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Safety, Tolerability, and Pharmacokinetics of NIM-1324 an Oral LANCL2 Agonist in a Randomized, Double-Blind, Placebo-Controlled Phase I Clinical Trial

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ABSTRACT

NIM-1324 is an oral investigational new drug for autoimmune disease that targets the Lanthionine Synthetase C-like 2 (LANCL2) pathway. Through activation of LANCL2, NIM-1324 modulates CD4+ T cells to bias signaling and cellular metabolism toward increased immunoregulatory function while providing similar support to phagocytes. In primary human immune cells, NIM-1324 reduces type I interferon and inflammatory cytokine (IL-6, IL-8) production. Oral NIM-1324 was assessed for safety, tolerability and PK in normal healthy volunteers in a randomized, double-blind, placebo-controlled trial. Subjects ($n = 57$) were randomized into five single ascending dose (SAD) cohorts (250, 500, 750, 1000, 1500 mg, p.o.) and three multiple ascending dose (MAD) cohorts (250, 750, 1500 mg QD for 7 days, p.o.). NIM-1324 did not increase total AE rates in individual cohorts or pooled active groups in SAD or MAD with no SAEs in the study. Oral NIM-1324 dosing does not result in any clinically significant findings by biochemistry, coagulation, ECG, hematology, or urinalysis when compared to placebo. Plasma exposure, as measured by area under the curve from 0 to 24 h ($AUC_{0\text{-}24}$), scaled dose proportionally over 250–1000 mg. At 250 mg, NIM-1324 successfully engaged the target with an upregulation of Lancl2 and key transcriptional biomarkers in whole blood. In conclusion, NIM-1324 treatment is well-tolerated up to daily oral doses of at least 1500 mg (nominal), a ≥ six-fold margin over the anticipated therapeutic dose, and 1000 mg (maximum observed exposure), at least a four-fold margin over the anticipated therapeutic dose with no dose limiting toxicities.

1 | Introduction

Recent therapeutic developments, including belimumab, anifrolumab, and voclosporin, have increased the therapeutic options available for the treatment of systemic lupus erythematosus (SLE). However, they have only modest success in managing chronic disease and may cause significant adverse side effects such as increased risks of infection, depression, hypertension, and acceleration of kidney damage, that have been associated with mortality. With the currently available therapeutic options, nearly 60% of SLE patients experience > 1 flare per year or have persistently active disease [1]. In as little as 10 years post-diagnosis, SLE patients accrue neuropsychiatric, renal, cardiovascular and musculoskeletal damage that cause chronic pain in 2/3 of patients [2]. This damage accrual leads to lower quality of life with development of lupus nephritis in up to 50% of patients and end-stage renal disease (ESRD) necessitating kidney transplants in 17% of patients due to poor disease management with current therapeutics [3]. Even after transplant, roughly one-third of patients will have ESRD recurrence. The treatment of SLE remains a complex paradigm which lacks a clear alternative to highly immunosuppressive drugs and steroids as first

Summary

- What is the current knowledge on the topic?
  - LANCL2 is a novel receptor that induces immunometabolic effects to reduce inflammation.
  - Previously, LANCL2 has been targeted by omilancor, a gut-restricted drug, for the treatment of IBD.
  - In Phases 1 and 2 clinical trials, omilancor presented with no dose limiting toxicities and an absence of any trends in adverse events relative to placebo.
  - NIM-1324 was recently developed as a LANCL2 agonist with an improved pharmacokinetic profile to treat systemic autoimmune diseases.
- What question did this study address?
  - This study addressed the safety, pharmacokinetics and target engagement of NIM-1324, a novel LANCL2 agonist, in humans.
- What does this study add to our knowledge?
  - This study provides the first-in-human safety data for the first systemically distributed LANCL2 therapeutic.
- How might this change clinical pharmacology or translational science?
  - NIM-1324 is an investigational new drug for systemic lupus erythematosus, for which the current drugs have a wide array of side effects.
  - This study provides first-in-human safety data to enable further clinical trials in patients with the goal of providing an alternative therapeutic option with reduced side effect profile.

line therapies and remains in need of highly potent therapies for advanced disease.

NIM-1324 is an oral, once-daily small molecule therapeutic with systemic exposure that binds to and activates LANCL2 which is highly expressed in the immune cells and enhanced in anti-inflammatory subsets. LANCL2 is a membrane receptor that was first described as the mammalian target for abscisic acid (ABA), a phytochemical and endogenously produced small molecule compound [4, 5]. Later, functional and expression-based studies elucidated LANCL2 as a critical receptor for Tregs [6–8]. In autoimmune disease, the gut-restricted LANCL2 agonist, omilancor, has proven to be effective in inducing clinical remission in ulcerative colitis and Crohn's disease in Phase 2 clinical trials [9, 10]. Furthermore, genetic deletion of LANCL2 in mice increases susceptibility to severe SLE-like disease [11]. NIM-1324, formerly BT-104, was advanced as a therapeutic lead targeting LANCL2 [12], from NCE libraries of privileged scaffolds based on medicinal chemistry approaches. In investigational new drug (IND)-enabling studies, a benign nonclinical safety profile for NIM-1324 was established. When administered to rats and dogs for 28 days, NIM-1324 had a NOAEL up to the tested limit dose of 1000 mg/kg/day with no observed side effects, hematological dysfunctions, histological changes or clinical symptoms resulting from drug. In safety pharmacology studies specifically focused on the potential for central nervous system, cardiovascular or respiratory effects, a similar 1000 mg/kg/day NOAEL was identified for NIM-1324. Moreover, no genotoxic potential for the molecule was identified through Ames tests, chromosomal aberration and micronucleus tests.

