Characterization of Infusion Reactions Within 1 Hour of Treatment With

Nanoencapsulated Sirolimus Plus Pegadricase: Pooled Results From the Phase 3 DISSOLVE I and DISSOLVE II Trials

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CONCLUSIONS

- Overall, only 4% (n=7/175) of nanoencapsulated sirolimus plus pegadricase (NASP)—treated patients experienced infusion reactions (IRs) within 1 hour of NASP infusion completion
- No patients required resuscitative efforts, ventilatory support, or hospitalization
- All IRs resolved with standard supportive treatment given at the infusion center, generally consisting of parenteral corticosteroids and antihistamines
- The low incidence of IRs suggests that nanoencapsulated sirolimus (NAS) is effective at mitigating anti-drug antibody (ADA) formation



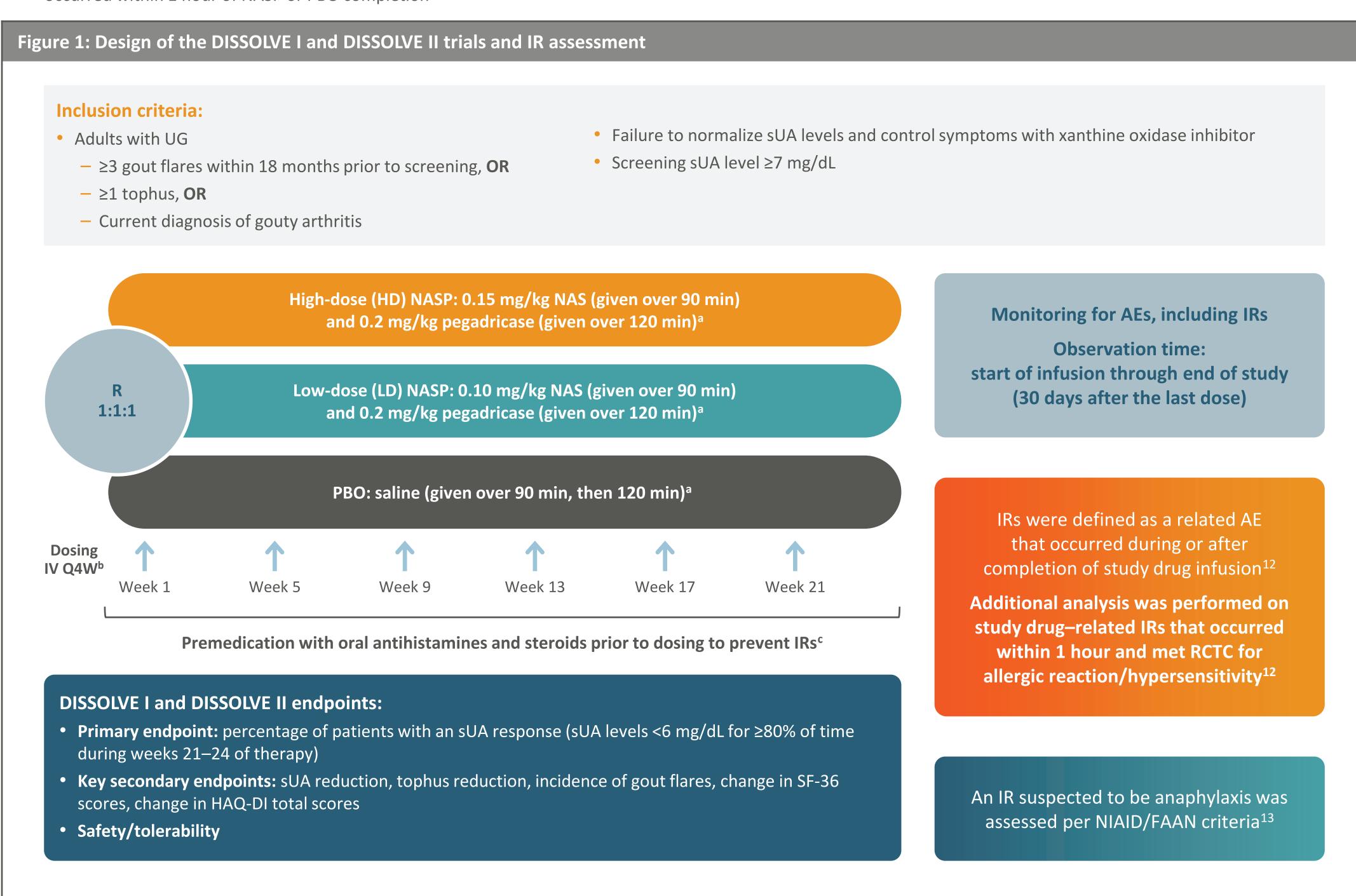
INTRODUCTION AND OBJECTIVES

- Uncontrolled gout (UG) is a chronic and systemic inflammatory arthritis caused by excess monosodium urate stores resulting from a persistent serum uric acid (sUA) elevation, despite the use of oral urate-lowering therapies (ULTs) and manifesting with joint pain, tophi, and gout flares¹
- Not all patients achieve adequate clinical responses to ULTs.¹ Guidelines recommend uricase therapy to reduce sUA in patients with UG²,³; although effective, uricase-based therapies often lead to ADA formation, which can lead to loss of efficacy and predispose patients to IRs⁴,⁵
- Currently, there is only one approved uricase-based therapy for gout⁶; therefore, there is an unmet need for effective enzyme-based alternative therapies for UG that attenuate ADA formation
- NASP (formerly SEL-212) is a novel, every 4-week, sequential, 2-component infusion therapy consisting of nanoencapsulated sirolimus (NAS; formerly SEL-110), which provides targeted immune tolerance to pegadricase through the induction of regulatory T cells, and pegadricase (P; formerly SEL-037), which converts uric acid to soluble allantoin,
- In clinical trials, NASP has demonstrated a statistically significant reduction in sUA levels compared with placebo (PBO). Additionally, reductions in gout flare incidence and the number of tender/swollen joints have been observed; few IRs were reported with NASP^{7,9}
