Effect of Nanoencapsulated Sirolimus Plus Pegadricase (NASP) on Kidney Outcomes: Results from the Phase 3 DISSOLVE Studies

Minesh Rajpal, MD[1], Vibeke Strand, MD[2], Rehan Azeem, MBBS, MPH[3], Ben Peace, MSc[4], Bhavisha Desai, PharmD[3], Richard J. Johnson, MD[5]

[1]Southwest Kidney Institute, Phoenix, AZ, USA; [2]Division of Immunology/Rheumatology, Stanford University, Palo Alto, CA, USA; [3]Sobi Inc., Waltham, MA, USA; [4]Sobi, Stockholm, Sweden; [5] Division of Renal Diseases and Hypertension, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

TH-PO1092

CONCLUSIONS

- A greater number of patients in the NASP-treated arms had an overall improvement in CKD stage as compared to placebo
- Overall, renal function remained stable throughout the study period in patients treated with NASP, with a slight improvement in creatine from baseline to Week 24
- These data and previously reported data[1] highlight NASP as a potential treatment option for patients with UG and CKD stage 3

INTRODUCTION

- Patients with uncontrolled gout (UG) are more likely to have chronic kidney disease (CKD) than patients with controlled gout,[2] and comorbid CKD increases the risk of mortality by 65–71% compared to gout alone.[3] Comorbidities such as CKD may limit the utility of oral urate-lowering therapies,[4] so patients with UG and CKD may have fewer treatment options
- NASP is a novel, investigational, every 4-week, sequential infusion therapy consisting of targeted immunomodulating, nanoencapsulated sirolimus (NAS) co-administered with pegadricase (a pegylated yeast uricase), which lowers serum uric acid (sUA) by converting uric acid to readily excreted allantoin. NAS shifts the immune response from stimulatory to regulatory, induces antigen-specific regulatory T cells and ultimately mitigates anti-drug antibodies to the co-administered pegadricase without the need for additional oral immunosuppressant drugs[5]
- Efficacy and safety of NASP in patients with CKD stage 3 (CKD-3) have been presented previously,[1] including adverse events of special interest and improvements in sUA levels and estimated glomerular filtration rate (eGFR)

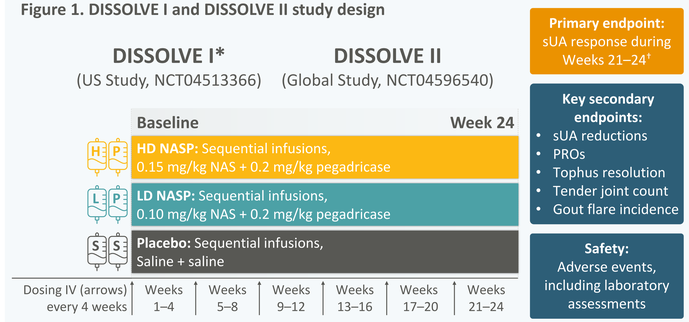
OBJECTIVE

- This *post hoc* analysis assessed additional renal outcomes in patients with CKD-3 ($30 \leq$ eGFR < 60 mL/min/1.73 m^2) at baseline from the Phase 3 DISSOLVE I and DISSOLVE II studies

METHODS

- DISSOLVE I (NCT04513366) and DISSOLVE II (NCT04596540) were replicate, randomized, double-blind studies investigating the efficacy and safety of NASP
- Patients were randomized 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 placebo every 4 weeks for a total of 6 doses (**Figure 1**)
- Changes in renal parameters and CKD stage, as well as safety were assessed in all patients with CKD-3 at baseline. Change in CKD stage was also assessed in a subset of patients with CKD-3 who received 6 doses of study drug

Figure 1. DISSOLVE I and DISSOLVE II study design



DISSOLVE I included n=38 patients randomized to receive HD NASP, n=37 to LD NASP, and n=37 to placebo, from 37 sites in the US. DISSOLVE II included n=49 patients randomized to receive HD NASP, n=51 to LD NASP, and n=53 to placebo, from 52 sites in the US, Russia, Ukraine, Georgia and Serbia.
*DISSOLVE I included the main 24-week double-blind study period followed by a 24-week double-blind extension phase.
†Primary efficacy endpoint defined as sUA <6 mg/dL for at least 80% of the time (0h, ~4.5h, and days 7, 14, 21 and 28) during Weeks 21–24.
H/HD, high-dose; IV, intravenous; L/LD, low-dose; NAS, nanoencapsulated sirolimus; NASP, nanoencapsulated sirolimus plus pegadricase; S, saline; P, pegadricase; PRO, patient-reported outcome; sUA, serum uric acid.

