

Nanoencapsulated Sirolimus Plus Pegadricase (NASP) Reduces Gout Clinical Manifestations in Patients With Uncontrolled Gout (UG) and Stage 3 CKD

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CONCLUSIONS

- Nanoencapsulated sirolimus plus pegadricase (NASP)–treated patients demonstrated rapid and sustained serum uric acid (sUA) control and 20–27-fold higher rates of complete resolution of tophi compared with placebo (PBO)–treated patients
- At treatment initiation (weeks 1–4) and through week 20, NASP- and PBO-treated patients did not experience an increase in gout flares, as has been observed with urate-lowering therapy (ULT) initiation¹
 - During weeks 21–24, 88.2% and 93.7% of patients receiving high-dose and low-dose NASP, respectively, were flare-free
- In patients with stage 3 chronic kidney disease (CKD3) at baseline, safety was similar to that in the overall intent-to-treat population
- These results build on previous findings, highlighting NASP in reducing disease burden in patients with uncontrolled gout (UG) and chronic kidney disease (CKD)



RESULTS

Population

- Among 265 patients in the overall intent-to-treat (ITT) population from the pooled DISSOLVE I and II trials, 20, 18, and 23 patients in the HD NASP, LD NASP, and PBO groups, respectively, had CKD3 with high disease burden at baseline (**Table 1**); additional baseline characteristics are shown in poster TH-PO1092²

	HD NASP n=20	LD NASP n=18	PBO n=23
Patient characteristics			
Age, years, mean (SD) [†]	63.5 (6.3)	59.1 (8.3)	62.1 (9.5)
BMI, kg/m ² , mean (SD) [†]	33.2 (6.2)	31.0 (5.9)	32.3 (5.8)
Male, n (%) [†]	18 (90.0)	15 (83.3)	22 (95.7)
Race, n (%)			
White [‡]	18 (90.0)	15 (83.3)	18 (78.3)
Black	1 (5.0)	2 (11.1)	3 (13.0)
Asian	0	1 (5.6)	0
Other	1 (5.0)	0	2 (8.7)
Comorbidities, [§] n (%)			
Hypertension	16 (80.0)	12 (66.7)	18 (78.3)
Hyperlipidemia	9 (45.0)	7 (38.9)	9 (39.1)
Dyslipidemia	5 (25.0)	5 (27.8)	3 (13.0)
Obesity	3 (15.0)	4 (22.2)	3 (13.0)

	HD NASP n=20	LD NASP n=18	PBO n=23
Disease characteristics			
Time since gout diagnosis, years, mean (SD)	12.6 (9.2)	11.0 (9.4)	13.3 (9.7)
Patients with tophi at baseline, n (%) [‡]	14 (70.0)	12 (66.7)	18 (78.3)
Number of tophi, mean (SD)	8.0 (5.5)	8.4 (5.1)	7.1 (6.2)
sUA at baseline, mg/dL, mean (SD)	8.9 (1.3)	8.5 (1.4)	8.9 (1.8)
Number of tender joints, mean (SD)	11.5 (14.7)	11.1 (14.4)	6.5 (10.4)
Number of swollen joints, mean (SD)	7.7 (13.7)	5.5 (8.5)	4.6 (8.3)

[†]Comorbidities, excluding gout and related disorders, that were present in ≥15% of patients with CKD3 at baseline. BMI, body mass index; CKD3, stage 3 chronic kidney disease; HD NASP, high-dose NASP; LD NASP, low-dose NASP; NASP, nanoencapsulated sirolimus plus pegadricase; PBO, placebo; SD, standard deviation; sUA, serum uric acid.

