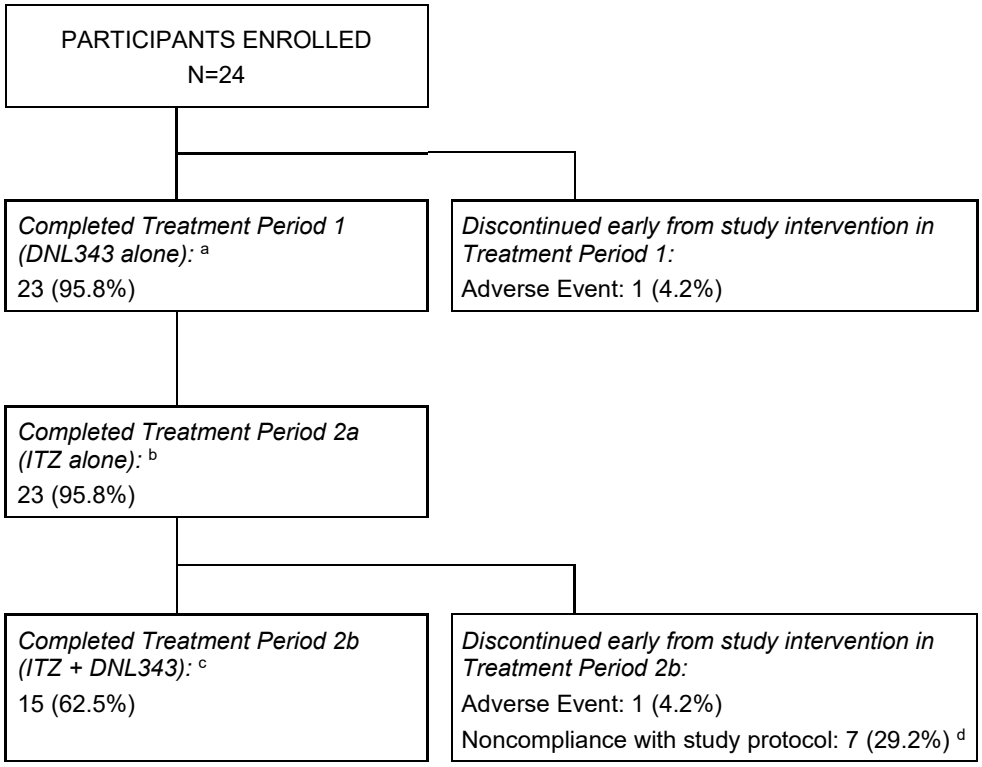
BASIC RESULTS SUMMARY

Study Title:	A Fixed-Sequence, Drug-Drug Interaction Study Evaluating the Effect of the Cytochrome P450 3A Inhibitor Itraconazole on DNL343 in Healthy Participants
Study Number:	DNLI-F-0005
Name of Investigational Product:	DNL343
Indication Studied:	Not applicable
Development Phase of the Study:	Phase 1
Study Sponsor:	Denali Therapeutics Inc. 161 Oyster Point Boulevard South San Francisco, CA 94080 USA
Clinical Study Report Type:	Final Report
Clinical Study Report Date:	21 July 2023

1. Participant Flow

Participant flow is summarized in Figure 1.

Figure 1: Participant Flow



Abbreviations: COVID-19, coronavirus disease 2019; ITZ, itraconazole; TEAE, treatment-emergent adverse event.

Notes: Percentages are based on the number of enrolled participants.

[a] Participants who completed Treatment Period 1 were treated with one dose of DNL343 and did not discontinue study intervention prior to the start of Treatment Period 2 (Day 15).

[b] Participants who completed Treatment Period 2a were treated with at least one dose of ITZ and did not discontinue study intervention prior to the start of Treatment Period 2b (Day 18).

[c] Participants who completed Treatment Period 2b were treated with the second dose of DNL343 (on Day 18) and did not discontinue study intervention.

[d] Seven participants had an important protocol deviation whereby they received DNL343 and ITZ in the fed state (ie, after breakfast) on Day 18 instead of in the fasted state as was stipulated in the study protocol. These 7 participants were discontinued early from study intervention the following day (Day 19) due to noncompliance with the study protocol.

2. Baseline Characteristics

Baseline characteristics are summarized in Table 1.

Table 1: Demographics and Baseline Characteristics

Characteristic	Total N = 24
Age (years)	
n	24
Mean (SD)	31.5 (8.94)
Median	30.5
Min, max	20, 53
Sex, n (%)	
Male	24 (100.0)
Female	0
Race, n (%) [a]	
American Indian or Alaska Native	0
Asian	1 (4.2)
Black or African American	1 (4.2)
Native Hawaiian or other Pacific Islander	0
White	22 (91.7)
Other	1 (4.2)
Ethnicity, n (%)	
Hispanic or Latino	2 (8.3)
Not Hispanic or Latino	22 (91.7)
Weight (kg) [a]	
n	24
Mean (SD)	80.44 (9.922)
Median	79.90
Min, max	64.7, 97.2
BMI (kg/m^2) [a]	
n	24
Mean (SD)	25.344 (2.442)
Median	25.519
Min, max	21.223, 30

Abbreviations: BMI, body mass index; min, minimum; max, maximum; SD, standard deviation.
Note: Percentages are based on the number of enrolled participants.
[a] Percentages for race may add to more than 100% since a participant may have more than one race chosen.

