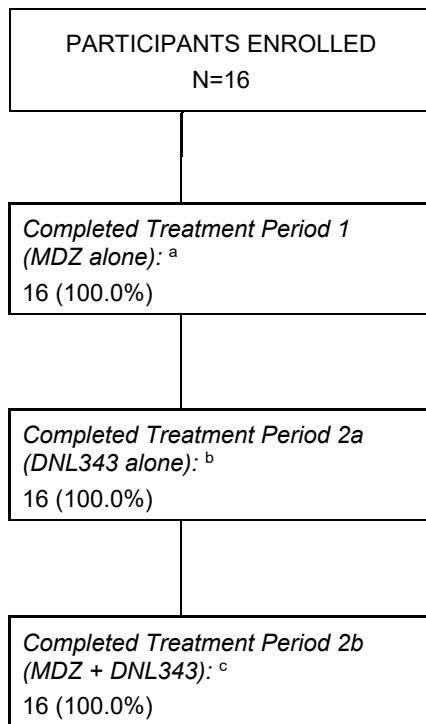




## **BASIC RESULTS SUMMARY**

|   |  |
|---|--|
| <b>Study Title:</b>                     | A Drug-Drug Interaction Study of the Effect of DNL343 on Midazolam Pharmacokinetics in Healthy Participants      |
| <b>Study Number:</b>                    | DNLI-F-0007  |
| <b>Name of Investigational Product:</b> | DNL343   |
| <b>Indication Studied:</b>              | Not applicable   |
| <b>Development Phase of the Study:</b>  | Phase 1  |
| <b>Study Sponsor:</b>                   | Denali Therapeutics Inc.<br>161 Oyster Point Boulevard<br>South San Francisco, CA 94080<br>USA                   |
| <b>Study Dates:</b>                     | First Participant Signed Informed Consent Form:<br>31 March 2023<br><br>Last Participant Completed: 09 June 2023 |
| <b>Clinical Study Report Type:</b>      | Final Report   |
| <b>Clinical Study Report Date:</b>      | 25 March 2024  |

## 1. Participant Flow



MDZ, midazolam.

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

- <sup>a</sup> Participants who completed Treatment Period 1 were treated with one dose of MDZ prior to the start of Treatment Period 2.
- <sup>b</sup> Participants who completed Treatment Period 2a were treated with at least one dose of DNL343 and did not discontinue study intervention prior to the start of Treatment Period 2b.
- <sup>c</sup> Participants who completed Treatment Period 2b were treated with the second dose of MDZ and did not discontinue DNL343.

## 2. Baseline Characteristics

Baseline characteristics are summarized in Table 1.

**Table 1: Demographic and Other Baseline Characteristics**

| Characteristic                        | Total<br>N = 16 |
|---------------------------------------|-----------------|
| Age (years) <sup>a</sup>              |                 |
| n                                     | 16              |
| Mean (SD)                             | 40.6 (11.5)     |
| Median                                | 38.5            |
| Min, max                              | 26, 65          |
| Sex, n (%)                            |                 |
| Male                                  | 14 (87.5)       |
| Female                                | 2 (12.5)        |
| Race, n (%)                           |                 |
| White                                 | 15 (93.8)       |
| Mixed                                 | 1 (6.3)         |
| Ethnicity, n (%)                      |                 |
| Hispanic or Latino                    | 1 (6.3)         |
| Not Hispanic or Latino                | 15 (93.8)       |
| Weight (kg) <sup>a</sup>              |                 |
| n                                     | 16              |
| Mean (SD)                             | 78.74 (10.05)   |
| Median                                | 78.95           |
| Min, max                              | 59.6, 102.4     |
| BMI (kg/m <sup>2</sup> ) <sup>a</sup> |                 |
| n                                     | 16              |
| Mean (SD)                             | 25.84 (1.61)    |
| Median                                | 25.76           |
| Min, max                              | 23.6; 29.6      |

Abbreviations: BMI, body mass index; min, minimum; max, maximum; SD, standard deviation.