Efficacy

- sUA levels were reduced within 1 hour of the first dose in NASP-treated patients to mean sUA levels of 0.2 mg/dL with HD NASP and 0.6 mg/dL with LD NASP. This translates to a mean sUA reduction of 97.8% and 92.9% with HD and LD NASP, respectively (**Figure 2**)
 - The reduction in sUA was sustained through week 24, with sUA ≤2.9 mg/dL for patients who stayed on treatment with HD NASP and ≤2.8 mg/dL for patients who stayed on treatment with LD NASP
 - For patients who discontinued treatment with NASP, sUA returned to >6.0 mg/dL through week 24 and was similar to sUA in PBO-treated patients
 - Most patients who discontinued NASP did not transition to an oral ULT
- For patients in the PBO group, sUA remained similar to baseline within 1 hour of the first dose, with a mean sUA of 8.8 mg/dL, which translates to a 1.1% mean reduction; mean sUA remained consistently above 6.0 mg/dL through week 24 (**Figure 2**)

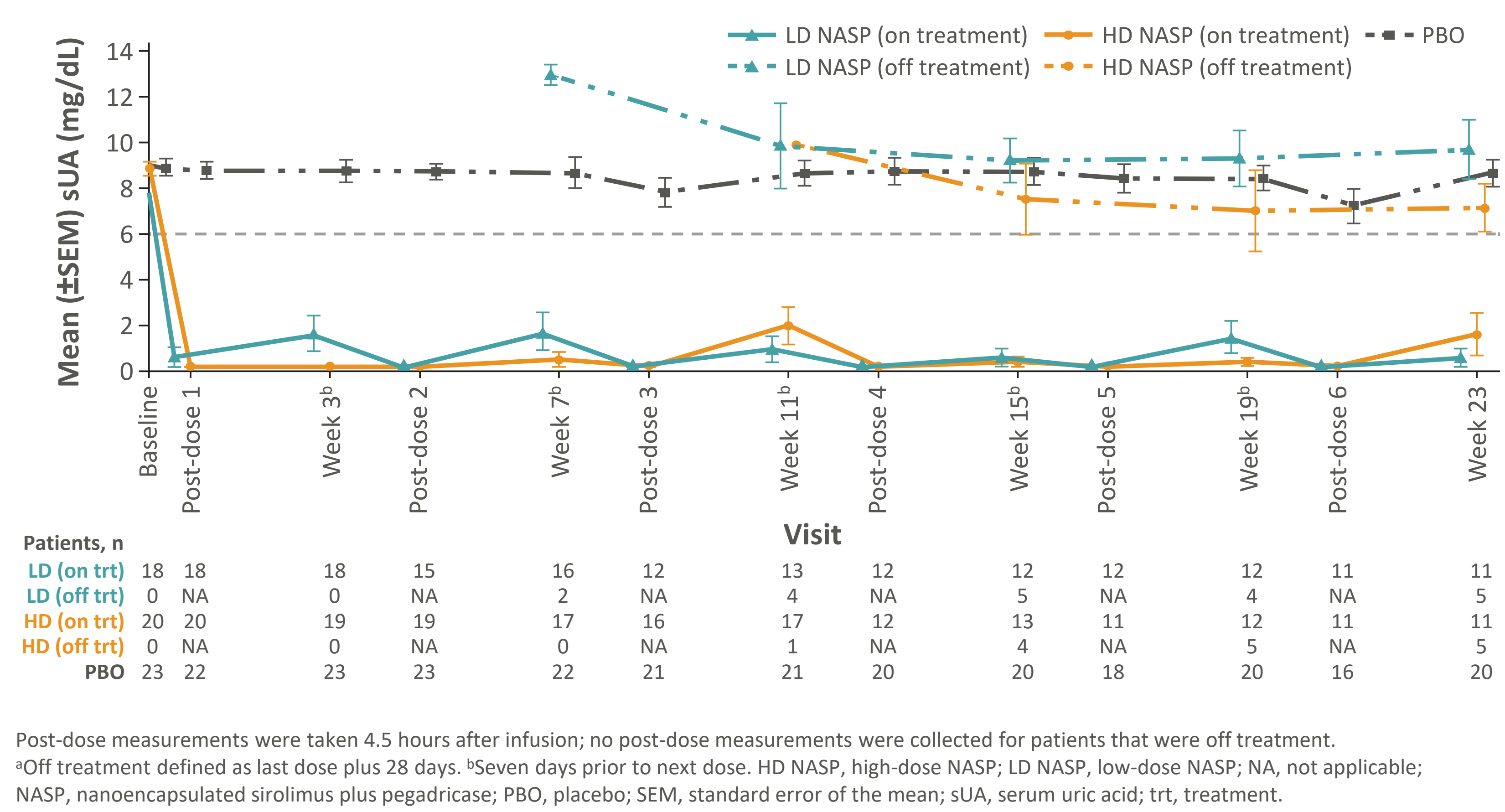
INTRODUCTION AND OBJECTIVES

- Patients with gout often have chronic kidney disease (CKD); gout increases the risk of stage 3 CKD (CKD3) more than two-fold, and nearly one-quarter of patients with gout also have CKD3²
- Here, uncontrolled gout (UG) is characterized by serum uric acid (sUA) levels persistently ≥6 mg/dL despite treatment with oral urate-lowering therapy (ULT); this results in ongoing clinical manifestations, including tophi, joint pain, impaired function, and poor quality of life³
 - Patients with UG are approximately twice as likely to develop CKD compared with patients with controlled gout⁴
