Efficacy and safety of SEL-212 in patients with refractory gout and chronic kidney disease: A *post hoc* analysis from the two Phase 3 DISSOLVE studies

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TH-PO1075

CONCLUSIONS

- Almost all patients with CKD stage 3 treated with NASP had rapid sUA reductions with 51% having a response of <2 mg/dL sustained through TP6, superior to placebo.
- Markers of kidney function (estimated glomerular filtration rate [eGFR] and albumin/creatinine ratio [ACR]) show that kidney function was not impacted in patients treated with nanoencapsulated sirolimus plus pegadricase (NASP) for up to 6 months, with a trend for improvement in eGFR for patients with CKG stage 3.
- NASP was well tolerated in patients with CKD stage 3, with no new safety signals identified.
- Data from DISSOLVE I and II endorsed the efficacy and safety of once-monthly NASP in patients with gout refractory to conventional therapy and CKD stage 3, who are often difficult to treat.

INTRODUCTION

- While chronic kidney disease (CKD) is common in gout, the prevalence increases for patients who develop chronic refractory gout (CRG), making the management of CRG more complex.[1] The treatment and prevention of gout flares are complicated by the contraindication of non-steroidal anti-inflammatory drugs (NSAIDs) and the increased risk of glucocorticoid-related infections, respectively. The use of urate-lowering therapies for managing gout in patients with CKD is limited by concerns about cardiovascular morbidity, medication interactions, and non-adherence.[2,3]
- Uricase-based therapy is approved for the treatment of CRG,[4] however, it is limited by immunogenicity-related efficacy reductions and infusion reactions.[5]
- To reduce the risk of anti-drug antibody development, uricase therapy is often co-administered with immunosuppressants such as methotrexate (MTX) or mycophenolate mofetil. MTX elimination is reduced in patients with impaired renal function, putting these patients at increased risk of MTX-related adverse reactions.[6,7]
- NASP (also referred to as SEL-212) is a novel, once-monthly, two-component therapy consisting of pegadricase (a pegylated uricase, also SEL-037), which converts uric acid to soluble allantoin resulting in reduced serum uric acid, and nanoencapsulated sirolimus (NAS, also SEL-110), an mTOR inhibitor which provides targeted antigen-specific immune tolerance to pegadricase through the induction of regulatory T cells.[8-11]
- Administration of NAS followed by pegadricase mitigates uricase immunogenicity in clinical studies, thereby enabling rapid, sustained, and clinically meaningful sUA control without the need for additional broad immunosuppression.[3-5]

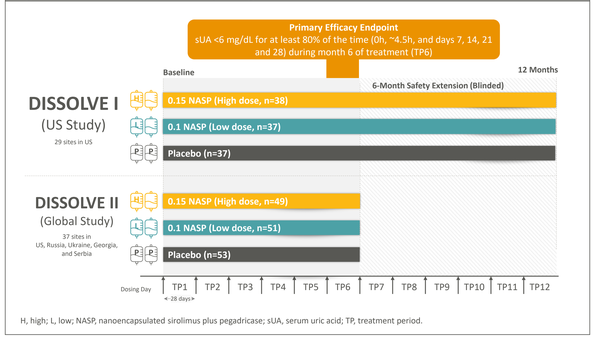
OBJECTIVES

- This *post hoc* analysis aims to describe the efficacy and safety of NASP in the subgroup of patients with CRG and CKD stage 3 in the DISSOLVE Phase 3 studies.

METHODS

- DISSOLVE I (NCT04513366) and DISSOLVE II (NCT04596540) investigated the efficacy and safety of NASP in patients with CRG (Figure 1).[11]
- In both studies, participants were randomized 1:1:1 between 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/pegadricase), and placebo (Figure 1).
- NASP or placebo were administered every 28 days for up to 6 treatment periods (TPs) in DISSOLVE II, or up to 12 TPs in DISSOLVE I (Figure 1).
- The primary endpoint was sUA reduction below 6 mg/dL for at least 80% of the time during TP6 (considered as responders at TP6).
- Secondary endpoints assessed sUA reduction and related outcomes.
- The ITT population included all patients who were randomized and who received at least one dose of study drug.
- In this *post hoc* analysis, the data from the DISSOLVE I and DISSOLVE II studies have been pooled, and outcomes in patients with CKD stage 3 (30 ≤ eGFR < 60 mL/min/1.73 m^2) at baseline were analyzed.