Preclinically, NIM-1324 has proven effective in three mouse models of SLE: the MRL/lpr, NZB/W F1 and bm12 adoptive transfer models [13]. Across these models, NIM-1324 results in increases of regulatory CD4+ T cells, and decreases of T follicular helper cells and T helper 17 cells. These immunological changes are paired with robust efficacy in SLE-relevant biomarkers including proteinuria, anti-dsDNA antibodies, and Type I interferon signature, and overall disease severity by survival, weight loss, kidney histology and organ weight. Mechanistically, the activation of LANCL2 results in potent immunometabolic effects directly within immune cells particularly within late-stage glycolysis [6]. These changes manifest by increases in pyruvate dehydrogenase activity and oxidative phosphorylation that align with regulatory phenotype, which are critically downregulated in human SLE [14–18]. The net result is an increase in number of regulatory CD4+ T cells (Tregs) and suppressive capacity of Tregs with NIM-1324 treatment, which can be potentially restorative to defects present in autoimmune disease [19]. The same immunometabolic pathways are also activated by LANCL2 in phagocytes, functioning to enable immunologically silent clearance of apoptotic debris and prevent autoreactivity [13]. Metabolically, phagocytes have a similar divide with a hyperglycolytic state present in inflammation and SLE [20–22], as opposed to the typical bias to anti-inflammatory responses upon apoptotic cell uptake caused by oxidative phosphorylation [23, 24]. Established in in vitro and in mouse models, these therapeutic actions have also been observed to translate to primary human cells. Peripheral blood mononuclear cells (PBMCs) from SLE patients produce less IL-6, IL-8 and interferon alpha after treatment with NIM-1324 ex vivo [13].

The target indications of NIM-1324 are the treatment of SLE and RA. To evaluate the safety of NIM-1324 in humans, this study tests single and multiple ascending doses of NIM-1324 in normal healthy volunteers in a blinded, placebo-controlled clinical design. As an investigational new therapy for autoimmune disease, particular notice was taken on the systemic hematological parameters after NIM-1324 dosing. Further, the pharmacokinetics of NIM-1324 was assessed within blood to confirm systemic exposure of NIM-1324 in humans. The safety and pharmacokinetic profile described herein is consistent with the nonclinical findings and supports the continued clinical development of NIM-1324.

2 | Methods

2.1 | Ethics

The clinical protocol and participant information and informed consent form (PICF) were reviewed and approved by an appropriate Human Research Ethics Committee (HREC)/IRB (Alfred Hospital Ethics Committee, Protocol LABP-104-1a (488/21)) before the study was initiated. Subsequent amendments to the protocol were reviewed and approved by the HREC/IRB prior to use on the study. The requirements for the conduct of clinical trials in accordance with the applicable regulations of the

Australian Therapeutic Goods Administration (TGA) under the Clinical Trial Notification (CTN) scheme were met before commencement of this study. This study was carried out according to the principles of the Declaration of Helsinki, the Notes for Guidance on Good Clinical Practice (2000) (CPMP/ICH/135/95) and the ICH GCP (as adopted in Australia) and the National Statement on Ethical Conduct in Human Research, (2007 incorporating all updates). Informed consent was obtained before a normal healthy volunteer could participate in the study. The contents and process of obtaining informed consent were in accordance with all applicable regulatory requirements and adhered to ICH GCP guidelines and the requirements in the Declaration of Helsinki.

2.2 | Study Design

The study was designed as a two-stage, single-center, double-blinded, randomized, placebo-controlled study of NIM-1324 in 56 healthy male and female volunteers. The two stages were single ascending dose (SAD), and multiple ascending dose (MAD), Figure 1. The study was run under FDA IND 153949 and registered in clinicaltrials.gov (NCT05019950). All study protocols and procedures were approved by a central IRB.

The SAD cohorts consisted of five groups of seven healthy male and female participants per cohort, each receiving a single oral dose of NIM-1324 or placebo in a 6-h fasted state. A total of five active and two placebo participants per cohort ($n=7$) were used. Upon review of all available safety data, the safety review committee (SRC) decided to progress to escalate to the next cohort of seven subjects (five active and two placebo). Five doses of NIM-1324 (250, 500, 750, 1000, 1500 mg) were evaluated. The MAD cohorts consisted of three cohorts of seven healthy male and female participants, each received an oral dose of NIM-1324 or placebo once daily for 7 days. A total of five active and two placebo participants per cohort ($n=7$) were used. Upon review of all available safety data, the SRC decided to progress to escalate to the next cohort of seven subjects (five active and two placebo). Three doses of NIM-1324 (250, 750, 1500 mg) were evaluated.

2.3 | Test Product

The test product was formulated into tablets containing 250 mg NIM-1324. The dose (NIM-1324 or placebo) was administered orally after at least 6 h fast. Doses of NIM-1324 were administered orally with a full cup (up to approximately 240 mL) of noncarbonated room temperature water. Test product was administered from HDPE bottles. Labeling was in compliance with 21 CFR 312.6. The final label was coded for blinding as appropriate to the study design and in compliance with the protocol. Placebo and NIM-1324 tablets were identical in appearance and dispensed by site pharmacy in compliance with a randomization schedule. The starting dose of 250 mg was selected to be the human equivalent dose representative of the saturating dose of efficacy parameters in nonclinical studies of SLE. The upper limit dose of 1500 mg was approximately 1/40th of the observed NOAEL in GLP repeat dose toxicity studies in rats and dogs.

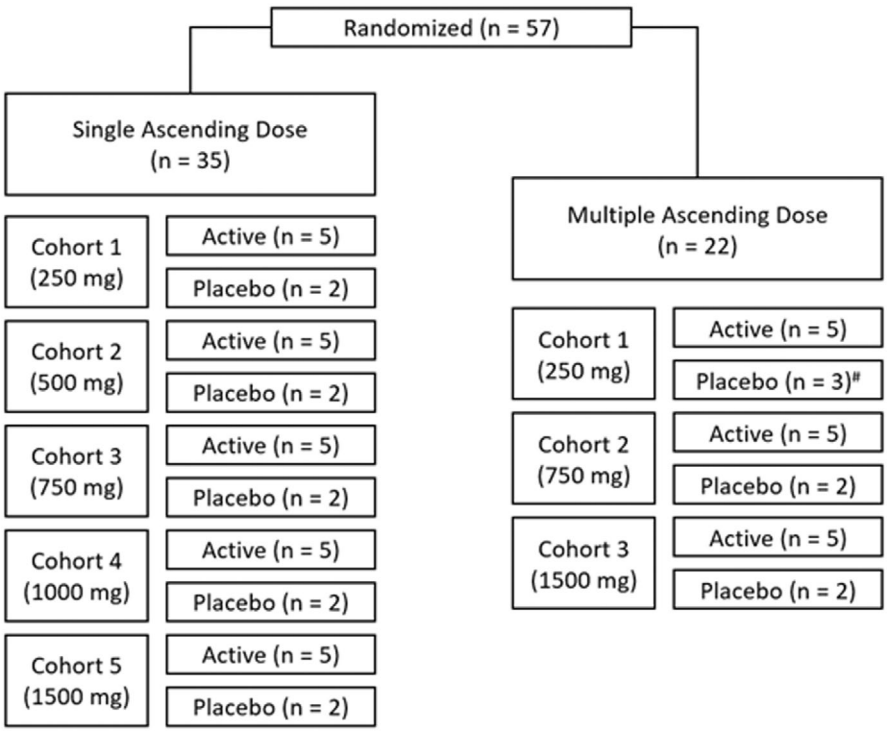

FIGURE 1 | Phase I study design. Five subjects were dosed with active and two subjects were dosed with placebo for each of the five SAD cohorts and each of the three MAD cohorts. #One additional subject was dosed with placebo for MAD cohort 1 due to the early withdrawal of one of the original placebo subjects.