RESULTS

Patient demographics and baseline characteristics

- Among 265 treated patients in DISSOLVE I and DISSOLVE II, 61 had CKD-3 (HD NASP, N=20; LD NASP, N=18; placebo, N=23)
- Baseline demographics and disease characteristics were well-balanced between treatment groups, and patients across all treatment groups had a high disease burden (**Table 1**)

Table 1. Baseline characteristics and comorbidities in patients with CKD-3

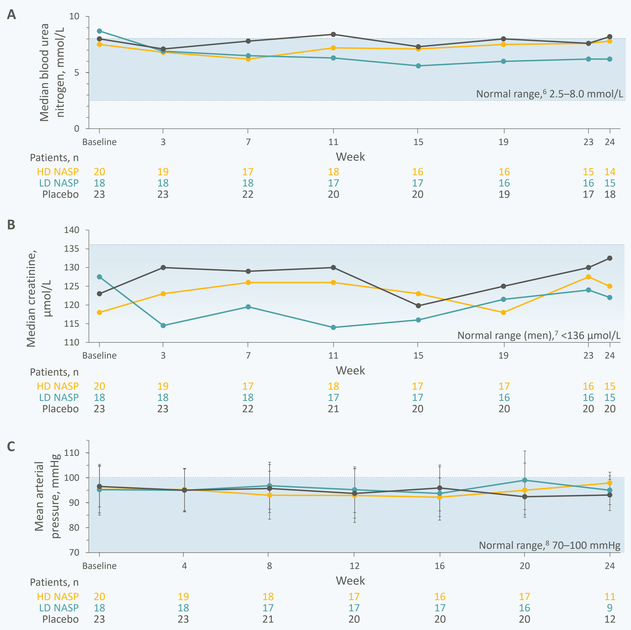
	HD NASP (N=20)	LD NASP (N=18)	Placebo (N=23)
Patient characteristics			
Age, years, mean (SD)	63.5 (6.3)	59.1 (8.3)	62.1 (9.5)
BMI, kg/m^2, mean (SD)	33.2 (6.2)	31.0 (5.9)	32.3 (5.9)
Gender, male, n (%)	18 (90.0)	15 (83.3)	22 (95.7)
Race, n (%)			
White	18 (90.0)	15 (83.3)	18 (78.3)
Black or African American	1 (5.0)	2 (11.1)	3 (13.0)
Other*	1 (5.0)	1 (5.6)	2 (8.7)
Disease characteristics			
Years since gout diagnosis, mean (SD)	12.6 (9.2)	11.0 (9.4)	13.3 (9.7)
sUA at baseline, mg/dL, mean (SD)	8.9 (1.3)	8.5 (1.4)	8.9 (1.8)
Patients with tophi at baseline, n (%)	14 (70.0)	12 (66.7)	18 (78.3)
eGFR, mL/min/1.73m^2, mean (SD)	52.9 (8.8)	54.4 (14.2)	57.0 (15.0)
Any comorbidity at baseline, n (%)	20 (100)	18 (100)	23 (100)
Most common 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)
Coronary artery disease	5 (25.0)	1 (5.6)	1 (3.4)
Type 2 diabetes mellitus	4 (20.0)	1 (5.6)	3 (13.0)
Obesity	3 (15.0)	4 (22.2)	3 (13.0)
Selected concomitant medications at baseline, n (%)			
ACE inhibitors	15 (75.0)	9 (50.0)	10 (43.5)
Statins	11 (55.0)	8 (44.4)	7 (30.4)
Calcium channel blockers	6 (30.0)	5 (27.8)	12 (52.2)
Beta blockers	6 (30.0)	5 (27.8)	6 (26.1)
Diabetes medications	6 (30.0)	2 (11.1)	3 (13.0)
Diuretics‡	5 (25.0)	5 (27.8)	3 (13.0)

