A First-in-Human Phase 1a Randomized, Double-Blind, Single-Ascending Dose Study of NAV-240, an anti-OX40L/TNF-α Bispecific Antibody, in Healthy Volunteers

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BACKGROUND

- Hidradenitis suppurativa (HS) is a debilitating, often chronic and progressive, inflammatory skin disease associated with significant physical and psychological comorbidities that impact the quality of life of patients. Typically, painful inflammatory nodules, abscesses and pus-discharging tunnels develop in axillary, inguinal, gluteal and perianal body sites. Over time these tunnels can lead to severe scarring and deformities.
- The estimated prevalence of HS is about 1% in most studied countries. In the US, estimated prevalence ranges from 1% to 4%. A genetic predisposition, smoking, obesity and hormonal factors are established etiological factors for HS.
- Therapeutic options for moderate to severe HS include antibiotic treatment, anti-TNFα and anti-IL17 biologic therapy, along with surgery. Clinical response to existing therapies in HS is suboptimal, with approximately half of treated patients failing to respond to the FDA-approved dose of adalimumab. Novel HS therapeutic options that aim at improving efficacy and dosing frequency are needed.

Figure 1. OX40L and TNFα signaling targets

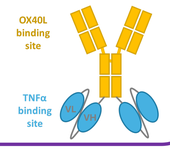
Immune Cells	Th1 (Macrophage, NK, CTL)	T_{reg} (CD4 & CD8 T cells)	Tfh (B cell → Auto-antibody)	Th17 (Neutrophil)	Th2 (Mast Cell, Eosinophil)
TNFα	+++++	+	+	+	+
OX40L	+++	+++	+++	+++	+++

- **OX40** and its ligand **OX40L** are members of the TNFR and TNF superfamilies that play a critical role in autoimmune diseases and are highly expressed on skin of patients with HS.[1] OX40L is present on antigen-presenting cells and activated T cells.
- OX40L signaling co-stimulates many types of immune reaction mediated by T cells, including regulatory cells (Treg), T helper 1 (Th1), T follicular helper (Tfh) cells, T helper 17 (Th17) cells, and T helper 2 (Th2) cells (**Figure 1**). Co-stimulation is essential for an efficient T cell response and, without costimulatory interactions between membrane bound receptor-ligand pairs, a T cell is ineffective.
- OX40L blockade is therefore expected to ameliorate autoantigen-specific T cell responses and reduce immune activity in autoimmune diseases and has shown promising single-agent efficacy in atopic dermatitis.[2] Dual blockade of OX40L and TNFα, a validated therapeutic target in HS, is a potential approach to treating HS.

About NAV-240

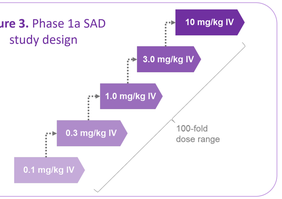
- NAV-240 is a tetravalent bispecific antibody designed to inhibit inappropriate activation of the immune system and inflammation by blocking TNFα and OX40L-induced signal transduction (**Figure 2**).
- NAV-240 acts through dual modification of inflammatory cytokines and adaptive immune responses to rebalance long-term immune homeostasis.
- The synergy of dual-targeting with NAV-240 has been demonstrated in preclinical models of inflammation.[3]

Figure 2. NAV-240 binds both OX40L and TNFα simultaneously



METHODS

Figure 3. Phase 1a SAD study design



- This was a Phase 1a, single-center, randomized, double-blind, placebo-controlled, sequential single ascending dose (SAD) study of NAV-240 in healthy volunteers (NCT06181786). The study comprised 5 single ascending dose cohorts: 0.1, 0.3, 1.0, 3.0, and 10.0 mg/kg. All subjects provided informed consent.
- Randomization: For each cohort, 8 participants were randomized in a 6:2 ratio to active (NAV-240): Control (matched placebo) and included sentinel dosing 1:1 within each cohort at least 48 hour prior to full cohort dosing. Participants received a single IV dose of study drug.
- Safety assessments included AEs (either reported by the participant or observed by the investigator), concomitant medication use, physical examination, ECG, vital signs, and laboratory assessments.
- The pharmacokinetics of NAV-240 were evaluated.

RESULTS

SUBJECTS

- Forty participants were randomized, 30 to NAV-240 and 10 to placebo. All received study drug (NAV-240 or placebo) and completed the study.
- Most participants were female (55.0%, 22/40) and Caucasian (75.0%, 30/40), and all were of Hispanic or Latino ethnicity.
- Mean age was 37 years (range 21-54 years), and mean BMI was 27.1 kg/m^2 (range 19.8-31.7 kg/m^2).