- ULTs are suboptimal because CKD limits their efficacy and compromises their safety^{3,5}
- Nanoencapsulated sirolimus plus pegadricase (NASP; formerly SEL-212) is an investigational, novel, every 4-week, sequential two-component infusion therapy consisting of nanoencapsulated sirolimus (NAS; formerly SEL-110) co-administered with a pegylated uricase (pegadricase [P]; formerly SEL-037); NASP is designed to reduce sUA in patients with UG
 - NAS provides targeted antigen-specific tolerance to sequentially administered pegadricase through induction of regulatory T cells⁶
- In the phase 3 DISSOLVE I and II trials, NASP demonstrated rapid and sustained sUA reduction in patients with CKD3 similar to the overall study population. High response rates were achieved with a trend toward improvement in estimated glomerular filtration rate (eGFR)⁷
- This post hoc analysis aims to describe additional efficacy and safety outcomes among patients with CKD3 (eGFR 30–59 mL/min/1.73 m²) at baseline in the pooled phase 3 DISSOLVE I and II trials

METHODS

- DISSOLVE I (NCT04513366; US) and DISSOLVE II (NCT04596540; global) were replicate, randomized, double-blind, placebo (PBO)–controlled, phase 3 trials that investigated the efficacy and safety of NASP
- Patients were randomized 1:1:1 to receive high-dose NASP (HD NASP), low-dose NASP (LD NASP), or PBO every 4 weeks via intravenous infusion (**Figure 1**)
- Patients meeting the stopping rule or discontinuing treatment who continued visits could restart ULT at investigator discretion 60 days after the last dose

Figure 2: sUA over time among patients on vs off NASP treatment[§]