*Native Hawaiian or other Pacific Islander, HD NASP, n=1; Asian, LD NASP, n=1; Hispanic, placebo, n=1; Asian – central/South Asian heritage AND Native Hawaiian or other Pacific Islander, placebo, n=1. †Comorbidities in ≥20% in any treatment arm, by preferred term. Not mutually exclusive. ‡Hydrochlorothiazide, furosemide, spironolactone, torasemide, bumetanide, chlortalidone, indapamide. ACR, albumin/creatinine ratio, ACE, angiotensin-converting enzyme; BMI, body mass index; CKD-3, chronic kidney disease stage 3; eGFR, estimated glomerular filtration rate; HD, high-dose; LD, low-dose; NASP, nanoencapsulated sirolimus plus pegadricase; SD, standard deviation; sUA, serum uric acid.

Changes in renal parameters

- Blood urea nitrogen, creatinine, and mean arterial pressure remained stable and largely within normal range throughout the study period **(Figure 2)**
- In patients with a Week 24 assessment, change from baseline to Week 24 in serum creatinine was -3 µmol/L for HD NASP, -10 µmol/L for LD NASP, and +12 µmol/L for placebo

Figure 2. Median blood urea nitrogen (A), median creatinine (B) and mean (SD) arterial pressure (C) over time in the CKD-3 population

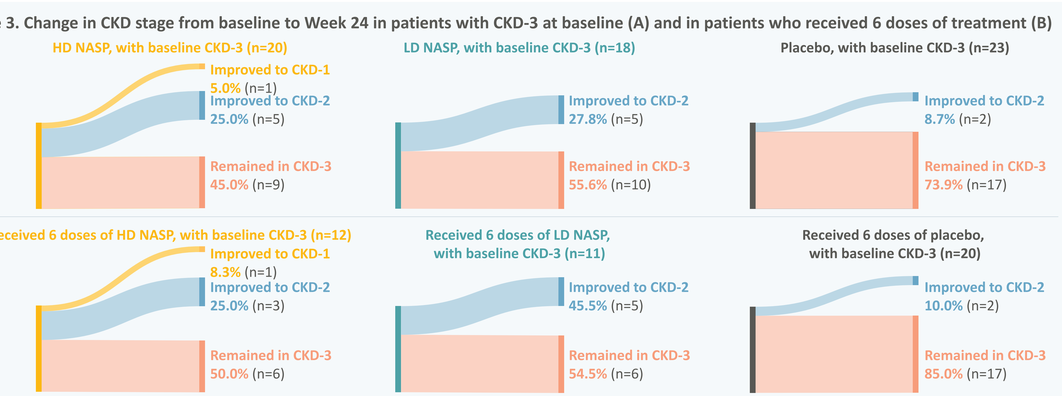


All measurements taken at the end of the week indicated. CKD-3, chronic kidney disease stage 3; HD, high-dose; LD, low-dose; NASP, nanoencapsulated sirolimus plus pegadricase; SD, standard deviation.

Change in CKD stage from baseline to Week 24

- Compared to placebo, 21.3% more patients on HD NASP and 19.1% on LD NASP improved in their CKD stage (**Figure 3A**)
- Additionally, in patients who received 6 doses of treatment, 23.3% more patients on HD NASP and 35.5% on LD NASP had improvements compared to placebo (**Figure 3B**)

Figure 3. Change in CKD stage from baseline to Week 24 in patients with CKD-3 at baseline (A) and in patients who received 6 doses of treatment (B)



Assessment of CKD stage at Week 24 was missing for 5 (25.0%) patients receiving HD NASP, 3 (16.7%) receiving LD NASP, and 4 (17.4%) receiving PBO. Among patients who received 6 doses, assessment of CKD stage at Week 24 was missing for 2 (16.7%) patients receiving HD NASP and 1 (5.0%) receiving PBO. No patient in any group experienced a worsening of CKD stage at the end of Week 24.
CKD-3, chronic kidney disease stage 3; HD, high-dose; LD, low-dose; NAS, nanoencapsulated sirolimus; NASP, nanoencapsulated sirolimus plus pegadricase; PBO, placebo.