- Here, we report patient-specific details of IRs within 1 hour of NASP completion from the phase 3 DISSOLVE I and DISSOLVE II trials to characterize events that met Rheumatology Common Toxicity Criteria for allergic reaction/hypersensitivity¹² and anaphylaxis

METHODS

resulting in reduced sUA

DISSOLVE I (NCT04513366; US) and DISSOLVE II (NCT04596540; global) were replicate, double-blind, randomized, PBO-controlled, phase 3 trials⁸⁻¹¹ (Figure 1)
 Data from the DISSOLVE I and DISSOLVE II trials were pooled to assess IRs that occurred within 24 hours of NASP or PBO completion and in the subset of patients with IRs that occurred within 1 hour of NASP or PBO completion



Administered as sequential infusions; for patients who received NASP, pegadricase infusion began within 30 min of completion of NAS infusion. barrows indicate time of study drug administration. Premedication included: prednisone 40 mg PO approximately 24 (±12) h predose, and methylprednisolone 100–125 mg (or equivalent) IV approximately 1 (±0.5) h predose. AE, adverse event; FAAN, Food Allergy and Anaphylaxis

Network; h, hour(s); HAQ-DI, Health Assessment Questionnaire-Disability Index; HD, high-dose; IR, infusion reaction; IV, intravenous; LD, low-dose; min, minute(s); NAS, nanoencapsulated sirolimus; NASP, nanoencapsulated sirolimus plus pegadricase; NIAID, National Institute

RESULTS

Infusion reactions

- The incidence of nonanaphylactic IRs within 24 hours of NASP or PBO completion was low; 5.7% (n=15/265) of patients experienced an IR within 24 hours (HD NASP: n=7/87, 8.0%; LD NASP: n=6/88, 6.8%; PBO: n=2/90, 2.2%)
- A low incidence of IRs within 1 hour of NASP infusion was observed. Of 175 patients from the pooled DISSOLVE I and II trials who received NASP, 4.0% experienced an IR, including anaphylaxis, within 1 hour (HD NASP: n=3/87, 3.4%; LD NASP: n=4/88, 4.5%; PBO: n=0; Table 1)
- Three of these events were hypersensitivity reactions (grade 1–2); signs and symptoms were mild, the most common being flushing. The other 4 IRs were anaphylactic reactions (all grade 3 except one); common signs and symptoms included rash and shortness of breath
- Most (n=6/7) occurred shortly after exposure to both NASP components; 1 patient (patient 3) experienced an IR during the NAS infusion only (the patient did not receive pegadricase)