Figure 1: DISSOLVE I and II study design[11]



H, high; L, low; NASP, nanoencapsulated sirolimus plus pegadricase; sUA, serum uric acid; TP, treatment period.

RESULTS

Patient demographics and baseline characteristics

- Among 265 treated patients in DISSOLVE I and II, 61 had CKD stage 3.
- Patient demographics, CRG disease characteristics, and severity based on tophi at baseline were largely balanced between the placebo ITT population and subgroup with CKD stage 3 (Table 1).
- All patients had comorbidities at baseline. In CKD stage 3 population, the most common comorbidities were hypertension (67–80%), hyperlipidemia (39–45%), dyslipidemia (13–28%), obesity (13–22%), and diabetes (13–30%).

Table 1: Baseline patient demographics and disease characteristics

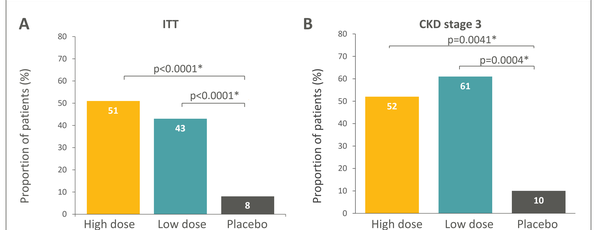
	ITT			CKD stage 3		
	High dose (N=87)	Low dose (N=88)	Placebo (N=90)	High dose (N=20)	Low dose (N=18)	Placebo (N=23)
Age, years, mean (SD)	55.2 (10.8)	54.2 (10.6)	55.3 (10.3)	63.5 (6.3)	59.1 (8.3)	62.1 (9.5)
Age ≥50 years, n (%)	62 (71.3)	58 (65.9)	64 (71.1)	19 (95.0)	14 (77.8)	20 (87.0)
BMI, kg/m^2, mean (SD)	33.5 (5.8)	32.9 (6.8)	32.9 (6.2)	33.2 (6.2)	31.0 (5.9)	32.3 (5.8)
Gender, male, n (%)	82 (94.3)	84 (95.5)	89 (98.9)	18 (90.0)	15 (83.3)	22 (95.7)
Race, white, n (%)	74 (85.1)	73 (83.0)	66 (73.3)	18 (90.0)	15 (83.3)	18 (78.3)
Time since gout diagnosis, years, mean (SD)	12.3 (9.7)	11.7 (9.3)	11.3 (8.5)	12.6 (9.2)	11.0 (9.4)	13.3 (9.7)
sUA level at screening, mg/dL, mean (SD)	8.9 (1.3)	8.9 (1.3)	8.8 (1.3)	8.8 (1.1)	9.0 (1.5)	9.1 (1.6)
Participants with tophi at baseline, n (%)	55 (63.2)	55 (62.5)	57 (63.3)	14 (70.0)	12 (66.7)	18 (78.3)
eGFR, mL/min/1.73 m^2, mean (SD)	72.5 (17.3)	76.0 (21.6)	72.9 (17.4)	52.9 (8.8)	54.4 (14.2)	57.0 (15.0)
Albumin/creatinine ratio, mg/g, mean (SD)	3.5 (3.4)	15.8 (59.0)	4.3 (10.7)	2.8 (2.7)	37.6 (104.7)	2.9 (3.8)

BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; n, number; SD, standard deviation; sUA, serum uric acid.

Primary endpoint: Response rate

- In CKD stage 3 and ITT, both the HD and LD were effective with response rates greater than placebo (Figure 2).

Figure 2: Response rates with NASP vs placebo during TP6 in (A) the pooled ITT population and (B) the CKD stage 3 population



* p-values for each treatment group are based on RD (97.5% CI); RD (97.5% CI) values for pooled ITT population were: high dose vs placebo: 43% (28%, 58%); low dose vs placebo: 35% (21%, 49%); RD values for CKD stage 3 were: high dose vs placebo: 40% (9%, 72%); low dose vs placebo: 50% (18%, 81%). Missing response data in TP6 were multiple imputed. Mantel-Haenszel test was performed with randomization of tophus presence (yes/no) with a two-sided error rate of α=2.5% to account for the two comparisons of study drug against placebo.
CI, confidence interval; CKD, chronic kidney disease; ITT, intent-to-treat; RD, risk difference; TP, treatment period.