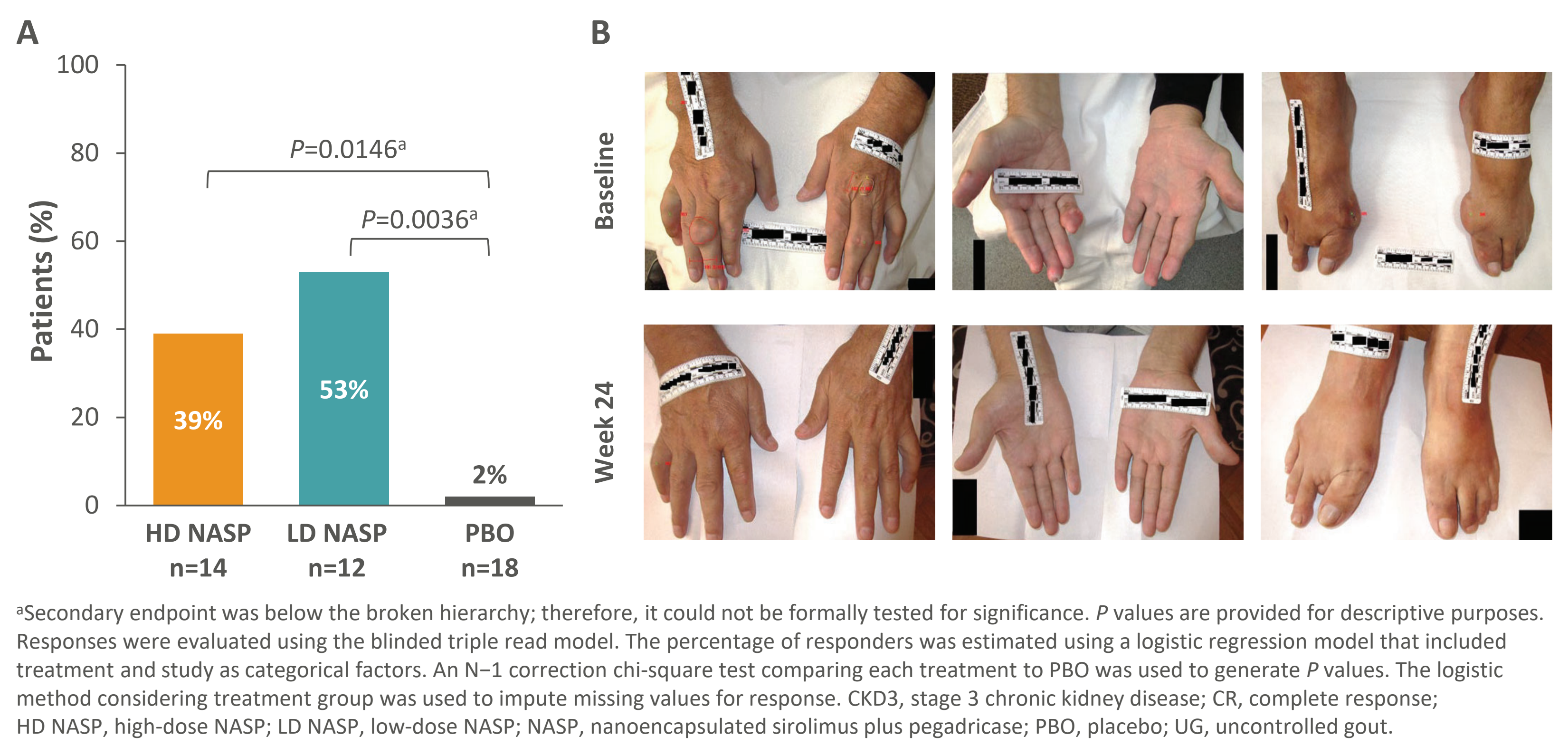


Post-dose measurements were taken 4.5 hours after infusion; no post-dose measurements were collected for patients that were off treatment.
[§]Off treatment defined as last dose plus 28 days. [†]Seven days prior to next dose. HD NASP, high-dose NASP; LD NASP, low-dose NASP; NA, not applicable; NASP, nanoencapsulated sirolimus plus pegadricase; PBO, placebo; SEM, standard error of the mean; sUA, serum uric acid; trt, treatment.

Efficacy (cont.)

- A greater proportion of NASP- vs PBO-treated patients had a complete resolution of tophi by week 24, where CR rates were approximately 20–27-fold higher in NASP-treated patients compared with PBO-treated patients (**Figure 3A**)
 - A response of at least a PR was achieved in 85% of patients treated with HD NASP, 88% treated with LD NASP, and 55% treated with PBO
- Example patient images are shown in **Figure 3B**

Figure 3: Tophus CR rates by week 24 (A) and an example of tophus response in a patient with UG who had CKD3 and tophi at baseline and CR after treatment at the end of the double-blind phase (B)