2.4 | Study Population

The study population consisted of healthy adult (ages 18–64) male and female volunteers of body weight 50.0–90.0 kg (inclusive) and body mass index 18–32 kg/m^2 (inclusive). Volunteers had read, confirmed understanding of, and signed the written informed consent form after the nature of the study and all essential elements of the informed consent document had been fully explained and all the volunteer's questions had been answered to his or her satisfaction, prior to initiation of any study procedures. Subjects were excluded if any clinically significant abnormality was identified in the screening history, physical examination (including vital signs), laboratory testing, or electrocardiographic testing. Subjects with any clinically significant cardiac, pulmonary, renal, metabolic, neurologic, or other medical, behavioral, or genetic condition that placed the volunteer at significantly increased risk or may have risked compromise of study objectives were excluded. Volunteers with any disorder that, in the investigator's judgment, may compromise his/her ability to provide legal written informed consent were also excluded. Participants were advised that they were free to withdraw from the study at any time for any reason and PI or medically trained nominee could discontinue a participant from the study to protect the participant's health. Randomization was based on a predetermined schedule. Each subject was assigned to receive either NIM-1324 or placebo. The study was double-blinded, and sealed subject-specific code break envelopes were produced by the contract research organization and retained at the clinical facility in a secure, accessible location.

2.5 | Safety and Tolerability

Safety endpoints were summarized by treatment group. Treatment-emergent AEs were coded using the latest version of MedDRA by SOC and Preferred Term (PT), classified from verbatim terms. The types and frequency of AEs, and SAEs, were summarized by treatment group according to SOC and Preferred Terms. Summaries of Treatment-Emergent Adverse Events (TEAE) were also presented by severity and relationship. The durations of AEs were determined and included in listings, along with the action taken and outcome. Adverse events related to study drug and of at least moderate severity, AEs leading to withdrawal, SAEs were similarly summarized or listed. Cardiac (12-Lead ECG), vital signs and safety laboratory parameters were summarized at each scheduled time point using descriptive statistics of N, mean, standard deviation, median, minimum and maximum value. Similar summaries were presented for change from baseline. The incidence of laboratory abnormalities was summarized. Physical examination findings were presented in listings. Interim safety data analysis was performed for each cohort. Blinded data were provided to the study sponsor. The data informed decisions regarding progression to the next cohorts.

2.6 | Pharmacokinetics

Plasma concentrations of NIM-1324 in samples collected at specified time points post-dose from all participants at different dose levels were used to calculate PK parameters. The PK parameters were determined using non-compartmental methods using Phoenix WinNonLin 8.0. Descriptive statistics of pharmacokinetic parameters included mean, standard deviation (SD), and coefficient of variation (CV), median, minimum and maximum. Dose-related trends in PK parameters were assessed. Accumulation and time dependence were assessed for multiple dosing.

2.7 | Analytical Methods

NIM-1324 concentrations were measured in plasma by a liquid/liquid extraction followed by LC/MS/MS detection method. Method was validated. The analytes were separated by UPLC on a C18 1.7 μm 2.1 × 50 mm column, and the eluates monitored by a Sciex 5500 QTRAP MS/MS detector in positive MRM mode. The extract was then assayed against a calibration curve. The data were acquired and processed by the data acquisition system Analyst (Sciex) linked directly to the MS/MS detector and then processed in Watson LIMS (Thermo Scientific), where applicable.

2.8 | Gene Expression

Whole blood was collected into PAXGene tubes (BD Biosciences) pre-dose on Day 0 and at 4 h post-dose on Day 7. Total RNA was isolated by RNA blood mini kit (Qiagen). Synthesis of cDNA was completed by iScript reverse transcriptase kit (BioRad). Quantitative real-time PCR for Lancl2, mt-Atp8, mt-Nd6, Sdc1, and Lin28a was conducted on a CFX96 instrument (BioRad) using a universal SYBR Green supermix (BioRad). Starting quantity of cDNA was calculated using linear regression against a standard curve.

2.9 | Statistical Analysis

Study was performed with adequate number of subjects per cohort for a first-in-human study to evaluate safety. Safety and PK data was summarized descriptively in tabular form. AEs were summarized by dose level and treatment with grouping according to system organ class and preferred term. Evaluation of severity and relationship to study treatment was also conducted. When relevant, change from baseline was evaluated in addition to standard analysis. Clinical laboratory parameters, vital signs and ECG parameters were tabulated and summarized by dose level. Individual profiles were presented for any parameters outside the standard reference range deemed as clinically significant. SAS 9.3 (SAS Institute Inc., Cary, NC, USA) was used for generating data listings, summary tables, associated figures and statistical analysis.

3 | Results

3.1 | Demographics

In total, 35 healthy subjects were randomized and treated in the SAD and 22 healthy subjects were randomized and treated in the MAD (Figure 1). One subject randomized to placebo developed an upper respiratory tract infection prior to completing dosing

and was withdrawn. The subject was replaced, resulting in the randomization of seven placebo subjects in the MAD cohorts as opposed to the original target of six. All other subjects completed the scheduled dosing and no drop-outs or premature discontinuations were present. SAD subjects were 54.3% male with mean age of 32.5 years and mean BMI of 23.97 kg/m^2 (Table 1). MAD subjects were 40.9% male with mean age of 36.5 years and mean BMI of 24.80 kg/m^2 (Table 1). No notable differences were present within the demographics of each cohort.

