Nanoencapsulated Sirolimus Plus Pegadricase (NASP) Provides a Sustained 48-Week Response, Reducing Serum Uric Acid and Preserving Renal Function in Patients With Uncontrolled Gout (UG) and Stage 3 Chronic Kidney Disease

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CONCLUSIONS

- In patients with uncontrolled gout (UG) and chronic kidney disease (CKD) stage 3 from the DISSOLVE I trial, once-monthly nanoencapsulated sirolimus plus pegadricase (NASP) rapidly reduced serum urate (SU) levels, with reductions sustained through 48 weeks vs placebo (PBO), while gout flare rates were low and similar between the NASP and PBO arms
- Measures of renal function, including blood urea nitrogen (BUN), serum creatinine, and estimated glomerular filtration rate (eGFR), remained generally stable and similar between patients treated with NASP or PBO for 48 weeks
- NASP was well tolerated in patients with CKD stage 3, with no new safety signals identified over 48 weeks of treatment

INTRODUCTION

- Patients with UG often have CKD, which complicates the management of disease, including the use of oral urate-lowering therapies due to contraindications, concerns about lack of efficacy, potential for increased cardiovascular risks, and medication interactions[1,2]
- Uricase therapy such as pegloticase is approved for the treatment of UG and is highly effective; however, due to immunogenicity, there is an increased risk of infusion reactions and/or loss of efficacy[3,4]
  - Co-administration with immunosuppressants such as methotrexate (MTX) may reduce immunogenicity; however, MTX elimination may be decreased in patients with impaired renal function, increasing the risk of MTX-related adverse reactions[5,6]
- NASP (formerly SEL-212) is an investigational, novel, every 4-week, 2-component, sequential infusion therapy consisting of nanoencapsulated sirolimus (NAS), an mTOR inhibitor that provides targeted antigen-specific immune tolerance, and pegadricase, a pegylated uricase that reduces SU levels in patients with uncontrolled gout[7-10]
- Previous findings from the phase 3 DISSOLVE I and II studies (NCT04513366, NCT04596540)[11,12] showed that NASP reduced SU levels, was generally well tolerated, and did not affect kidney function in the subgroup of patients with UG and CKD **stage 3** through 24 weeks[13]
- Here, we report efficacy and safety outcomes in the subgroup of patients with UG and CKD **stage 3** from the DISSOLVE I trial who received 12 doses of NASP or PBO through 48 weeks

METHODS

DISSOLVE I inclusion criteria:

- Adults with 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 xanthine oxidase inhibitors (or contraindication to xanthine oxidase inhibitors)
- Screening SU level ≥7 mg/dL

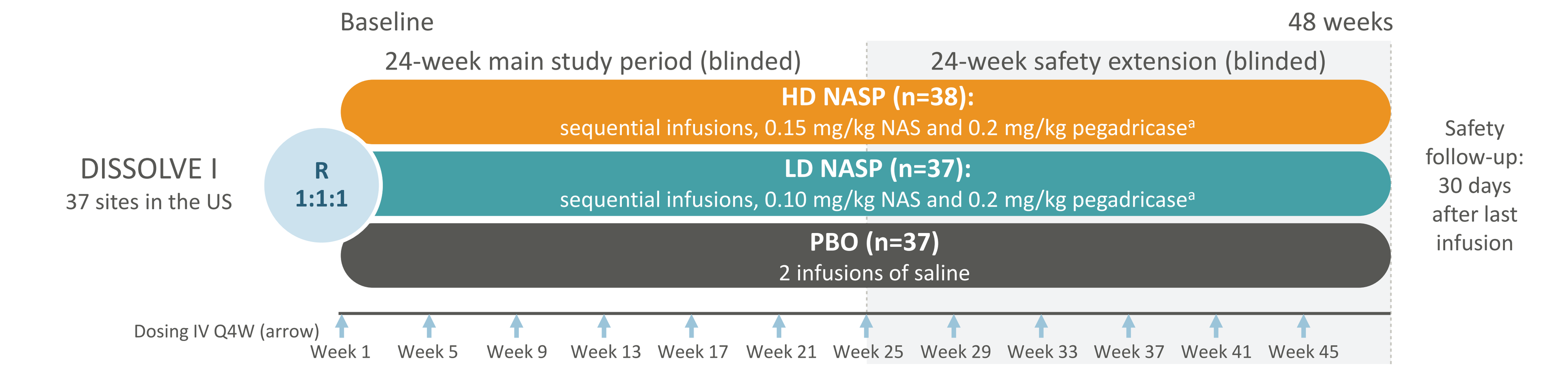
DISSOLVE I study design (Figure 1):

