. Neither was assessed as related to study drug
- The reported percentages include all infections (**Table 1**). No mycobacterial, fungal or herpes zoster infections were reported, and the majority of infections were assessed as not related to study drug

Figure 2. Select AESIs by severity* (pooled Safety Set, N=265)

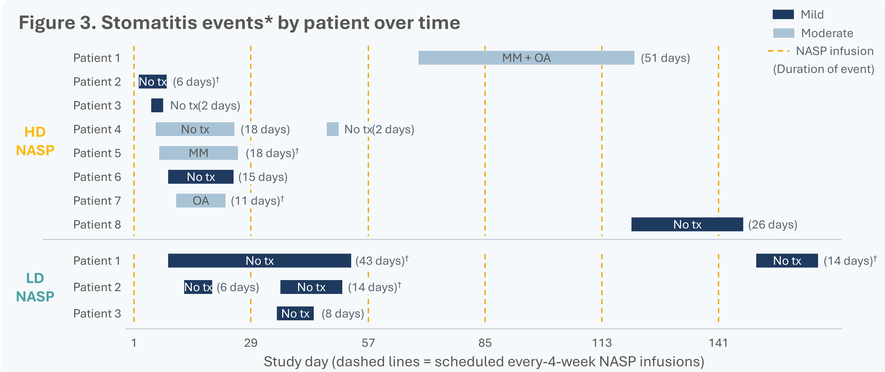


* Severity classified according to the Rheumatology Common Toxicity Criteria, version 2.0[8] (Grade 1, mild; Grade 2, moderate; Grade 3, severe, Grade 4, life-threatening). † 1 severe gout flare in each NASP arm was considered study drug-related and reported as a serious AE. ‡ 1 severe infection occurred in each NASP arm; neither were considered study drug-related. AE, adverse event; AESI, adverse event of special interest; HD, high dose; LD, low dose; NASP, nanoencapsulated sirolimus plus pegadricase.

Stomatitis and other sirolimus-associated events

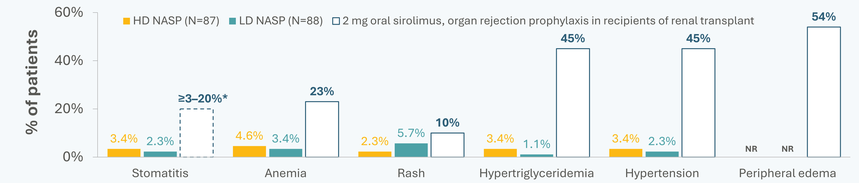
- Stomatitis (including mouth and aphthous ulcers) is a known AE of oral sirolimus and was reported more frequently with HD NASP than with LD NASP, with no events with PBO (**Table 1**)
  - Fewer than 50% of events were considered possibly related to study drug
  - All events were mild to moderate (**Figure 2**), and none led to treatment discontinuation
  - Most events began within the first treatment period, were limited in duration and resolved, and did not recur; the majority required no treatment (**Figure 3**)
- Other sirolimus-associated ADRs were uncommon across system organ classes, with no specific signal for a related term. Sirolimus-associated ADRs with NASP were substantially lower than published rates with oral sirolimus[9] (**Figure 4**)

Figure 3. Stomatitis events* by patient over time



* Including events of stomatitis, mouth ulceration, and aphthous ulcer. † Assessed as possibly related to study drug. No event was severe and none led to treatment discontinuation; one event led to a dose interruption.
HD, high dose; LD, low dose; MM, magic mouthwash; NASP, nanoencapsulated sirolimus plus pegadricase; OA, oral analgesic; tx, treatment.

Figure 4. Sirolimus-associated ADRs in NASP vs published oral sirolimus[9]



NASP bars are Preferred Terms; the stomatitis bar is therefore lower than the stomatitis AESI in **Table 1**, which pools stomatitis, mouth ulceration and aphthous ulcer. Published rates come from renal transplant recipients on chronic daily oral sirolimus 2 mg with cyclosporine and corticosteroids, assessed at ≥12 months, and are shown for context only; no formal statistical analysis was made. Oral sirolimus AE rates are indication-dependent: in lymphangioleiomyomatosis, stomatitis and peripheral edema are each reported at ≥20%.[9] * Per Rapamune label, stomatitis is not reported as a discrete rate and falls within the ≥3% to <20% band.[9] No other adverse event in this figure is reported at ≥20% in lymphangioleiomyomatosis.[9]
ADR, adverse drug reaction; AE, adverse event; HD, high dose; LD, low dose; NASP, nanoencapsulated sirolimus plus pegadricase; NR, not reported at or above the 2.3% threshold of the sirolimus ADR output.

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Disclosures

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