3.2 | Adverse Events

In the study, 10 total adverse events were reported within the SAD arm in 9 subjects (Table 2) and 22 total adverse events were reported within the MAD arm in 15 subjects (Table 2). Of these total events, all TEAEs were Grade 1 (mild) in both the SAD and the MAD. Additionally, 6/10 (60.0%) and 16/22 (72.7%) were judged as unrelated or unlikely to be related to test product in the SAD and MAD, respectively. No severe adverse events were reported. No trends in AE presentation were observed in comparison between active and placebo or between specific cohorts. In the SAD, 24% of active subjects experienced at least one TEAE compared to 30% in placebo with seven total TEAEs (0.28 TEAE per subject) in active and three total TEAEs (0.30 TEAE per subject) in placebo and no identified target system organ class. Similar trends in total TEAEs were observed within the MAD with 14 TEAEs (0.93 TEAE per subject) in active and five TEAEs (1.14 TEAE per subject) in placebo. No dose dependent trends emerged in total TEAEs. The most commonly reported adverse event in the SAD arm was fatigue with two reported cases, one in 500 mg active and one in placebo. The most commonly reported adverse event in the MAD arm was headache with five reported cases, one in each dose level of active and two in placebo. Fatigue was reported in three cases in the MAD arm and remained proportionally balanced between active (13.3% of subjects) and placebo (14.3% of subjects). The incidence of infections and infestations was marginally higher in placebo (SAD: 10.0%; MAD: 28.6%) than active (SAD: 0.0%; MAD: 20.0%) in both arms of the study.

3.3 | Clinical Laboratory Results

None of the clinical laboratory results, including serum chemistry, hematology, coagulation and urinalysis, outside the reference range were considered to be clinically significant in either the SAD or MAD. No TEAEs related to study treatment arose from abnormalities in clinical laboratory results in either the SAD or MAD. Further, no treatment or dose related trends in clinical laboratory results or changes from baseline were observed with study treatment. Representative clinical laboratory results, as change from baseline, are presented within Table 3 for the SAD 24 h after single dose and Table 3 for the MAD 24 h after the seventh and final dose. No change from baseline in white blood cell count, red blood cell count or percentages of specific immune cell subsets were observed in blood at a statistically significant rate relative to placebo in any one cohort or across all active subjects. Chemistry markers associated with liver function, including alanine aminotransferase and bilirubin, were not impacted by NIM-1324 at any dose. Similarly, markers associated with kidney function, including creatinine clearance, were not affected. No hypoglycemia occurred in the study and changes from baseline were consistent across all cohorts.

There was no indication of a drug effect or dose–response relationship to NIM-1324 in vital signs, physical examination or electrocardiogram. Additionally, no effect of NIM-1324 was observed on creatine kinase; further supporting the absence of any acute toxicity to the cardiovascular system when paired with a similar lack of effect on QTcF interval and systolic blood pressure. As such, no results were considered clinically significant or reported as TEAEs. No trends in body weight change were observed between active and placebo.

3.4 | Pharmacokinetics

NIM-1324 concentrations were quantified within blood at 13 timepoints (0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 h postdose) on Day 1 of the SAD and Days 1 and 7 of the MAD. Predose trough concentrations were also collected on Days 2–6 of the MAD. Calculated PK parameters are presented in Table 4. Plasma NIM-1324 had a median t_{max} of 0.75–1.5 h (mean: 1.1–1.8 h) across all SAD cohorts with no dose-dependent trend in timing of peak concentration. Plasma NIM-1324 had a median t_{max} of 1.0–1.5 h (mean: 1.2–2.7 h) across all MAD cohorts on both Days 1 and 7 with no dose-dependent trend in timing of peak concentration. After reaching an initial peak, plasma NIM-1324 concentrations declined in a multi-exponential manner in both the SAD and the MAD. $AUC_{0\text{-}24}$ and C_{max} generally increased in a dose proportional manner when doses were increased from 250 to 1000 mg in the SAD arm (mean $AUC_{0\text{-}24}$ range 148.68–621.10 ng × h/mL, mean C_{max} range 47.93–101.95 ng/mL) and when doses were increased from 250 to 750 mg in the MAD arm (mean $AUC_{0\text{-}24}$ range 247.29708.68 ng × h/mL, mean C_{max} range 49.98–122.21 ng/mL). No added exposure was observed at the 1500 mg dose in either arm of the study. Mean accumulation ratio values of 250, 750, and 1500 mg NIM-1324 given once-daily were 1.99, 1.02, and 1.35 for AUC_{τ}, respectively, and were 1.23, 0.80, and 0.93 for C_{max}, respectively. Trough concentrations of NIM-1324 were not observed to increase over the 7-day dosing period. The results indicate little to no accumulation following 1 week of once-daily dosing. The mean $t1/2_{eff}$, observed to be in a range of 4.5–9.1 h across cohorts, were generally consistent with the lack of observed drug accumulation based on the once-daily dosing schedule with no dose-dependent trends.

3.5 | Target Engagement

To evaluate target engagement, whole blood was collected pretreatment and on Day 7 of dosing of the 250 mg MAD cohort in PAXgene tubes. Dosing with 250 mg of NIM-1324 resulted in a 50% increase in whole blood Lancl2 expression relative to baseline (Figure 2A). In comparison, Lancl2 expression had a 0% change from baseline in placebo subjects. Additional biomarkers for LANCL2 engagement were tested in whole blood. NIM-1324 increased markers of mitochondrial metabolism including mt-Atp8 (Figure 2B) and Nd6 (Figure 2C) while decreasing phagocyte activation markers like Lin28a (Figure 2D) and Sdc1

TABLE 1 | Study demographics.