- Patients were randomly assigned 1:1:1 to receive 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), or PBO
- NASP or PBO was administered every 4 weeks for up to 6 doses during the 24-week main study period; patients could then enter a 24-week double-blind safety extension period to receive up to 6 additional doses of NASP or PBO

This post hoc analysis:

- Included patients with UG and CKD stage 3 (eGFR ≥30 and <60 mL/min/1.73 m^2) at baseline who completed 12 doses of NASP or PBO
- Outcomes for the analysis: renal function tests, SU, and safety
  - HD NASP and LD NASP treatment arms were pooled (NASP) for outcomes analyses

Figure 1: Design of the DISSOLVE I trial



- **Exploratory endpoints for extension phase** included:
  - Change from baseline in SU level
  - Gout flare incidence
- **Safety endpoints** included:
  - AEs, AESIs, SAEs
  - Laboratory testing: hematology, eGFR

AE, adverse event; AESI, adverse event of special interest; eGFR, estimated glomerular filtration rate; HD NASP, high-dose NASP; IV, intravenous; LD NASP, low-dose NASP; NAS, nanoencapsulated sirolimus; NASP, nanoencapsulated sirolimus plus pegadricase; PBO, placebo; Q4W, every 4 weeks; R, randomization; SAE, serious adverse event; SU, serum urate.

RESULTS

Population

- Among 112 patients randomized and dosed (intention-to-treat [ITT]: HD NASP, n=38; LD NASP, n=37; PBO, n=37) in DISSOLVE I, 21 patients had CKD stage 3
- Of the treated patients with CKD stage 3, 7 patients in the NASP group and 6 patients in the PBO group completed all 12 doses
  - Baseline characteristics for these patients (**Table 1**) were similar to those previously presented for the subset of patients with CKD stage 3[13]

Table 1: Characteristics of patients who had CKD stage 3 at baseline and completed 12 doses of NASP or PBO

	NASP (n=7)	PBO (n=6)
Patient characteristics at baseline		
Age, years, mean (SD)	67.6 (4.7)	68.2 (4.9)
BMI, kg/m^2, mean (SD)	33.2 (7.9)	34.2 (6.0)
Male, n (%)	5 (71.4)	6 (100)
Race, n (%)		
White	7 (100)	3 (50.0)
Black or African American	0	1 (16.7)
Other or multiple	0	2 (33.3)
Common[a] comorbidities, n (%)		
Hypertension	6 (85.7)	5 (83.3)
Hyperlipidemia	4 (57.1)	3 (50.0)
Type 2 diabetes mellitus	2 (28.6)	2 (33.3)
Benign prostatic hyperplasia	1 (14.3)	3 (50.0)
Hypothyroidism	2 (28.6)	2 (33.3)

	NASP (n=7)	PBO (n=6)
Disease characteristics at baseline		
Time since gout diagnosis, years, mean (SD)	6.9 (4.7)	13.9 (6.2)
SU levels, mg/dL, mean (SD)	8.1 (1.3)	8.1 (1.3)
Patients with tophi, n (%)	2 (28.6)	4 (66.7)
eGFR, mL/min/1.73 m^2, mean (SD)	53.7 (3.3)	53.5 (5.1)
Serum creatinine, mg/dL, mean (SD)	1.2 (0.2)	1.4 (0.2)
BUN, mg/dL, mean (SD)	20.7 (2.8)	20.2 (5.9)
Selected concomitant medications during the study, n (%)		
ACE inhibitors/ARBs	6 (85.7)	5 (83.3)
Statins and other lipid-modifying agents	6 (85.7)	3 (50.0)
Diuretics[b]	4 (57.1)	2 (33.3)
Calcium channel blockers	2 (28.6)	3 (50.0)
Beta blockers	2 (28.6)	3 (50.0)
Diabetes medications	2 (28.6)	2 (33.3)