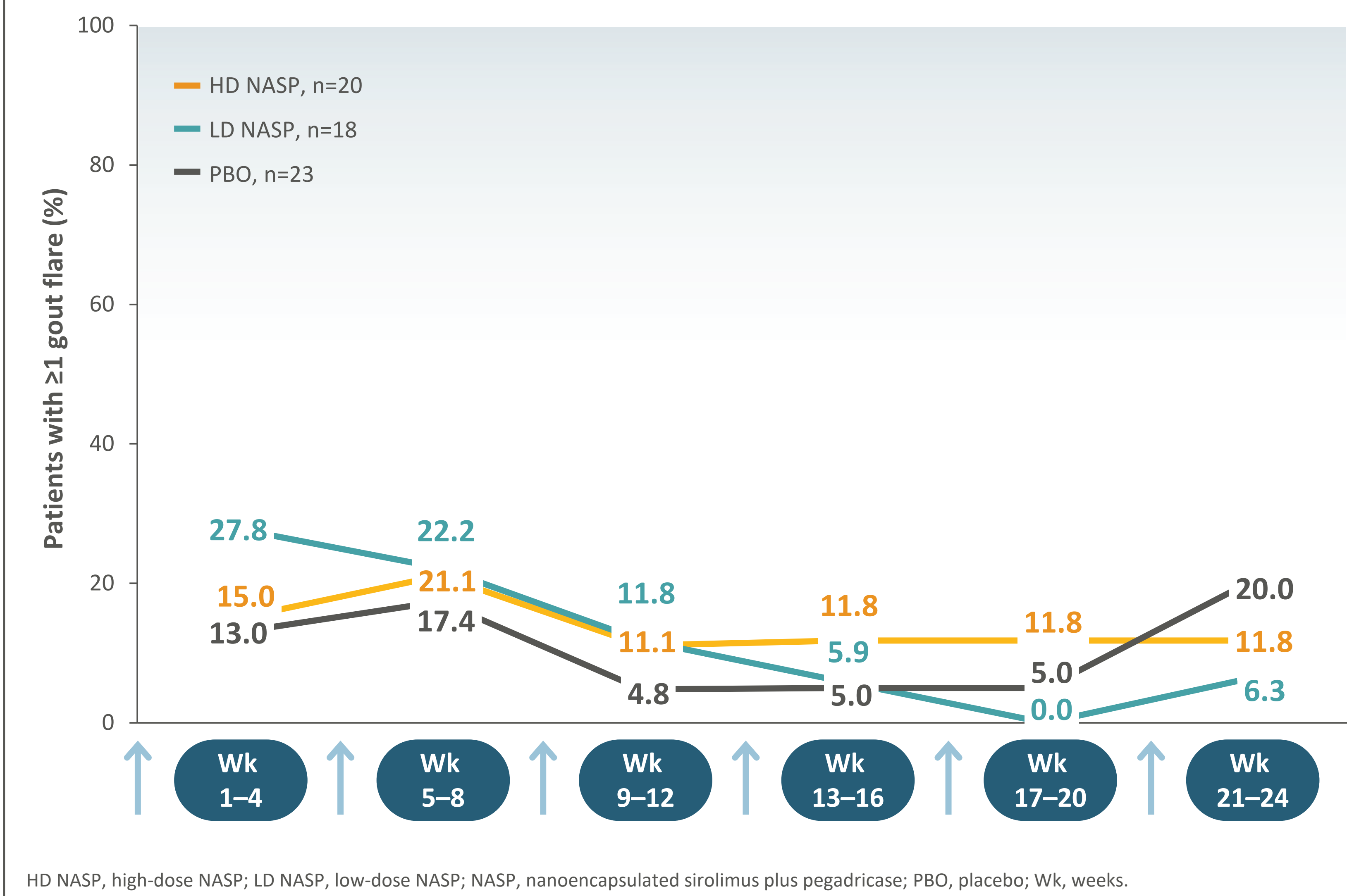


[§]Secondary endpoint was below the broken hierarchy; therefore, it could not be formally tested for significance. *P* values are provided for descriptive purposes. Responses were evaluated using the blinded triple read model. The percentage of responders was estimated using a logistic regression model that included treatment and study as categorical factors. An *N*-1 correction Chi-square test comparing each treatment to PBO was used to generate *P* values. The logistic method considering treatment group was used to impute missing values for response. CKD3, stage 3 chronic kidney disease; CR, complete response; HD NASP, high-dose NASP; LD NASP, low-dose NASP; NASP, nanoencapsulated sirolimus plus pegadricase; PBO, placebo; UG, uncontrolled gout.

Efficacy (cont.)

- At treatment initiation (weeks 1–4), despite rapid sUA reductions, a similar proportion of HD NASP- and PBO-treated patients experienced gout flares. A slightly higher proportion of LD NASP-treated patients experienced gout flares upon treatment initiation, but the proportion decreased during subsequent weeks (**Figure 4**)
- As patients continued treatment, the proportion experiencing gout flares remained consistently low or decreased in HD NASP- and LD NASP-treated patients (**Figure 4**)

Figure 4: Percentage of patients experiencing gout flares over the study period



HD NASP, high-dose NASP; LD NASP, low-dose NASP; NASP, nanoencapsulated sirolimus plus pegadricase; PBO, placebo; Wk, weeks.