Table 1: Patient characteristics, IRs, and IR treatments among patients who experienced IRs within 1 hour of NASP completion

- All IRs occurred early, within the first 12 weeks of treatment
- Hypersensitivity reactions resolved the same day, all within ~1 hour; most anaphylactic reactions resolved the same day, although in 1 case (patient 4), symptoms lasted for ~3 days
- IRs leading to treatment discontinuation occurred in 3.4% of patients who received LD NASP (n=3; 2 were anaphylactic reactions) and 3.4% of patients who received HD NASP (n=3; 2 were anaphylactic reactions)

For those who discontinued treatment, discontinuation typically occurred on the day of the IR

- No patients required resuscitative efforts, ventilatory support, or hospitalization, and all IRs resolved with standard supportive treatment given at the infusion center, generally consisting of parenteral corticosteroids and antihistamines; 2 patients received epinephrine
- IRs occurring beyond 1 hour did not meet the Rheumatology Common Toxicity Criteria for allergic reaction/hypersensitivity

		Hypersensitivity Reactions			Anaphylactic Reactions ^a			
		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
	Patient characteristics ^b							
	Age, y	35	43	39	63	61	61	40
	Sex	Male	Male	Male	Male	Male	Male	Male
	Race	White	White	White	White	White	Black	White
	BMI, kg/m ²	40.7	37.1	27.8	30.2	35.4	38.6	23.7
	Country	United States	Georgia	Georgia	United States	United States	United States	United States
	Baseline sUA, mg/dL	9.4	8.6	10.8	7.6	9.7	7.3	8.2
	Treatment	HD NASP	LD NASP	LD NASP	HD NASP	HD NASP	LD NASP	LD NASP
	Timing of onset	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3	Dose 3	Dose 2
	Notable signs and symptoms	Rash, nausea, flushing	Itching, flushing	Shortness of breath, sweating, chest pain, flushing, tremble	Nausea, stomachache, rash, flushing, sweating, wheezing, low oxygen saturation, vomiting	Tongue swelling, shortness of breath, flushing, coughing, chest pressure, hives	Restlessness, flushing, rash, low blood pressure, itching, shortness of breath	Vomiting, malaise, low blood pressure, rash, incontinence
Ţ	Grade ^c	1	1	2	3	3	3	4
G ASSET	Medical intervention ^d							
	Methylprednisolone (125 mg)	IM	None	None	IV	IV	IV	None
	Diphenhydramine	None	10 mg IV	None	None	50 mg IV, 25 mg PO	50 mg IV, 25 mg PO	25 mg IV
	Other	Cimetidine 200 mg PO	None	None	Ondansetron 4 mg IV	Epinephrine 0.3 mg IM, albuterol 2 puffs, famotidine 20 mg PO	Fluids	Epinephrine 0.5 mg SC, fluids
	Hospitalization required	No	No	No	No	ER, same-day observation only ^e	No	ER, same-day observation only ^e
	Study drug discontinued	Yes	Nof	Yes	Yes	Yes	Yes	Yes

Anaphylaxis Network; HD NASP, high-dose NASP; IM, intramuscular; IR, infusion reaction; IV, intravenous; LD NASP, low-dose NASP, nanoencapsulated sirolimus plus pegadricase; NIAID, National Institute of Allergy and Infectious Diseases; PO, oral; SC, subcutaneous; sUA, serum uric acid; y, year(s)

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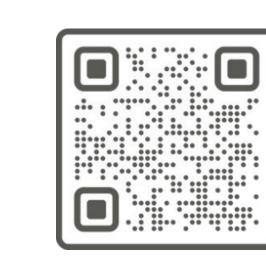
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Disclosur

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of Allergy and Infectious Diseases; PBO, placebo; PO, oral; Q4W, every 4 weeks; R, randomization; RCTC, Rheumatology Common Toxicity Criteria; SF-36, 36-Item Short Form Health Survey; sUA, serum uric acid; UG, uncontrolled gout.