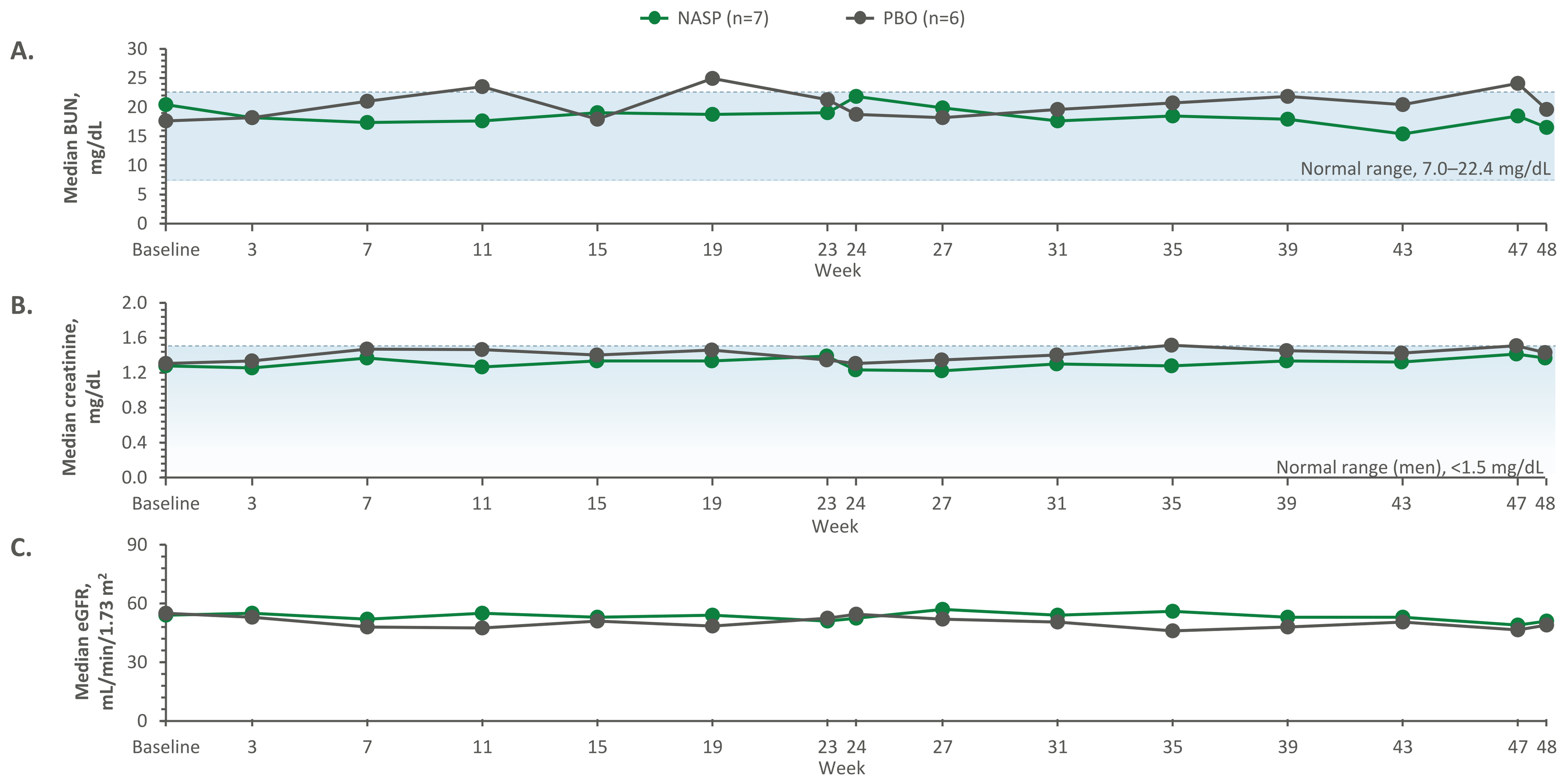
[a]Occurring in >30% of all 13 patients included in this post hoc analysis, by preferred term, not mutually exclusive. [b]Hydrochlorothiazide, furosemide, bumetanide, spironolactone, chlorthalidone.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NASP, nanoencapsulated sirolimus plus pegadricase; PBO, placebo; SD, standard deviation; SU, serum urate.