	SAD								MAD					
Parameter	**Cohort 1 250 mg (*N* = 5)**	**Cohort 2 500 mg (*N* = 5)**	**Cohort 3 750 mg (*N* = 5)**	**Cohort 4 1000 mg (*N* = 5)**	**Cohort 5 1500 mg (*N* = 5)**	**Total active (*N* = 25)**	**Placebo (*N* = 10)**	**All subjects (*N* = 35)**	**Cohort 1 250 mg (*N* = 5)**	**Cohort 2 750 mg (*N* = 5)**	**Cohort 3 1500 mg (*N* = 5)**	**Total active (*N* = 15)**	**Placebo (*N* = 7)**	**All subjects (*N* = 22)**
Mean age, years (SD)	29.2 (10.4)	28.8 (8.9)	31.4 (15.4)	43.8 (15.3)	26.8 (8.7)	32.0 (12.7)	33.7 (15.1)	32.5 (13.2)	35.8 (13.0)	35.8 (15.5)	38.0 (12.2)	36.5 (12.7)	36.3 (13.3)	36.5 (12.5)
Sex, *n* (%)														
Female	3 (60.0)	2 (40.0)	3 (60.0)	3 (60.0)	1 (20.0)	12 (48.0)	4 (40.0)	16 (45.7)	2 (40.0)	4 (80.0)	3 (60.0)	9 (60.0)	4 (57.1)	13 (59.1)
Male	2 (40.0)	3 (60.0)	2 (40.0)	2 (40.0)	4 (80.0)	13 (52.0)	6 (60.0)	19 (54.3)	3 (60.0)	1 (20.0)	2 (40.0)	6 (40.0)	3 (42.9)	9 (40.9)
Race, *n* (%)														
Asian	—	3 (60.0)	—	—	1 (20.0)	4 (16.0)	1 (10.0)	5 (14.3)	1 (20.0)	—	1 (20.0)	2 (13.3)	—	2 (9.1)
Native Hawaiian or other Pacific islander	—	—	1 (20.0)	—	—	1 (4.0)	—	1 (2.9)	—	—	—	—	—	—
White	5 (100.0)	2 (40.0)	4 (80.0)	4 (80.0)	4 (80.0)	19 (76.0)	9 (90.0)	28 (80.0)	4 (80.0)	4 (80.0)	4 (80.0)	12 (80.0)	7 (100)	19 (86.4)
Unknown	—	—	—	1 (20.0)	—	1 (4.0)	—	1 (2.9)	—	1 (20.0)	—	1 (6.7)	—	1 (4.5)
Mean BMI, kg/m^2 (SD)	25.3 (2.9)	23 (2.5)	22.5 (2.2)	25.4 (2.6)	23.3 (1.7)	23.9 (2.7)	24.1 (2.4)	24 (2.6)	25 (3.0)	24.1 (2.4)	25.3 (1.0)	24.8 (2.3)	24.8 (3.8)	24.8 (2.9)

TABLE 2 | Summary of treatment emergent adverse events.

	SAD								MAD					
	Cohort 1 250 mg (*N* = 5)	**Cohort 2 500 mg (*N* = 5)**	**Cohort 3 750 mg (*N* = 5)**	**Cohort 4 1000 mg (*N* = 5)**	**Cohort 5 1500 mg (*N* = 5)**	**Total active (*N* = 25)**	**Placebo (*N* = 10)**	**All subjects (*N* = 35)**	**Cohort 1 250 mg (*N* = 5)**	**Cohort 2 750 mg (*N* = 5)**	**Cohort 3 1500 mg (*N* = 5)**	**Total active (*N* = 15)**	**Placebo (*N* = 7)**	**All subjects (*N* = 22)**
At least 1 Grade 3+ TEAE, *n* (%)	0 (0)	2 (40.0)	3 (60.0)	0 (0)	1 (20.0)	6 (24.0)	3 (30.0)	9 (25.7)	2 (40)	5 (100)	3 (60)	10 (67)	5 (71)	15 (68.2)
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)	0 (0)	0 (0)
All body systems, *n* (%)	0 (0)	2 (40.0)	4 (60.0)	0 (0)	1 (20.0)	7 (24.0)	3 (30.0)	10 (25.7)	3 (40)	5 (100)	6 (60)	14 (67)	8 (71)	22 (68.2)
General, *n* (%)	0 (0)	1 (20.0)	0 (0)	0 (0)	0 (0)	1 (4.0)	1 (10.0)	2 (2.9)	0 (0)	1 (20)	2 (40)	3 (20)	2 (29)	5 (22.7)
Procedures and investigations, *n* (%)	0 (0)	0 (0)	1 (20.0)	0 (0)	0 (0)	1 (4.0)	1 (10.0)	2 (5.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal, *n* (%)	0 (0)	0 (0)	1 (20.0)	0 (0)	0 (0)	1 (4.0)	0 (0)	1 (2.9)	1 (20)	0 (0)	1 (20)	2 (13)	0 (0)	2 (9.1)
Ear + Labyrinth, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (20.0)	1 (4.0)	0 (0)	1 (2.9)	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)	1 (2.9)	0 (0)	2 (40)	1 (20)	3 (20)	2 (29)	5 (22.7)
Musculoskeletal, *n* (%)	0 (0)	0 (0)	1 (20.0)	0 (0)	0 (0)	1 (4.0)	0 (0)	1 (2.9)	1 (20)	1 (20)	1 (20)	3 (20)	2 (29)	5 (22.7)
Headache, *n* (%)	0 (0)	1 (20.0)	1 (20.0)	0 (0)	0 (0)	2 (8.0)	0 (0)	2 (5.7)	1 (20)	1 (20)	1 (20)	3 (20)	2 (29)	5 (22.7)

TABLE 3 | Clinical laboratory parameters as change from baseline.

