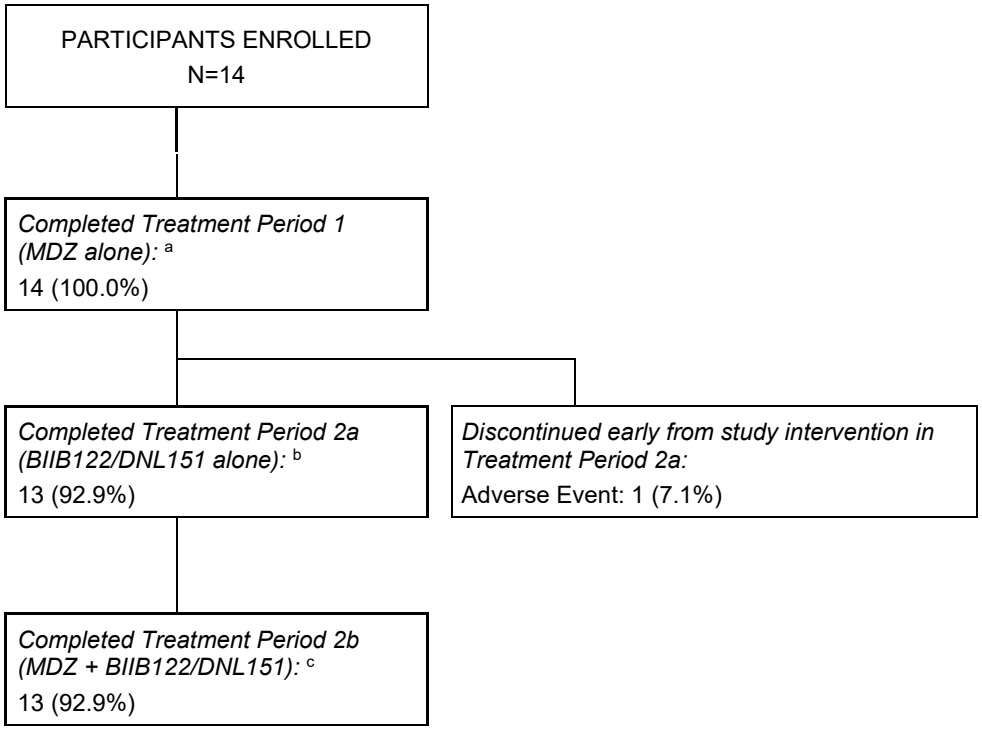
BASIC RESULTS SUMMARY

Study Title:	A Drug-Drug Interaction Study of the Effect of BIIB122/DNL151 on Midazolam Pharmacokinetics in Healthy Participants
Study Number:	DNLI-C-0008
Name of Investigational Product:	BIIB122/DNL151
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
Study Dates:	First Participant Signed Informed Consent Form: 27 September 2021 Last Participant Completed: 19 November 2021
Clinical Study Report Type:	Final Report
Clinical Study Report Date:	19 August 2022

1. Participant Flow

Participant flow is summarized in Figure 1.

Figure 1: Participant Flow



MDZ, midazolam.

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

[a] Participants who completed Treatment Period 1 were treated with one dose of MDZ prior to the start of Treatment Period 2.

[b] Participants who completed Treatment Period 2a were treated with at least one dose of BIIB/DNL151 and did not discontinue study intervention prior to the start of Treatment Period 2b.

[c] Participants who completed Treatment Period 2b were treated with the second dose of MDZ and did not discontinue BIIB122/DNL151.

2. Baseline Characteristics

Baseline characteristics are summarized in Table 1.