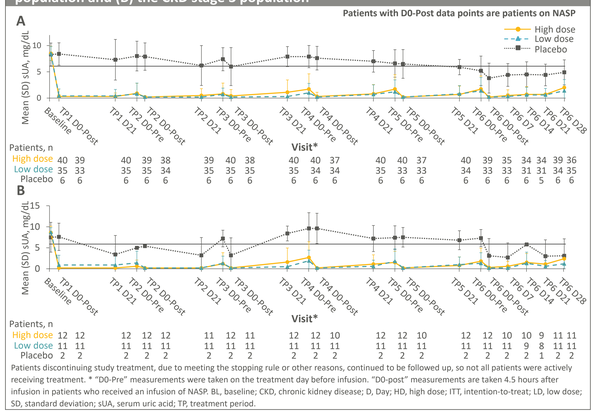
sUA reduction

- In almost all CKD stage 3 responder patients at TP6, NASP treatment resulted in rapid sUA control as early as TP1 and was maintained through TP6 (Figure 3A, B).
- Responders at TP6 had sustained sUA <2 mg/dL throughout the study period.

Laboratory endpoints

- Estimated glomerular filtration rate (eGFR) remained stable in patients treated with HD or LD NASP for up to 6 months in the ITT population and in patients with CKD stage 3 (Figure 4A, B).
  - In the CKD stage 3 population, a trend in improvement in eGFR was observed in the HD and LD groups where the mean (SD) change in eGFR from baseline to Day 28 of TP6 was 3.3 (11.3) and 3.7 (7.5), while a decrease of -2.7 (8.1) was observed in placebo patients.
- Neither HD nor LD NASP treatment for up to 6 months had a major effect on the albumin/creatinine ratio (ACR) in HD- and LD-treated patients in the ITT population and in patients with CKD stage 3 (Figure 4C, D).

Figure 3: sUA reductions from baseline to TP6 in responders for (A) the pooled ITT population and (B) the CKD stage 3 population



Patients discontinuing study treatment, due to meeting the stopping rule or other reasons, continued to be followed up, so not all patients were actively receiving treatment. * "D0-Pre" measurements were taken on the treatment day before infusion. "D0-post" measurements are taken 4.5 hours after infusion in patients who received an infusion of NASP. BL, baseline; CKD, chronic kidney disease; D, Day; HD, high dose; ITT, intention-to-treat; LD, low dose; SD, standard deviation; sUA, serum uric acid; TP, treatment period.

Figure 4: Mean (SD) eGFR over time for (A) the pooled ITT population and (B) the CKD stage 3 population and mean (SD) ACR over time for (C) the pooled ITT population and (D) the CKD stage 3 population

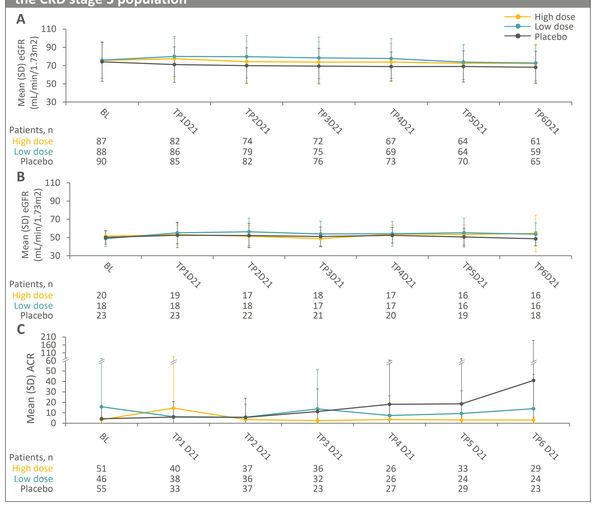
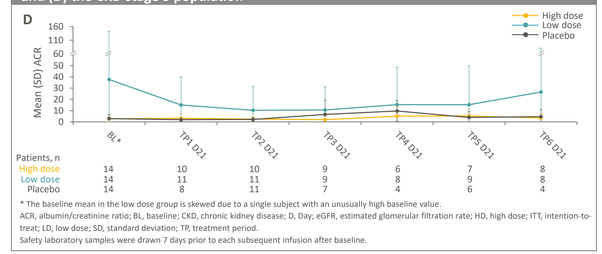