	SAD								MAD					
	Cohort 1 250 mg (*N* = 5)	**Cohort 2 500 mg (*N* = 5)**	**Cohort 3 750 mg (*N* = 5)**	**Cohort 4 1000 mg (*N* = 5)**	**Cohort 5 1500 mg (*N* = 5)**	**Total active (*N* = 25)**	**Placebo (*N* = 10)**	**All subjects (*N* = 35)**	**Cohort 1 250 mg (*N* = 5)**	**Cohort 2 750 mg (*N* = 5)**	**Cohort 3 1500 mg (*N* = 5)**	**Total active (*N* = 15)**	**Placebo (*N* = 7)**	**All subjects (*N* = 22)**
White cell count, 10^6/mL (SD)	0.32 (1.094)	0.22 (0.638)	0.42 (1.085)	−0.30 (0.534)	−0.54 (1.428)	0.02 (0.999)	−0.29 (1.016)	−0.07 (0.999)	−0.14 (0.907)	−0.30 (0.791)	0.20 (0.992)	−0.08 (0.861)	−0.93 (1.271)	−0.32 (1.039)
Erythrocyte count, 10^9/mL (SD)	0.228 (0.105)	0.080 (0.263)	0.078 (0.173)	0.076 (0.288)	0.238 (0.386)	0.140 (0.251)	0.174 (0.267)	0.150 (0.252)	−0.002 (0.122)	−0.086 (0.354)	−0.194 (0.171)	−0.094 (0.235)	−0.258 (0.332)	−0.141 (0.268)
Lymphocytes, % (SD)	−1.70 (3.587)	−2.06 (2.377)	−2.38 (6.290)	0.62 (6.648)	1.64 (4.647)	−0.78 (4.829)	1.87 (5.578)	−0.02 (5.116)	0.32 (2.18)	0.76 (12.48)	−0.28 (7.07)	0.27 (7.77)	5.58 (8.13)	1.79 (8.05)
Alanine aminotransferase, U/L (SD)	4.8 (9.18)	−1.0 (1.22)	−0.8 (1.10)	−1.2 (1.30)	0.6 (0.89)	0.5 (4.49)	−0.2 (1.40)	0.3 (3.85)	14.8 (26.55)	1.2 (3.56)	1.0 (2.55)	5.7 (15.86)	−2.3 (8.91)	3.4 (14.48)
Bilirubin, μmol/L, (SD)	2.8 (1.92)	1.0 (5.24)	−2.0 (4.30)	0.2 (34.2)	−0.4 (4.04)	0.3 (3.94)	2.4 (2.41)	0.9 (3.67)	0.0 (2.92)	−1.2 (4.44)	−4.6 (2.07)	−1.9 (3.65)	−2.3 (6.71)	−2.0 (4.54)
Creatine kinase, U/L (SD)	−69.8 (92.83)	−20.2 (9.68)	−25.0 (22.57)	−17.2 (9.34)	−48.6 (56.92)	−36.2 (50.13)	−29.6 (29.99)	−34.3 (44.96)	−19.2 (19.72)	−25.2 (44.55)	−57.8 (65.68)	−34.1 (47.10)	−33.2 (27.30)	−33.8 (41.71)
Creatinine clearance, mL/min (SD)	2.6 (10.74)	2.4 (16.29)	8.2 (5.93)	2.8 (6.83)	1.0 (11.58)	3.4 (10.29)	−2.0 (8.11)	1.9 (9.91)	6.0 (12.19)	8.8 (9.83)	2.8 (11.10)	5.9 (10.57)	10.2 (8.66)	7.1 (10.04)
Glucose, mmol/L (SD)	−0.24 (0.321)	0.08 (0.179)	−0.32 (0.327)	0.18 (0.277)	0.08 (0.130)	−0.04 (0.311)	0.06 (0.306)	−0.01 (0.309)	0.08 (0.164)	−0.10 (0.265)	0.12 (0.487)	0.03 (0.324)	−0.17 (0.372)	−0.02 (0.342)
QTcF, ms (SD)	−12.2 (12.44)	−9.0 (8.43)	−6.8 (9.28)	−7.4 (10.04)	−7.2 (8.35)	−8.5 (9.19)	−6.0 (11.81)	−7.8 (9.90)	−3.2 (4.71)	−4.6 (9.45)	−13.4 (6.50)	−7.1 (8.11)	−8.5 (8.26)	−7.5 (7.97)
Systolic blood pressure, mmHg (SD)	1.8 (7.01)	−2.6 (11.93)	−1.4 (6.80)	−1.0 (4.90)	8.2 (10.92)	1.0 (8.90)	7.1 (8.28)	2.7 (9.05)	1.0 (8.97)	2.4 (12.54)	−0.2 (11.32)	1.1 (10.28)	3.7 (8.16)	1.8 (9.60)

TABLE 4 | Plasma pharmacokinetic parameters.

	SAD					MAD		
	Cohort 1 250 mg (*N* = 5)	Cohort 2 500 mg (*N* = 5)	Cohort 3 750 mg (*N* = 5)	Cohort 4 1000 mg (*N* = 5)	Cohort 5 1500 mg (*N* = 5)	Cohort 1 250 mg (*N* = 5)	Cohort 2 750 mg (*N* = 5)	Cohort 3 1500 mg (*N* = 5)
Cmax, ng/mL (SD)	47.93 (21.298)	101.95 (29.635)	67.88 (27.279)	100.78 (34.794)	80.01 (19.094)	49.98 (24.856)	122.21 (47.518)	85.39 (25.752)
Day 7: Day 1	—	—	—	—	—	1.23	0.80	0.93
tmax, h (SD)	1.2 (0.30)	1.4 (0.37)	1.5 (0.00)	1.8 (1.12)	1.1 (0.37)	2.7 (2.69)	1.2 (0.48)	1.5 (0.51)
AUC0-24, h*ng/mL (SD)	148.68 (87.652)	267.13 (119.199)	253.33 (92.951)	621.10 (362.505)	340.99 (114.651)	247.29 (152.457)	708.68 (442.663)	435.82 (166.618)
Day 7: Day 1	—	—	—	—	—	1.99	1.02	1.35
Dose proportionality	—	1.80	1.70	4.18	2.29	—	2.87	1.76
t1/2, h (SD)	4.8 (0.82)	7.6 (3.50)	4.5 (0.66)	6.3 (1.18)	9.1 (3.35)	7.6 (1.48)	6.4 (1.55)	7.8 (3.16)
Trough concentration, ng/mL (SD)	1.25 (0.693)	2.91 (0.614)	1.82 (0.774)	7.61 (3.580)	7.03 (2.606)	2.98 (3.141)	9.92 (5.478)	8.14 (5.010)

(Figure 2E). In mice with SLE, percent change relative to vehicle controls were +50% (mt-ATP8), +70% (mt-Nd6), −37% (Lin28a), and −43% (Sdc1). Differences in healthy mice were on average 40% less than those in SLE mice.

4 | Discussion

The primary objective of this first-in-human study was to investigate the safety and tolerability of single and multiple doses of NIM-1324 in healthy volunteers. All TEAEs were of mild severity and did not present at differing rates between NIM-1324 and placebo groups, regardless of the dose of NIM-1324. NIM-1324 cohorts had marginally lower rates of infection relative to placebo. While promising, subjects were only dosed for a maximum of 7 days and under confinement to the clinical site, indicating that continued comparison is needed. However, unlike most immunosuppressants used in SLE, such as prednisone, azathioprine, and mycophenolate mofetil, NIM-1324 did not result in a change in white blood cell count or other hematology related parameters. These initial results are consistent with findings from nonclinical studies and suggest a lower risk for systemic immunosuppression with NIM-1324 relative to market competition. A primary drawback for current SLE therapeutics is the risk for side effects. Patients on belimumab experience higher rates of depression, headache, rash, and diarrhea [25]. Anifrolumab is associated with increased rates of respiratory and infectious adverse events including nasopharyngitis, bronchitis, influenza, and herpes zoster [26]. Voclosporin is associated with hypertension, decreases in glomerular filtration rate, and headache in parallel to increase risk of respiratory infection-associated mortality. As a result, these newly approved therapeutics are generally limited to use in advanced or refractory disease. Yet first-line therapeutics still possess risks for severe side effects such as teratogenicity, progressive multifocal leukoencephalopathy, skin malignancies, and infections for mycophenolate mofetil or retinal toxicity and cardiomyopathy with hydroxychloroquine.