Table 1: Baseline Characteristics

Characteristic	Total N = 14
Age (y)	
n	14
Mean (SD)	36.4 (6.2)
Median (min, max)	36.5 (25, 47)
Sex (n [%])	
Male	14 (100.0)
Race (n [%])	
Asian	1 (7.1)
White	12 (85.7)
Mixed	1 (7.1)
Ethnicity (n [%])	
Not Hispanic or Latino	14 (100.0)
Weight (kg)	
n	14
Mean (SD)	79.02 (9.16)
Median (min, max)	79.30 (68.0, 97.0)
Height (cm)	
n	14
Mean (SD)	178.29 (4.36)
Median (min, max)	177.50 (170.0, 185.0)
BMI (kg/m^2)	
n	14
Mean (SD)	24.86 (2.74)
Median (min, max)	24.72 (21.2, 29.9)

Abbreviations: BMI, body mass index; max, maximum; min, minimum; SD, standard deviation.
Note: Weight, height, BMI, and age were assessed at screening.

3. Pharmacokinetics Results

Geometric mean ratios and associated 90% confidence intervals for the comparison of MDZ C_{max}, AUC_{last}, and AUC_{∞} for MDZ + BIIB122/DNL151 on Day 11 to MDZ alone on Day 1 are shown in Table 2. Administration of MDZ with BIIB122/DNL151 resulted in no change in MDZ C_{max} and an approximately 27% decrease in MDZ AUC_{last} and AUC_{∞} compared with administration of MDZ alone, indicating weak induction of cytochrome P450 (CYP) 3A.

Table 2: Statistical Analysis of Plasma Midazolam Pharmacokinetic Parameters in the Presence and Absence of BIIB/DNL151

MDZ PK Parameter	MDZ (Day 1) N = 14	MDZ + BIIB122/DNL151 (Day 11) N = 13	Comparison MDZ + BIIB122/DNL151 (Day 11) vs MDZ (Day 1)
C_{max}			
n	14	13	
Geometric LS mean (ng/mL)	12.7	12.8	
GMR (90% CI) (%)			101 (89.2, 114)
AUC_{last}			
n	14	13	
Geometric LS mean (ng·h/mL)	30.5	22.4	
GMR (90% CI) (%)			73.4 (64.0, 84.2)
AUC_{∞}			
n	14	13	
Geometric LS mean (ng·h/mL)	31.1	22.7	
GMR (90% CI) (%)			72.9 (63.4, 83.9)

Abbreviations: AUC_{∞}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from time zero to time of last measurable concentration; CI, confidence interval; C_{max}, maximum concentration; GMR, geometric mean ratio; LS, least-squares; MDZ, midazolam; PK, pharmacokinetic(s).

Notes: A single oral dose of MDZ was administered on Days 1 and 11. Multiple oral doses of BIIB122/DNL151 were administered once daily on Days 2 through 11.

All values were estimated from a linear mixed-effects model on log-transformed values of the parameter.

Participants with evaluable parameters on either Day 1 or Day 11 were included in the model.

4. Adverse Events

All treatment-emergent adverse events reported are summarized by Preferred Term in Table 3.

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

	Treatment Period 1 (Day 1) MDZ N = 14	Treatment Period 2			Total N = 14
		Period 2a (Day 2–10) BIIB122/DNL151 N = 14	Period 2b (Day 11) MDZ+BIIB122/DNL151 N = 13	Total Period 2 N = 14	
Preferred Term	Number of Participants (%)				
Participants with ≥ 1 TEAE	0	4 (28.6)	1 (7.7)	4 (28.6)	4 (28.6)
Back pain	0	1 (7.1)	0	1 (7.1)	1 (7.1)
Headache	0	1 (7.1)	1 (7.7)	1 (7.1)	1 (7.1)
Muscle spasms	0	1 (7.1)	0	1 (7.1)	1 (7.1)
Upper respiratory tract infection	0	1 (7.1)	0	1 (7.1)	1 (7.1)

Abbreviations: MDZ, midazolam; TEAE, treatment-emergent adverse event.

Notes: A single oral dose of MDZ was administered on Days 1 and 11. Oral doses of BIIB122/DNL151 were administered once daily on Days 2 through 11.