<sup>a</sup> Assessed at screening.

## 3. Pharmacokinetic Results

Median midazolam (MDZ)  $t_{\max}$  was similar following administration of MDZ + DNL343 and MDZ alone (Table 2). Overall, geometric mean  $C_{\max}$ ,  $AUC_{\text{last}}$ , and  $AUC_{\infty}$  values for MDZ were lower when MDZ was administered with DNL343 vs without DNL343; mean MDZ half-life ( $t_{1/2}$ ) was similar across both study days. (Table 2).

**Table 2: Plasma MDZ PK Parameters in Healthy Participants Administered a Single Oral Dose of MDZ Alone and With DNL343 (PK Population)**

| MDZ PK Parameter                | MDZ<br>(Day 1)<br>N = 16 | MDZ + DNL343<br>(Day 15)<br>N = 16 |
|---------------------------------|--------------------------|------------------------------------|
| $t_{\max}$ (h) <sup>a</sup>     |                          |                                    |
| n                               | 16                       | 16                                 |
| Median (min, max)               | 0.63 (0.25, 0.75)        | 0.63 (0.25, 0.75)                  |
| $C_{\max}$ (ng/mL)              |                          |                                    |
| n                               | 16                       | 16                                 |
| Mean (SD)                       | 7.00 (3.31)              | 3.14 (1.29)                        |
| CV (%)                          | 47.4                     | 41.2                               |
| Geometric mean (CV [%])         | 6.42 (42.6)              | 2.89 (44.2)                        |
| $AUC_{\text{last}}$ (ng · h/mL) |                          |                                    |
| n                               | 16                       | 16                                 |
| Mean (SD)                       | 15.6 (7.16)              | 6.33 (3.59)                        |
| CV (%)                          | 45.9                     | 56.8                               |
| Geometric mean (CV [%])         | 14.4 (40.8)              | 5.67 (48.2)                        |
| $AUC_{\infty}$ (ng · h/mL)      |                          |                                    |
| n                               | 16                       | 16                                 |
| Mean (SD)                       | 15.9 (7.44)              | 6.39 (3.72)                        |
| CV (%)                          | 46.8                     | 58.2                               |
| Geometric mean (CV [%])         | 14.6 (41.3)              | 5.71 (48.8)                        |
| $t_{1/2}$ (h) <sup>a</sup>      |                          |                                    |
| n                               | 16                       | 16                                 |
| Mean (SD)                       | 4.74 (0.76)              | 4.98 (1.87)                        |

Abbreviations:  $AUC_{\infty}$ , area under the concentration-time curve from time zero to infinity;  $AUC_{\text{last}}$ , area under the concentration-time curve from time zero to time of last measurable concentration;  $C_{\max}$ , maximum concentration; CV, coefficient of variation; max, maximum; MDZ, midazolam; min, minimum; PK, pharmacokinetic(s); QD, once daily; SD, standard deviation;  $t_{1/2}$ , elimination half-life;  $t_{\max}$ , time to reach maximum concentration.

Notes: A single oral dose of MDZ was administered on Days 1 and 15. Multiple oral doses of DNL343 were administered on Days 2 through 15.

<sup>a</sup> Geometric mean/CV statistics were not calculated for  $t_{\max}$  and  $t_{1/2}$ .

Geometric mean ratios (GMRs) and associated 90% confidence intervals (CIs) for the comparison of MDZ  $C_{\max}$  and  $AUC_{\infty}$  for MDZ + DNL343 vs MDZ alone are shown in Table 3. Administration of MDZ with DNL343 resulted in a decrease in MDZ  $C_{\max}$  and  $AUC_{\infty}$  of approximately 55% and 61%, respectively, compared with administration of MDZ alone.