A potential underlying cause of these side effects for currently marketed drugs is the need for chronic corticosteroid use to prevent or treat disease flares. Corticosteroids have side effects including cataracts, osteoporeosis, and cardiovascular damage [27, 28]. With common steroid doses ranging from 7.5 to 100 mg, every 1 mg/day increase in steroid use results in a 2.8% increase in risk for new organ damage in SLE [29], making the need for new steroid-sparing alternatives crucial. SLE is recognized to be comprised of a highly heterogeneous population. The current treatment paradigm reflects this in its complexity but also in the stacking of multiple highly immunosuppressive agents to achieve efficacy [30]. We believe that NIM-1324 has the potential to possess a similar benign safety profile when evaluated in placebo-controlled trials stratified for baseline medications. In preclinical development, the full panel of CYP isoforms, metabolic enzymes, and transporters were evaluated with NIM-1324. None were observed to be inhibited or induced by NIM-1324 at physiologically relevant concentrations. In the present study, NIM-1324 did not result in white blood cell depletion, a common detriment of the currently available immunosuppressive agents for SLE. With the promising safety results presented in

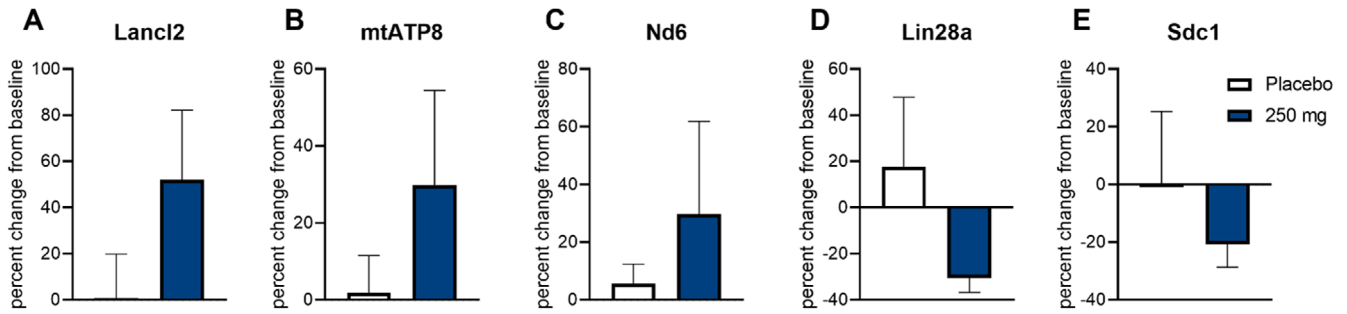

FIGURE 2 | Gene expression of LANCL2 associated markers in whole blood. qRT-PCR based gene expression of Lancl2 (A), mt-Atp8 (B), mt-Nd6 (C), Lin28a (D), and Sdc1 (E). Data are presented as mean percent change from baseline at 4 h post-dose on Day 7 of the MAD cohort for placebo ($n = 6$) and 250 mg NIM-1324 ($n = 5$).

this manuscript along with the low drug–drug interaction potential from previous evaluation of metabolic enzymes and drug transporters [12, 31], NIM-1324 is an intriguing candidate for combination therapy due to its potentially lower risk to amplify side effects.

This study validates this lower risk of systemic LANCL2 activation for the first time in humans. After 7 days of dosing in the MAD, the four most common adverse events by system organ class were headache, musculoskeletal, infections, and general disorders and administration site conditions, each occurring in five subjects. The rate of occurrence in the active groups was proportionally lower (20%) than the placebo group (29%) in each instance. The majority (14/22) of these TEAEs were considered unrelated to study drug, with 5/8 of the possibly related or higher TEAEs being headache, which was evenly distributed across active doses and placebo. The remaining three possibly related TEAEs were an upper respiratory tract infection in placebo, constipation in the 250 mg group and diarrhea in the 1500 mg group. Given the single occurrence of gastrointestinal disorders, the lack of dose dependency, and the confinement to study site diets, these adverse events would not be expected to persist throughout the clinical development of NIM-1324. The absence of dose limiting toxicities in this study were confirmed through quantitative laboratory results, as key markers for hematological, liver, cardiac and renal health all showed no clinically significant change from baseline or trends relative to placebo.

The well tolerated nature of NIM-1324 is in agreement with prior Phase 1 studies of LANCL2 agonists. In a single-site SAD/MAD Phase 1 study in normal healthy volunteers, the gut-restricted omilancor had a similar lack of TEAE trends and absence of detrimental effects on hematological parameters across doses and compared to placebo. At the time, a partial explanation was attributed to the gut-restricted PK profile, in which < 1% of administered drug was absorbed. While the delivery of high concentrations of omilancor directly to the site of inflammation is still advantageous to the treatment of IBD, the study presented within this manuscript suggests that the absence of TEAEs is more likely to be inherent to the safety of the LANCL2 mechanism than the gut-restricted PK. This conclusion is further reinforced by the generally recognized as safe (GRAS) status of the natural LANCL2 ligand, ABA, which itself has supportive nonclinical data exceeding 1000 mg/kg/day [5, 32, 33].

Across cohorts, daily exposure increased in a generally dose proportional manner within the range of 250–1000 mg, with the calculated ratio of 4.18 for a four-fold dose increase for the highest and lowest SAD doses tested of this range and a 2.87 for a three-fold dose increase for the highest and lowest MAD doses tested of this range. Importantly, the one cohort that does not match this trend, SAD Cohort 3, is a nominal dose that is also tested in the MAD (Cohort 2), in which it does match the expected trend. Given that the MAD had similar results on both Days 1 and 7, it is more likely that the SAD cohort was an outlier, potentially attributable to the low number of subjects ($n = 5$) per cohort. In both the SAD and MAD, the 1500 mg dose did not result in a higher exposure. Notably, a difference in demographics was present between the highest dose and second highest dose in the SAD, with the highest dose cohort comprised with a greater proportion of males. Given the slight decrease in exposure at 1500 mg, this difference in demographics likely explains the variation from an exact plateau of exposure but does not suggest that any increase in exposure is likely to occur in a case of matching demographics. In about 30% of drugs, exposure is higher in women than in men [34]. While differences in body weight, body fat, and overall volume of distribution likely contribute to this, women also possess a slower gastric emptying time, a lesser glomerular filtration rate and altered expression of metabolic enzymes in the liver [35–37]. As NIM-1324 appears to be both passively absorbed early in the gastrointestinal tract and passively cleared by the kidney, it is reasonable to hypothesize that the difference in gastric emptying time and lower glomerular filtration rate contribute to any sex differences in NIM-1324 peak concentrations and daily exposures.