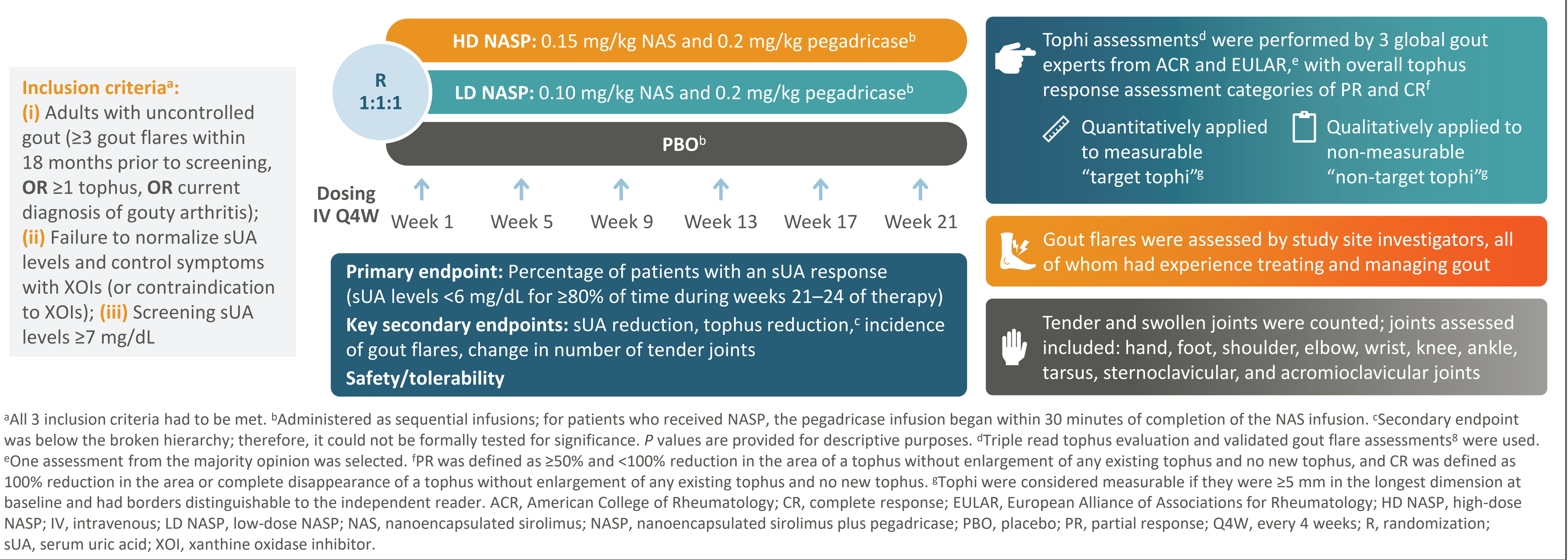
- NASP-treated patients showed substantial improvements in the number of tender and swollen joints from baseline to week 24 when compared with PBO (**Table 2**)

Table 2: Change in the number of tender and swollen joints

	HD NASP n=20	LD NASP n=18	PBO n=23
Tender joints, n	16	15	18
Mean change from baseline to week 24 (SD)	−8.94 (12.28)	−7.73 (11.12)	−1.11 (5.07)
Least-square mean difference vs PBO (SE) [§]	−3.1 (1.52)	−3.8 (1.53)	
Swollen joints, n	16	15	18
Mean change from baseline to week 24 (SD)	−6.25 (12.97)	−2.80 (6.14)	−1.83 (4.42)
Least-square mean difference vs PBO (SE) [§]	−0.9 (0.98)	−0.4 (0.98)	

[§]Least-square mean difference (SE) in the change in number of tender or swollen joints from baseline to week 24. HD NASP, high-dose NASP; LD NASP, low-dose NASP; NASP, nanoencapsulated sirolimus plus pegadricase; PBO, placebo; SD, standard deviation; SE, standard error.

