P0556

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

Dana McClintock, MD[1], Tim Mack, PhD[1], Lara Pupim, MD[1], Michael Tagen, PhD[2], Junghyun Lilly Huh[3], Chi Hye Park[3], Gyong Sik Ha, PhD[3], Naveen Daryani, PharmD[1], William Bonificio, PhD[1], Stephen Thomas, PhD[1], Kristie Grebe, PhD[1]

[1]Navigator Medicines, Inc., Scotch Plains, NJ. [2]Verdient Science LLC, Denver, CO. [3]IMBiologics Corp, Republic of Korea

- **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; only one TEAE in a NAV-240 participant in the lowest dose group (0.1 mg/kg) was deemed possibly related to study drug.**
- **NAV-240 demonstrated linear, dose-proportional PK with minimal evidence of target mediated drug disposition.**
- **NAV-240 demonstrated pronounced, concentration-dependent reductions in TARC, a chemokine implicated in both Th2-mediated inflammatory diseases, such as atopic dermatitis[6] as well as in non-type 2 inflammatory diseases such as rheumatoid arthritis[7]**
- **Immunogenicity assessments determined 36.7% of participants in the study were ADA-positive. No apparent impact of ADA on clearance was observed.**
- **Population pharmacokinetic, pharmacokinetic-pharmacodynamic, and exposure-response models are being developed to select dose regimens for future studies.**
- **Preliminary modeling and simulation based on these results suggest that monthly administrations of 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.

INTRODUCTION

- **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.
- **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 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 demonstrated by thymus and activation-regulated chemokine (TARC) concentrations (**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] A recent Phase 2 study assessing dual blockade of OX40L and TNFα using a bispecific nanobody demonstrated clinically meaningful improvement in biologic naive patients with moderate-to-severe HS.[3]

About NAV-240

- NAV-240 is a tetravalent bispecific antibody designed to inhibit overactivation 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 in both in vitro and in vivo settings.[3]
- NAV-240 demonstrated enhanced suppression of cytokine responses compared to single agent or combination treatment when tested in human T cells were stimulated to produce an enhanced inflammatory response (**Figure 3**).

METHODS

- 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 included 5 single ascending dose cohorts: 0.1, 0.3, 1.0, 3.0, and 10.0 mg/kg (**Figure 4**). All subjects provided informed consent.
- For each cohort, 8 participants were randomized (6:2) to active (NAV-240): Control (matched placebo). Participants received a single dose of study drug via IV infusion.
- 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, pharmacodynamics, and immunogenicity 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, and no TEAEs leading to withdrawal from the study.

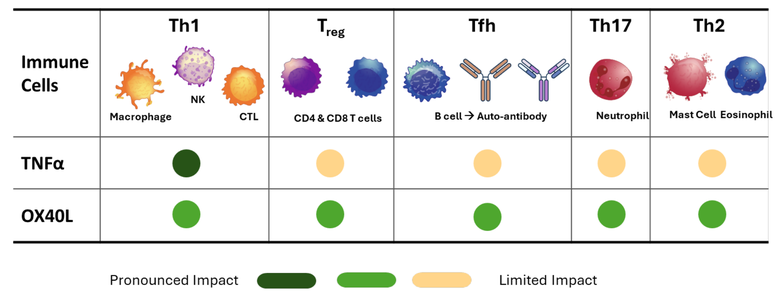
PHARMACOKINETICS & PHARMACODYNAMICS

- The exposure of NAV-240 appeared to increase in a dose-proportional manner over the dose range from 0.1 to 10 mg/kg (**Figure 5**).
  - 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 (**Table 2**).
  - The $T_{½}$ was slightly longer with higher doses and ranged from 6.35 to 11.9 days.
- Concentration-dependent reductions in TARC were observed after NAV-240 administration (**Figure 6**).

IMMUNOGENICITY

- The overall prevalence of anti-drug antibodies (ADA) was 36.7% with ADA detected in 11 out of 30 participants administered NAV-240.

Figure 1. OX40L and TNFα signaling targets



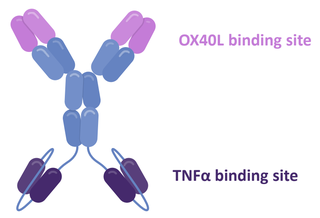
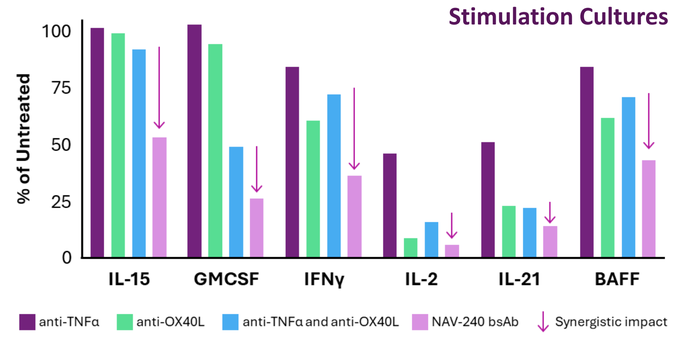


