Safety and Tolerability of NIM-1324, an Oral, Once-daily LANCL2 Agonist, in a Randomized, Double-Blind, Placebo-Controlled Phase 1 Study in Normal Healthy Volunteers

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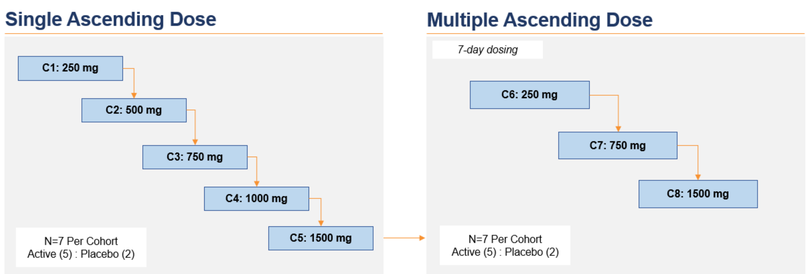
Background. Systemic lupus erythematosus is a complex disease in which the immune system is dysfunctional at multiple levels including impaired regulatory responses, altered self-antigen processing and increased autoantibody production. LANCL2 is a novel therapeutic target that has been first targeted by a gut-restricted compound, omilancor, currently in clinical development for inflammatory bowel diseases. NIM-1324 functions through similar LANCL2-dependent immunometabolic mechanisms, increasing the suppressive capacity and stability of regulatory CD4+ T cells (Treg) while also supporting the metabolic demands of autophagy in phagocytes. The preclinical efficacy of NIM-1324 has been validated in NZB/W, MRL, and pristane-induced models of lupus and the preclinical safety has been demonstrated up to a NOAEL of 1,000 mg/kg/d.

Methods. Oral NIM-1324 was evaluated for safety and tolerability in normal healthy volunteers (n = 56) in a randomized, double-blind, placebo-controlled trial. Volunteers were randomized into five single ascending dose cohorts (250 – 1500 mg, p.o.) and three multiple ascending dose cohorts (250 – 1500 mg QD for seven days, p.o.). Safety and tolerability were assessed by adverse event (AE) reporting, vital signs, ECG, hematology, and clinical chemistry. Blood concentrations of NIM-1324 were measured. Whole blood gene expression and serum cytokines were analyzed as markers of target engagement.

Results. Single and seven-day dosing with NIM-1324 did not result in and SAEs or increases in total AE rates in individual dose cohorts and overall pooled active group relative to placebo. Oral NIM-1324 dosing did not result in any clinically significant findings by biochemistry, coagulation, ECG, hematology, or urinalysis. NIM-1324 was rapidly absorbed after oral dosing and did not accumulate over the seven-day dosing period. Plasma exposure of NIM-1324 was observed to scale in a dose-proportional manner within the range of 250 to 1000 mg/d. Using a whole blood transcriptomic signature developed during preclinical efficacy testing, NIM-1324 upregulated the mRNA expression of genes associated with mitochondrial metabolism and downregulated markers of phagocyte activation. The magnitude of effect in the 250 mg cohort was like those observed preclinically at maximally effective doses.



The mean (SD) age of participants in the SAD arm was 32.5 (13.2) years. The majority of participants where white (28 [80.0%]), with the remainder of subjects Asian (14.3%), Pacific islander (2.9%) and other (2.9%). Gender was reasonably evenly represented (16 [45.7%] females, 19 [54.3%] males). The mean (SD) BMI was 23.97 (2.66) kg/m^2. The mean (SD) age of participants in the MAD arm was 36.5 (12.5) years. The majority of participants where white (19 [86.4%]). Gender was reasonably equally represented (13 [59.1%] females, 9 [40.9%] males). The mean (SD) BMI was 24.80 (2.98) kg/m^2.

Plasma was collected at multiple timepoints up to 24 hours post dosing in both the SAD and MAD arms of the study (**Fig. 1**). Similar but marginally higher exposures were found in the MAD relative to the SAD but a near 1:1 dose proportionality was observed up to doses of 1000 mg/d. The target plasma levels based on nonclinical efficacy and PK/PD studies were achieved within the tested dose levels. The maximum total daily exposure was roughly half of the allowable exposure level based upon GLP toxicity studies.

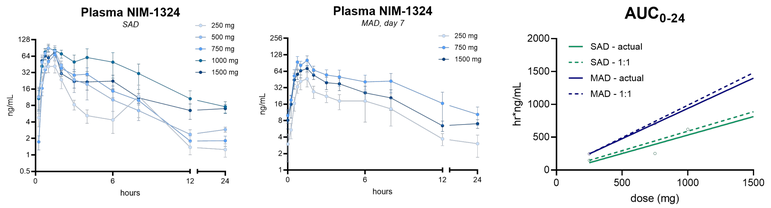


Figure 1. Plasma pharmacokinetics of NIM-1324

TEAE occurred at similar rates in the active dose groups relative to placebo in both the SAD (active: 24%; placebo: 30%) and the MAD (active: 67%; placebo: 71%). System order classes are summarized in **Table 1** with no apparent trends by dose level or relative to placebo. The most commonly occurring TEAE was headache which was reported in a similar number of active (12.5%) and placebo (11.8%) participants. No serious adverse events were experienced and no discontinuations occurred in the active dose groups. Oral NIM-1324 dosing did not result in any clinically significant findings by biochemistry, coagulation, ECG, hematology, or urinalysis. No reduction of white blood cell counts were observed in the active group from baseline or versus placebo.