Figure 4 (cont'd): Mean (SD) eGFR over time for (A) the pooled ITT population and (B) the CKD stage 3 population and mean (SD) ACR over time for (C) the pooled ITT population and (D) the CKD stage 3 population



* The baseline mean in the low dose group is skewed due to a single subject with an unusually high baseline value.
ACR, albumin/creatinine ratio; BL, baseline; CKD, chronic kidney disease; D, Day; eGFR, estimated glomerular filtration rate; HD, high dose; ITT, intention-to-treat; LD, low dose; SD, standard deviation; TP, treatment period.
Safety laboratory samples were drawn 7 days prior to each subsequent infusion after baseline.

Safety

- There were no new safety signals in patients with CKD stage 3 treated with NASP and most patients in both groups experienced only mild and moderate treatment-emergent adverse events (TEAEs) (Table 2).
- Serious treatment-related TEAE were rare (3.4% and 3.4% in the HD and LD arms for the ITT group; and 5.0% and 0.0% in the HD and LD arms for the stage 3 CKD group).
- Infections and stomatitis in the CKD stage 3 population were slightly lower in the HD and LD arms compared to the ITT population HD and LD groups.
- In the CKD stage 3 population, renal and urinary disorders were observed in 5% and 11.1% of the HD and LD groups, respectively.
  - In the HD group, renal impairment was observed in 5.0% (n=1).
  - In the HD group, acute kidney injury resulted in treatment discontinuation in 5.0% (n=1).
  - In the LD group, renal impairment and microalbuminuria were observed in 5.6% (n=1) each.

Table 2. Adverse events of special interest, ITT and CKD stage 3*

	ITT			CKD stage 3		
Safety set, patients, n (%)	High dose (N=87)	Low dose (N=88)	Placebo (N=90)	High dose (N=20)	Low dose (N=18)	Placebo (N=23)
≥1 AESI*	56 (64.4)	59 (67.0)	49 (54.4)	12 (60.0)	13 (72.2)	12 (52.2)
Gout flare	37 (42.5)	39 (44.3)	39 (43.3)	9 (45.0)	9 (50.0)	9 (39.1)
Infections (including viral)	20 (23.0)	16 (18.2)	15 (16.7)	3 (15.0)	3 (16.7)	5 (21.7)
Nasopharyngitis	2 (2.3)	0	3 (3.3)	2 (10.0)	0	0
Urinary tract infection	2 (2.3)	3 (3.4)	0	1 (5.0)	2 (11.1)	0
Pneumonia	0	2 (2.3)	0	0	2 (11.1)	0
Infusion-related reaction (24h)	7 (8.0)	6 (6.8)	2 (2.2)	1 (5.0)	2 (11.1)	1 (4.3)
IR (1h)† including anaphylaxis‡	3 (3.4)	4 (4.5)	0	1 (5.0)	0	0
Stomatitis¶	8 (9.2)	3 (3.4)	0	2 (10.0)	1 (5.6)	0

*Most common AESIs in at least 10% in any CKD stage 3 treatment arm. AESIs included gout flares, infections, malignancies, viral infections, interstitial lung disease, stomatitis, infusion-related reactions including anaphylaxis, thrombosis, and the following laboratory tests, if deemed clinically significant by the investigator: hyperlipidemia, worsening of renal function tests, proteinuria, and leukopenia. †IRs within 1h were also included in IRs within 24h. ‡One patient with CKD stage 3 experienced an IR (Grade 3 – Severe anaphylactic reaction) within 1 hour of administration in the HD group. The patient recovered with intravenous diphenhydramine, acetaminophen, and methylprednisolone without hospitalization. ¶Includes mouth ulceration and aphthous ulcer. AE, adverse event; AESI, adverse event of special interest; CKD, chronic kidney disease; incl., including; ITT, intent-to-treat.

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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 Kathleen York, CMPP 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 Kai Neelsen, PhDb of nspm, A 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

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