Figure 2. NAV-240 binds both OX40L and TNFα simultaneously

Figure 3. T Cell Stimulation Cultures



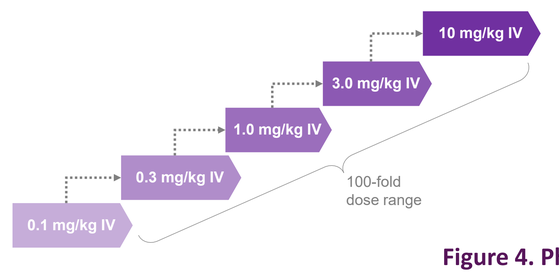


Figure 4. Phase 1a SAD study design

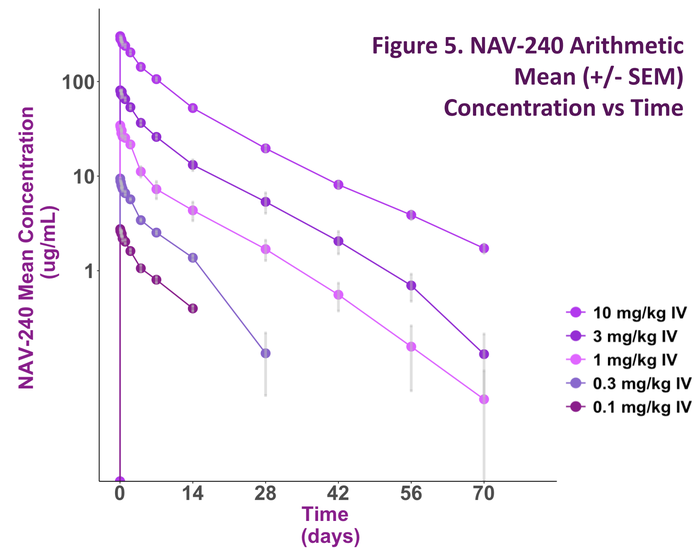


Figure 5. NAV-240 Arithmetic Mean (+/- SEM) Concentration vs Time

Table 1. Summary of Treatment-emergent Adverse Events

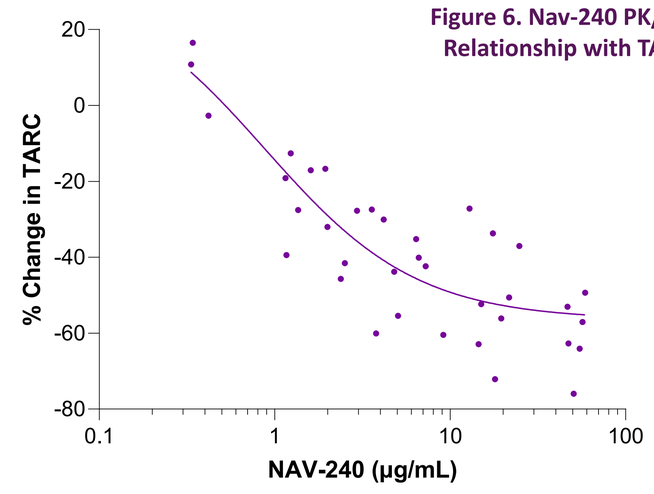
	Statistic	Placebo (n=10)	0.1 mg/kg (n=6)	0.3 mg/kg (n=6)	1 mg/kg (n=6)	3 mg/kg (n=6)	10 mg/kg (n=6)
TEAEs	E	**5**	**2**	**0**	**2**	**0**	**2**
Subjects with ≥1 TEAE	n (%)	**3 (30.0)**	**2 (33.3)**	**0**	**2 (33.3)**	**0**	**1 (16.7)**
Drug-related[1] TEAEs	E	**2**	**1**	**0**	**0**	**0**	**0**
Severe[2]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

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)

Figure 6. Nav-240 PK/PD Relationship with TARC



Presented at the European Academy of Dermatology & Venereology (EADV) Congress, 17-20 September 2025, Paris, France

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. 6. Kakinuma T et al. 2001 J Allergy Clin Immunol 107(3):535-41. 7. Achuthan A et al. 2016 J Clin Invest 26(9): 3453-3466.

Acknowledgements and Disclosure of Industry Support: Authors except MT are employees of Navigator Medicines, Inc or IMBiologics Corp. MT is a consultant to Navigator Medicines. The study was sponsored by Navigator Medicines and IMBiologics Corp. Medical writing and editing assistance were provided by Kate Lewis, MA, funded by Navigator Medicines.