3. Pharmacokinetics Results

Geometric mean ratios and associated 90% confidence intervals for the comparison of DNL343 pharmacokinetic (PK) parameters for DNL343 alone (Treatment Period 1) and ITZ + DNL343 (Treatment Period 2) were within 80% to 125%, indicating no clinically significant drug-drug interaction; therefore, DNL343 is not considered to be a sensitive substrate of CYP3A. Pharmacokinetic results are presented for the primary PK analysis in Table 2.

Table 2: Primary Analysis: Statistical Analysis of Plasma DNL343 PK Parameters

PK Parameter	LS Geometric Mean [a]		Ratio of LS Geometric Mean [b] (Test:Reference) (90% CI) [a]	Intraparticipant CV (%)
	DNL343 Alone (Reference) N = 17	ITZ + DNL343 (Test) N = 16		
C_{max} (μM)	n = 17 0.617	n = 16 0.533	86.32 (80.09, 93.03)	12.2
AUC_{last} (μM · h)	n = 17 43.9	n = 15 [c] 49.0	111.68 (102.27, 121.95)	13.8
AUC_{∞} (μM · h)	n = 17 44.5	n = 16 50.5	113.49 (104.81, 122.89)	12.9

Abbreviations: AUC_{last}, area under the concentration-time curve from time zero to time of last measurable concentration, AUC_{∞}, AUC from time zero to infinity; CI, confidence interval; C_{max}, maximum concentration; CV, coefficient of variation; ITZ, itraconazole; LS, least-squares; PK, pharmacokinetic(s).
Note: Participants with an important protocol deviation and unevaluable PK data for Treatment Period 2 were not included in the primary analysis per the statistical analysis plan.

[a] LS means and 90% CIs were obtained from a linear mixed-effects model on log-transformed values of the parameter, which were transformed back to the original unit for presentation.

[b] Ratio of the LS geometric means for Test and Reference as a percentage.

[c] Two PK blood samples were not collected for one participant due to an adverse event in Treatment Period 2, resulting in a truncated plasma concentration-time profile; therefore, the AUC_{last} for this participant was excluded from the Treatment Period 2 analysis.

4. Adverse Events

All treatment-emergent adverse events reported are summarized by Preferred Term in Table 4. No deaths, other serious adverse events (SAEs), or adverse events of special interest (AESIs) were reported. All TEAEs were assessed as Grade 1 or Grade 2 in severity by the investigator.

Table 3: Summary of All Treatment-Emergent Adverse Events by Preferred Term

Preferred Term	Treatment Period 1 (DNL343 Alone) N = 24	Treatment Period 2a (ITZ Alone) N = 23	Treatment Period 2b (ITZ + DNL343) N = 23	Total Treatment Period 2 N = 23	Total N = 24
Number of participants with at least one event	3 (12.5)	1 (4.3)	3 (13.0)	4 (17.4)	7 (29.2)
Asymptomatic COVID-19 [a]	1 (4.2)	0	0	0	1 (4.2)
Diarrhoea	0	0	1 (4.3)	1 (4.3)	1 (4.2)
Fatigue	0	1 (4.3)	0	1 (4.3)	1 (4.2)
Headache	1 (4.2)	0	0	0	1 (4.2)
Nasal congestion	1 (4.2)	0	0	0	1 (4.2)
Nausea [b]	0	0	1 (4.3)	1 (4.3)	1 (4.2)
Rash	0	0	1 (4.3)	1 (4.3)	1 (4.2)
Tinnitus	0	0	1 (4.3)	1 (4.3)	1 (4.2)

Preferred Term	Treatment Period 1 (DNL343 Alone) N = 24	Treatment Period 2a (ITZ Alone) N = 23	Treatment Period 2b (ITZ + DNL343) N = 23	Total Treatment Period 2 N = 23	Total N = 24
Upper respiratory tract infection	0	0	1 (4.3)	1 (4.3)	1 (4.2)

Abbreviations: AESI, adverse events of special interest; COVID-19, coronavirus disease 2019; ITZ, itraconazole; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Notes: Treatment Period 1 was defined as the time period from the first dose of DNL343 through the first dose of ITZ (Day 15). Treatment Period 2a was defined as the time period from the first dose of ITZ through the second dose of DNL343 (Day 18). Treatment Period 2b was defined as the time period from the second dose of DNL343 through the end of follow up.

Percentages are based on the number of participants in each treatment period or total.
Participants are counted once within each Preferred Term.
[a] TEAE led to discontinuation of study intervention.