Figure 1: Design of the DISSOLVE I and DISSOLVE II trials and key secondary endpoint evaluation



[†]All 3 inclusion criteria had to be met. [§]Administered as sequential infusions; for patients who received NASP, the pegadricase infusion began within 30 minutes of completion of the NAS infusion. [‡]Secondary endpoint was below the broken hierarchy; therefore, it could not be formally tested for significance. *P* values are provided for descriptive purposes. [¶]Triple read tophus evaluation and validated gout flare assessments[§] were used. [¶]One assessment from the majority opinion was selected. [¶]PR was defined as ≥50% and <100% reduction in the area of a tophus without enlargement of any existing tophus and no new tophus, and CR was defined as 100% reduction in the area or complete disappearance of a tophus without enlargement of any existing tophus and no new tophus. [¶]Tophi were considered measurable if they were ≥5 mm in the longest dimension at baseline and had borders distinguishable to the independent reader. ACR, American College of Rheumatology; CR, complete response; EULAR, European Alliance of Associations for Rheumatology; HD NASP, high-dose NASP; IV, intravenous; LD NASP, low-dose NASP; NAS, nanoencapsulated sirolimus; NASP, nanoencapsulated sirolimus plus pegadricase; PBO, placebo; PR, partial response; Q4W, every 4 weeks; R, randomization; sUA, serum uric acid; XO, xanthine oxidase inhibitor.

Safety

- Adverse events of special interest in patients with CKD3 at baseline (**Table 3**) were similar to those in the ITT population (previously presented)¹⁰
 - Poster TH-PO1092 shows additional safety data, including low rates of anemia, increased blood creatinine, and thrombocytopenia⁹
- One case of proteinuria was observed in each NASP arm and was considered not drug related

Table 3: Adverse events in patients with CKD3 at baseline

	HD NASP n=20	LD NASP n=18	PBO n=23
≥1 TEAE, n (%)	16 (80.0)	14 (77.8)	15 (65.2)
≥1 SAE, n (%)	3 (15.0)	3 (16.7)	1 (4.3)
≥1 AESI, n (%)	12 (60.0)	13 (72.2)	12 (52.2)
Gout flare [‡]	9 (45.0)	9 (50.0)	9 (39.1)
Stomatitis ^{§,7}	2 (10.0)	1 (5.6)	0
Infections (including viral) [‡]	3 (15.0)	3 (16.7)	5 (21.7)
COVID-19	1 (5.0)	0	2 (8.7)
Infusion-related AE within 24 h of treatment [‡]	1 (5.0)	2 (11.1)	1 (4.3)
Infusion-related AE within 1 h of treatment	1 (5.0)	0	0
Select renal and urinary disorders ^b	1 (5.0)	2 (11.1)	0
Renal impairment	1 (5.0)	1 (5.6)	0
Microalbuminuria	0	1 (5.6)	0

[†]Includes stomatitis, mouth ulceration, oral ulcer, and aphthous ulcer. [‡]Other renal and urinary disorders included acute kidney injury, hematuria, micturition urgency, and nephrolithiasis (each occurred in 1 patient in either the HD NASP arm or the LD NASP arm). AE, adverse event; AESI, adverse event of special interest; CKD3, stage 3 chronic kidney disease; COVID-19, coronavirus disease 2019; h, hour(s); 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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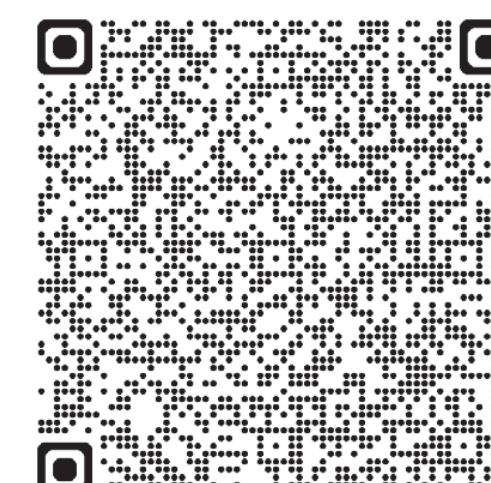
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Disclosures

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