Table 3. Selected TEAEs in patients with CKD-3

	HD NASP (N=20)	LD NASP (N=18)	Placebo (N=23)
≥1 TEAE	16 (80.0)	14 (77.8)	15 (65.2)
Renal and urinary disorders	2 (10.0)	3 (16.7)	0
Renal impairment	1 (5.0)	1 (5.6)	0
Acute kidney injury*	1 (5.0)	0	0
Hematuria	1 (5.0)	0	0
Microalbuminuria	0	1 (5.6)	0
Micturition urgency	0	1 (5.6)	0
Nephrolithiasis	0	1 (5.6)	0
Additional selected TEAEs			
Anemia	2 (10.0)	3 (16.7)	0
Blood creatinine increased	1 (5.0)	0	0
Thrombocytopenia	1 (5.0)	0	0

*Not related to study drug.
HD, high-dose; LD, low-dose; NASP, nanoencapsulated sirolimus plus pegadricase; TEAE, treatment-emergent adverse event.

Safety

- Adverse events (AEs) of special interest in patients with CKD-3 have been reported previously.[1] Here we report additional renal and other selected AEs (**Table 3**)
- Low rates of renal and urinary disorder AEs were reported, and no incidences of proteinuria or leukopenia were reported in patients with CKD-3 during the 24-week study period
- Among the AEs reported here, three events were reported as severe: 2 cases of anemia and 1 serious case of acute kidney injury were reported with HD NASP, all deemed not related to study drug. All other events were mild or moderate in severity

Acknowledgements

The DISSOLVE I & II (NCT04513366 and NCT04596540) studies were jointly funded by Sobi and Selecta Biosciences, Inc. The authors wish to acknowledge the contribution of the study participants, investigators and their teams. The authors also acknowledge Daniela Bruni, PharmD, PhD, from Sobi for publication coordination. This poster was created by the authors in accordance with Good Publication Practice (GPP) 2022 guidelines (https://www.ismpp.org/gpp-2022). Medical writing and editorial assistance, funded by Sobi, was provided by Cactus Life Sciences® Company (Meggen, Switzerland). Sobi reviewed and provided feedback on the poster. The authors had full editorial control of the poster and provided their final approval of all content.

Disclosures

M Rajpal: Speaker: AstraZeneca, Bayer, GSK, Travere; Advisory boards: Alexion, AstraZeneca, Bayer. **V. Strand:** Advisor/Review Panel Member, Consultant: AbbVie, Alpine Immune Sciences, Alumis, Amgen, AstraZeneca, Bayer, Blackrock Pharmaceuticals, Boehringer Ingelheim, Bristol Mysers Squibb, Celltrion, Citryll, COntura, Equillium, Fortress Biotech, Genentech/Roche, GSK, Inmedix, Janssen, Kiniksa, Lilly, Novartis, Omeros, Pfizer, Priovant Therapeutics, RAPT, Regeneron, R-Pharm, Samsung, Sandoz, Sanofi, Sciper, SetPoint Medical, Sobi, Sperix, SynAct Pharma, Takeda Pharmaceuticals. **R. Azeem:** Stock options or bond holdings in a for-profit corporation or self-directed pension plan: Selecta Biosciences; Employee and/or shareholder: Sobi. **B. Peace:** Contractor: Employee of Veramed contracted to Sobi. **B. Desai:** Employee and/or shareholder: Sobi. **R. J. Johnson:** Consultant: Horizon Pharmaceuticals; Employee and/or shareholder: Colorado Research Partners LLC, RxSugar.

References

1. Khanna P, et al. ASN 2024; 2. Francis-Sedlak M, et al. *Rheumatol Ther* 2021; 3. Jaffe DH, et al. *BMC Rheumatol* 2019; 4. Fels E, et al. *Curr Opin Rheumatol* 2008; 5. Baraf H et al. *Arthritis Rheumatol* 2023; 6. Liu J, et al. *Horm Metab Res* 2025; 7. Schillaci G, et al. *Arch Intern Med* 2001; 8. Tien LYH, et al. *Am J Hypertens* 2023.