Renal outcomes

- Median BUN (baseline: 20.4 mg/dL; week 48: 16.5 mg/dL [NASP arm]), serum creatinine (baseline: 1.3 mg/dL; week 48: 1.4 mg/dL [NASP arm]), and eGFR (baseline: 54.0 mL/min/1.73 m^2; week 48: 51.0 mL/min/1.73 m^2 [NASP arm]) remained stable over 48 weeks (**Figure 2A-C**)
  - Renal outcomes were similar and remained stable in patients treated with NASP
  - While 1 patient had a decline in eGFR resulting in worsening of CKD (**Table 2**), the remaining NASP-treated patients had stable (n=4) or improved (n=2) CKD staging, as reflected by eGFR values
  - BUN and creatinine were largely within normal range[14,15] throughout the study period

Figure 2: Median BUN (A), serum creatinine (B), and eGFR (C) through week 48 in patients with CKD stage 3 who received 12 doses of NASP or PBO



Normal range for BUN based on Liu et al.[14] Normal range for creatinine (men) based on Schillaci et al.[15] At week 24, renal outcome data not available for 1 patient from HD NASP group.
BUN, blood urea nitrogen; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HD NASP, high-dose NASP; NASP, nanoencapsulated sirolimus plus pegadricase; PBO, placebo.