	SAD							MAD				
	250 mg (n = 5)	500 mg (n = 5)	750 mg (n = 5)	1000mg (n = 5)	1500mg (n = 5)	Active (n = 25)	Placebo (n = 10)	250 mg (n = 5)	750 mg (n = 5)	1500mg (n = 5)	Active (n = 15)	Placebo (n = 7)
At least 1 TEAE, n (%)	0 (0)	2 (40)	3 (60)	0 (0)	1 (20)	6 (24)	3 (30)	2 (40)	5 (100)	3 (60)	10 (67)	5 (71)
At least 1 Grade 3+ TEAE, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
All body systems, n (%)	0 (0)	2 (40)	3 (60)	0 (0)	1 (20)	6 (24)	3 (30)	2 (40)	5 (100)	3 (60)	10 (67)	5 (71)
General, n (%)	0 (0)	1 (20)	0 (0)	0 (0)	0 (0)	1 (4)	1 (10)	0 (0)	1 (20)	2 (40)	3 (20)	2 (29)
Gastrointestinal, n (%)	0 (0)	0 (0)	1 (20)	0 (0)	0 (0)	1 (4)	0 (0)	1 (20)	0 (0)	1 (20)	2 (13)	0 (0)
Ear + Labyrinth, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (20)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Infections, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	2 (40)	1 (20)	3 (20)	2 (29)
Musculoskeletal, n (%)	0 (0)	0 (0)	1 (20)	0 (0)	0 (0)	1 (4)	0 (0)	1 (20)	1 (20)	1 (20)	3 (20)	2 (29)
Headache, n (%)	0 (0)	1 (20)	1 (20)	0 (0)	0 (0)	2 (8)	0 (0)	1 (20)	1 (20)	1 (20)	3 (20)	2 (29)

Table 1. TEAE Summary

In the MAD portion of the study, no differences in absorption, metabolism or excretion were observed between days 1 and 7 (**Fig. 2**). NIM-1324 did not accumulate and daily plasma trough levels were stable throughout the seven days of dosing. Target expression LANCL2, was increased by 50% relative to baseline after 7 days of 250 mg of NIM-1324.

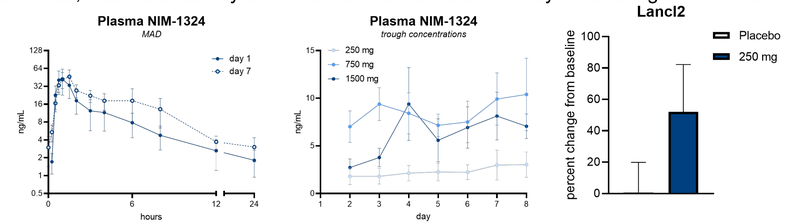


Figure 2. Effects of multiple daily dosing on plasma levels and LANCL2 expression

In healthy mice and murine models of lupus, NIM-1324 provides a consistent upregulation of mitochondrial metabolism and downregulation of phagocyte activation in whole blood. These markers were tested in whole blood RNA collected from placebo and 250 mg dosed subjects (**Fig. 3**). NIM-1324 increased markers of mitochondrial metabolism including mt-ATP8 and Nd6 while decreasing the phagocyte activation markers like Lin28a and Sdc1.

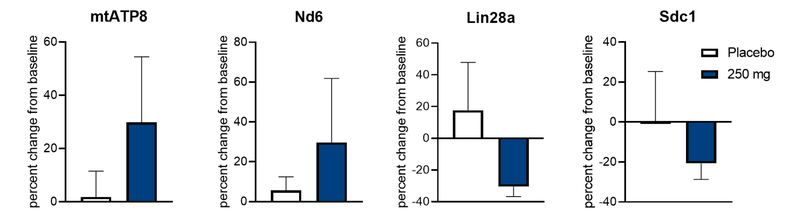


Figure 3. Whole blood RNA expression following 7 days of oral dosing.

The plasma concentrations experienced in the 250 mg cohort are consistent with the observed dose dependency of NIM-1324 in the prevention of type I interferon production in PBMCs collected from SLE patients and treated with NIM-1324 ex vivo (**Fig. 4**).

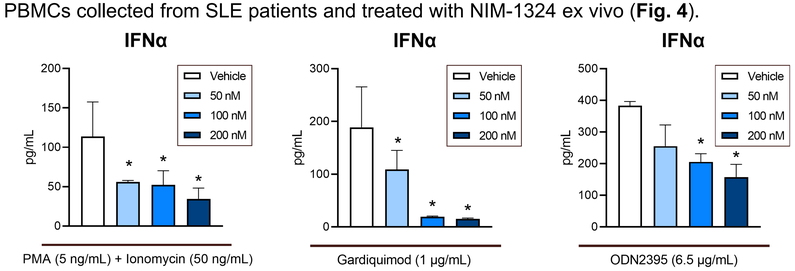


Figure 4. SLE PBMC responses to NIM-1324

Conclusions. Oral treatment with NIM-1324 is well tolerated and safe in humans up to the tested limit dose of 1500 mg/d. Based on the observed safety, pharmacokinetics and target engagement profile, a first-in-patient clinical trial of NIM-1324 in systemic lupus erythematosus is currently planned.