Trough values were low (< 10 ng/mL) in all cohorts of the study. A slight elevation was observed in cohorts that experienced daily exposure beyond approximately 400 h*ng/mL, including the two highest dose levels in each arm. Notably, trough concentrations in this study were defined as 24 h since the last dose. Preclinically, when times extending beyond 24 h were evaluated, clearance to undetectable drug levels occurred around 36–48 h. This suggests that concentrations are higher in these cohorts simply due to higher peak concentrations combined with the 24-h timepoint still coinciding with a linear rate of elimination. However, the cohort with the highest average trough concentration, MAD Cohort 2, had a Day 7: Day 1 accumulation ratio of 1.02 in daily exposure, suggesting that this is a limited concern for accumulation with chronic

dosing. Additionally, daily trough concentrations were not observed to vary in a time-dependent manner with average day-to-day gain ranging from 4.8% in the low-dose group to 3.6% in the high-dose group and no monotonic increasing trend in any dose.

Based on in vitro metabolism studies, limited drug is metabolized in hepatocytes and microsomes. Further, no induction of CYP isoforms was observed in vitro, making it unlikely that increasing dose meaningfully shifted plasma concentrations based on liver metabolism. Urine concentrations were generally low in comparison to blood concentrations and stable across doses, suggesting that elimination occurs at a constant passive rate. NIM-1324 did not influence MRP2 activity nor was it a substrate of P-gp, further suggesting that elimination is an unlikely cause of concentration plateau. Given the conventional profile of plasma NIM-1324 in most patients, enterohepatic circulation of the drug is unlikely. With an absence of excretion and metabolism mechanisms, it is reasonable to speculate the saturation of NIM-1324 beyond 1000 mg oral doses is due to a saturation of absorption for the formulation used in this study.

Preclinical studies in mouse models of lupus and other autoimmune diseases, NIM-1324 had a maximum efficacious dose of 20 mg/kg/day [13]. Using standard human equivalent dose adjustments, this dose translates to 1.63 mg/kg/day for a human or roughly 105 mg/day, assuming an average weight of 65 kg. In PK studies parallel to the murine efficacy studies, the daily exposure in mice at 20 mg/kg/day was approximately 200 h × ng/mL, making this the proposed therapeutic threshold. This is lower than the average daily exposure in the 250 mg group of the MAD, which had an average $AUC_{0\text{-}24}$ of 247.29 h × ng/mL, suggesting that a target dose for efficacy would be in the range of 105–250 mg. Notably, this threshold was achieved by 4/5 subjects in MAD Cohort 1 and 5/5 subjects in MAD Cohort 2. Further, Days 1–7 variability within individual subjects was low in the MAD, suggesting that stable exposure can be titrated by oral dose in individual patients, if needed. Prior study of LANCL2 agonists indicated that expression of LANCL2 in the target tissue was the most predictive marker for target engagement and response to therapy [38]. At 250 mg, NIM-1324 provided a 50% increase in whole blood LANCL2 expression relative to baseline after 7 days of dosing. It is unlikely that this is attributable to a change in diet or other site considerations given the placebo group had no percent change from baseline observed. The other four selected markers were originally identified from a large group of differentially expressed genes from SLE patient PBMCs. To assess in both healthy and disease states, we then tested this group of genes preclinically in mice, wherein healthy wild-type mice and SLE-like MRL/lpr mice were treated with placebo or NIM-1324. RNA was isolated from whole blood after treatment and sequenced. Genes that were differentially expressed by treatment in both WT and MRL/lpr were analyzed to identify a predicted target engagement signature. Sdc1, mt-ATP8, mt-Nd6, and Lin28a were among the most predictive genes in the study. Each of these genes is also mechanistically linked to aspects of SLE pathogenesis including mitochondrial dysfunction, myeloid cell activation, cell death and activation of T follicular helper cell expansion by germinal center B cells. A key downstream effect of LANCL2 activation in immune cells in support of mitochondrial metabolism, which was also validated at this dose level by expression of mt-Atp8 [39] and Nd6 [40]. The observation of sufficient target engagement, by gene expression of LANCL2 and biomarkers in whole blood, further indicates that 250 mg may be the maximum dose needed for therapeutic effects in humans.

With anticipated therapeutic doses of 250 mg and lower, in the form of a once-a-day dosing by oral tablets, the results of this study provide a safety margin of ≥ 6-fold based on nominal dose and ≥ 4-fold based on exposure in humans and no concerns about dose-limiting toxicities. These studies further validate the benign safety profile identified in IND-enabling studies including 28-day repeat dose GLP toxicity studies in rats and dogs up to oral doses of 1000 mg/kg/d. NIM-1324 is a safe and well tolerated oral investigational new drug that activates a unique immunometabolic LANCL2 pathway in SLE. Through systemic action, NIM-1324 provides not only a decrease in inflammation but an increase in regulatory responses mediated by Tregs and phagocytes that may prove critical in the induction and maintenance of clinical responses during treatment of SLE.

Following SAD and MAD studies, oral NIM-1324 dosing is well-tolerated up to nominal oral doses of 1500 mg with no trends in TEAEs or clinical laboratory results relative to placebo. Oral NIM-1324 poses minimal risk for systemic immunosuppression with no changes to white blood cell counts after 7 days of dosing. Plasma concentrations scale in a dose proportional manner within the target therapeutic range and up to 1000 mg/day. NIM-1324 is judged to be well-tolerated to advance into Phase 1b/2a clinical trials in SLE patients.

Author Contributions

Andrew Leber and Josep Bassaganya-Riera wrote the manuscript; Andrew Leber, Raquel Hontecillas, and Josep Bassaganya-Riera designed the research; Andrew Leber performed the research; Andrew Leber, Nuria Tubau-Juni, and Josep Bassaganya-Riera analyzed the data.

Conflicts of Interest

JBR is a shareholder of NImmune Biopharma. The authors declared no additional conflicts of interest.

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