**Table 3: Geometric Least-Squares Means and Geometric Mean Ratios for MDZ PK Parameters (PK Population)**

| MDZ PK Parameter           | Geometric LS Mean  |                              | Geometric Mean Ratio (Day 15:Day 1) (90% CI) <sup>a</sup> | Intraparticipant CV (%) <sup>b</sup> |
|----------------------------|--------------------|------------------------------|---|--------------------------------------|
|                            | MDZ (Day 1) N = 16 | MDZ + DNL343 (Day 15) N = 16 |   |                                      |
| C <sub>max</sub> (ng/mL)   | n = 16<br>6.42     | n = 16<br>2.89               | 45.01<br>39.73, 51.00                                     | 20.4                                 |
| AUC <sub>∞</sub> (ng·h/mL) | n = 16<br>14.6     | n = 16<br>5.71               | 38.95<br>33.10, 45.84                                     | 26.7                                 |

Abbreviations: AUC<sub>∞</sub>, area under the concentration-time curve from time zero to infinity; CI, confidence interval; C<sub>max</sub>, maximum concentration; CV, coefficient of variation; LS, least-squares; MDZ, midazolam; PK, pharmacokinetic(s); QD, once daily.

Notes: A single oral dose of MDZ was administered on Days 1 and 15. Multiple oral doses of DNL343 were administered on Days 2 through 15.

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 15 were included in the model.

<sup>a</sup> Ratio expressed as a percentage.

<sup>b</sup>  $100 \times \sqrt{\exp(\text{MSE})^{-1}}$ , where MSE is the mean square error of the log-transformed parameter.

#### 4. Adverse Events

All TEAEs reported in the study are summarized by Preferred Term in Table 4.

**Table 4: Summary of All Treatment-Emergent Adverse Events by Preferred Term**

| Preferred Term                | Treatment Period 1         |                              | Treatment Period 2                 |                         |                |
|-------------------------------|----------------------------|------------------------------|------------------------------------|-------------------------|----------------|
|                               | MDZ<br>N= 16               | Period 2a<br>DNL343<br>N= 16 | Period 2b<br>MDZ + DNL343<br>N= 16 | Total Period 2<br>N= 16 | Total<br>N= 16 |
|                               | Number of Participants (%) |                              |                                    |                         |                |
| Participants with<br>≥ 1 TEAE | 0                          | 7 (43.8)                     | 0                                  | 7 (43.8)                | 7 (43.8)       |
| Abnormal dreams               | 0                          | 4 (25.0)                     | 0                                  | 4 (25.0)                | 4 (25.0)       |
| Fatigue                       | 0                          | 3 (18.8)                     | 0                                  | 3 (18.8)                | 3 (18.8)       |
| Abdominal pain<br>upper       | 0                          | 1 (6.3)                      | 0                                  | 1 ( 6.3)                | 1 (6.3)        |
| Arthralgia                    | 0                          | 1 (6.3)                      | 0                                  | 1 (6.3)                 | 1 (6.3)        |
| Headache                      | 0                          | 1 (6.3)                      | 0                                  | 1 (6.3)                 | 1 (6.3)        |
| Memory impairment             | 0                          | 1 (6.3)                      | 0                                  | 1 (6.3)                 | 1 (6.3)        |
| Toothache                     | 0                          | 1 (6.3)                      | 0                                  | 1 (6.3)                 | 1 (6.3)        |
| Vision blurred                | 0                          | 1 (6.3)                      | 0                                  | 1 (6.3)                 | 1 (6.3)        |

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Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; MDZ, midazolam; TEAE, treatment-emergent adverse event.

Notes: Each distinct Preferred Term is counted once per participant in the number of participants with that event.

Percentages are based on the number of participants in each treatment period or total.

TEAEs were coded using MedDRA Version 26.0.

Treatment Period 1 covers the time period of first administration of MDZ (Day 1) to prior to the first administration of DNL343 (Day 2). Treatment Period 2a covers the time period from the first administration of DNL343 (Day 2) to prior to the second dose of MDZ (Day 15). Treatment Period 2b covers the time period from the second dose of MDZ (Day 15) through the end of follow-up (Day 25).