SAFETY

- 5/30 (16.7%) of participants receiving NAV-240 experienced at least 1 treatment-emergent adverse event (TEAE). Only 1 TEAE, at the lowest (0./1 mg/kg) dose level, was possibly related to the study drug.
- 3/10 (30.0%) participants receiving placebo experienced at least 1 TEAE.
- There were no SAEs, or TEAE leading to withdrawal from the study.

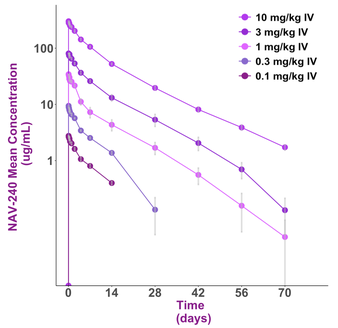
Table 1. Summary of Treatment-emergent Adverse Events

	Statistic	Placebo (n=10)	0.1 mg/kg (n=6)	0.3 mg/kg (n=6)	1 mg/kg (n=6)	3 mg/kg (n=6)	10 mg/kg (n=6)
TEAEs	E	**5**	**2**	**0**	**2**	**0**	**2**
Subjects with ≥1 TEAE	n (%)	**3 (30.0)**	**2 (33.3)**	**0**	**2 (33.3)**	**0**	**1 (16.7)**
Drug-related[1] TEAEs	E	**2**	**1**	**0**	**0**	**0**	**0**
Severe[2] TEAEs	E	**2**	**0**	**0**	**0**	**0**	**0**
Serious TEAEs	E	**0**	**0**	**0**	**0**	**0**	**0**
Discontinuation due to TEAE	n (%)	**0**	**0**	**0**	**0**	**0**	**0**
Deaths due to TEAE	E	**0**	**0**	**0**	**0**	**0**	**0**

E = event, n = number of patients. 1. Relationship to study drug is categorized as "possible," "probable," or "definite". 2. Severity is categorized as Grade 3 or higher.

PHARMACOKINETICS

Figure 4. NAV-240 Arithmetic Mean (+/- SEM) Concentration vs Time



SEM=standard error of mean. Arithmetic mean concentration values below the lower limit of quantification are not shown in the figure above.

Table 2.Summary of Pharmacokinetic Parameters (Geometric Mean (%GCV))

	0.1 mg/kg (n=6)	0.3 mg/kg (n=6)	1 mg/kg (n=6)	3 mg/kg (n=6)	10 mg/kg (n=6)
$AUC_{0\text{-}INF}$ (µg*mL/day)	**16.8** (11.4)	**58.9** (6.70)	**209** (40.2)	**624** (22.6)	**2530** (9.20)
C_{max} (µg/mL)	**2.79** (14.7)	**9.52** (10.1)	**35.2** (9.78)	**84.4** (7.53)	**304** (12.9)
CL (l/day)	**0.456** (12.8)	**0.384** (16.7)	**0.360** (46.1)	**0.336** (17.5)	**0.312** (13.0)
$T_{1/2}$ (days)	**7.20** (28.9)	**7.34** (24.3)	**6.35** (111)	**7.79** (38.8)	**11.9** (5.70)

- The exposure of NAV-240 appeared to increase in a dose-proportional manner over the dose range from 0.1 to 10 mg/kg.
- The geometric means for $AUC_{0\text{-}INF}$ ranged from 16.8 to 2,530 µg*mL/day and for C_{max} from 2.79 to 304 µg/mL.
- The $T_{½}$ was slightly longer with higher doses and ranged from 6.35 to 11.9 days.

DISCUSSION & CONCLUSIONS

- **NAV-240 IV administration of a single dose (up to 10 mg/kg) was generally well-tolerated in healthy participants. There were no deaths, SAEs or TEAE leading to withdrawal from the study, with only one TEAE in a NAV-240 participant that was deemed possibly related to study drug in the lowest dose group (0.1 mg/kg).**
- **NAV-240 demonstrated linear, dose-proportional PK with minimal evidence of target mediated drug disposition.**
- **Population pharmacokinetic and exposure-response models are being developed to select dosing regimens for future studies.**
- **Preliminary modeling and simulation based on these results suggest that monthly administration NAV-240 will lead to serum exposures exceeding a target Ctrough in HS patients, who are known to have an increased clearance of antibodies compared to other disease states such as psoriasis.[4,5]**

Collectively, these data support the continued development of NAV-240 in complex autoimmune conditions such as hidradenitis suppurativa.

References: 1. Navrazhina K et al. 2024 J Am Acad Dermatol 90(4):749-758. **2**. Weidinger S et al. 2024 J Allergy Clin Immunol S0091-6749(24)01175-8. **3.** Kwon HS et al. American College of Rheumatology 2023, abstract 1770. **4.** Nader A et al. 2017 Clin Pharmacokinet 56(9):109-1102. **5.** Jönssen S et al. 15th Annual American Conference on Pharmacometrics 2024, abstract T-041

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