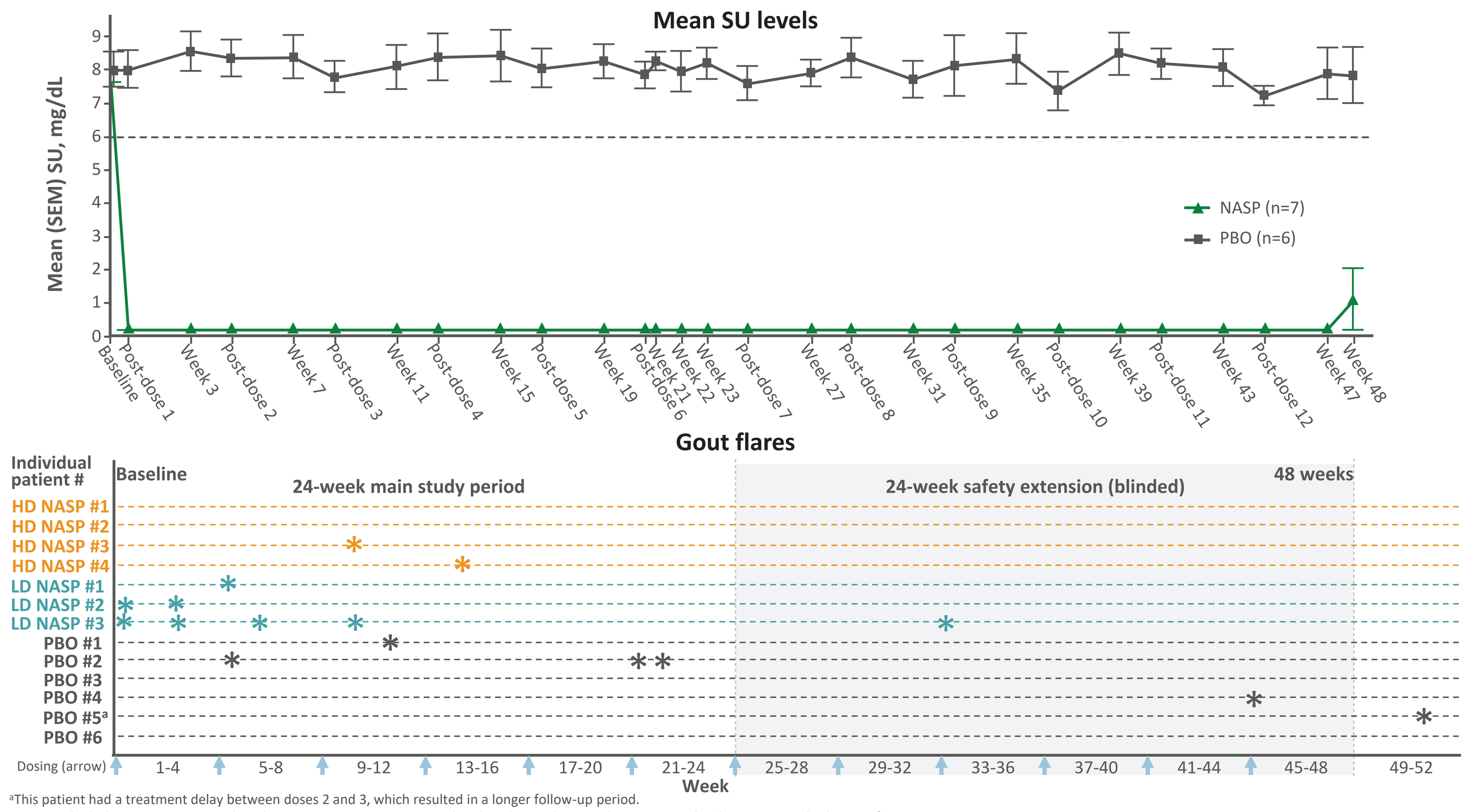
SU and gout flares

- NASP led to a rapid and sustained reduction in SU (**Figure 3 top panel**)
  - Following the first NASP dose, mean (SD) SU decreased from 8.1 (1.3) mg/dL at baseline to 0.2 (0.0) mg/dL and remained low through 48 weeks of NASP treatment, whereas patients receiving PBO had high levels of SU that did not change substantially from baseline during the entire course of PBO treatment
- Across 48 weeks, **NASP-treated patients showed a 96.3% reduction in cumulative SU area under the curve** (mean 104.9 mg/dL*days) **vs PBO** (mean, 2858.9 mg/dL*days)

SU and gout flares (cont'd)

- Occurrences of gout flare (**Figure 3 bottom panel**) remained low throughout the 48-week study period with the exception of 1 patient in the LD NASP group who experienced 5 flares over 48 weeks
  - Despite a small sample size, there was a pattern of decreasing gout flares over time in patients with CKD stage 3 who received 12 doses of treatment; this pattern was similar to that observed in the ITT population[16]
- Although flare rates were low in the PBO group, the SU levels remained consistently high, whereas in the NASP group, most patients were flare-free and had low levels of SU

Figure 3: Mean SU (top panel) and gout flares (bottom panel) through Week 48 in patients with CKD stage 3 who received 12 doses of NASP or PBO



[a]This patient had a treatment delay between doses 2 and 3, which resulted in a longer follow-up period.
HD NASP, high-dose NASP; LD NASP, low-dose NASP; NASP, nanoencapsulated sirolimus plus pegadricase; PBO, placebo; SEM, standard error of mean; SU, serum urate.

Safety

- No new safety signal was identified in this subset of patients with CKD stage 3 who received 12 doses of treatment (**Table 2**), compared to previously reported for the ITT population[16] and the patients with CKD stage 3[13]

Table 2: Adverse events in patients with CKD stage 3 who received 12 doses of NASP or PBO

	HD NASP (n=4)	LD NASP (n=3)	PBO (n=6)
≥1 TEAE, n (%)	3 (75.0)	3 (100)	5 (83.3)
≥1 SAE, n (%)	1 (25.0)	0	1 (16.7)
AESI, n (%)	3 (75.0)	3 (100)	5 (83.3)
Gout flare	3 (75.0)	3 (100)	4 (66.7)
Infections (including viral)	2 (50.0)	1 (33.3)	1 (16.7)
COVID-19	2 (50.0)	0	0
Bronchitis	0	0	1 (16.7)
Upper respiratory tract infection	0	1 (33.3)	0

	HD NASP (n=4)	LD NASP (n=3)	PBO (n=6)
AESI cont'd, n (%)			
Infusion-related AE within 24 hours	0	1 (33.3)	1 (16.7)
Deep vein thrombosis	0	0	1 (16.7)
Stomatitis	1 (25.0)[a]	0	0
Hypertriglyceridemia	0	1 (33.3)	0
Renal and urinary disorders			
Worsening CKD	0	1 (33.3)[b]	0
Micturition urgency	0	1 (33.3)	0

[a]This patient had mouth ulceration. [b]This patient had CKD stage 3 at baseline, which worsened to CKD stage 4 at week 48. AE, adverse event; AESI, adverse event of special interest; CKD, chronic kidney disease; HD NASP, high-dose NASP; LD NASP, low-dose NASP; NASP, nanoencapsulated sirolimus plus pegadricase; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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Disclosures

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