ISRCTN26840121 https://doi.org/10.1186/ISRCTN26840121

A drug-drug interaction study of DNL343 on midazolam in healthy participants

Submission date 12/04/2023	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 21/04/2023	**Overall study status** Completed	
Last Edited 07/06/2024	**Condition category** Other	

Plain English summary of protocol

Background and Study Aims
This is a drug-drug interaction (DDI) study to investigate the effect of DNL343 on the pharmacokinetics (PK) of oral midazolam (MDZ). A DDI study is conducted to see how the two drugs interact in the body; evaluating PK is figuring out how participants' bodies handle a drug or drugs in combination.

Who Can Participate?
Healthy volunteers aged 18 to 65 years.

What does the Study Involve?
The total duration of each participant’s involvement in the study will be approximately 53 days from screening through follow-up.

What are the Possible Benefits and Risks of Participating?
Healthy volunteers will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the study interventions and procedures. DNL343 has been extensively evaluated in nonclinical studies (ie, animal studies and studies done with cells in a petri dish) and evaluation in clinical studies to characterize its safety profile.

Where is the study run from?
Denali Therapeutics Inc. (USA)

When is the study starting and how long is it expected to run for?
November 2022 to June 2023

Who is funding the study?
Denali Therapeutics Inc. (USA)

Who is the main contact?
Clinical Trials Disclosures Group at Denali Therapeutics, clinical-trials-disclosures@dnli.com

Contact information

Type(s)
Principal investigator

Contact name
Dr Helen Philpott

Contact details
Simbec-Orion Clinical Pharmacology
Merthyr Tydfil Industrial Park
Cardiff Road
Merthyr Tydfil
United Kingdom
CF48 4DR
+44 (0)1443694315
helen.philpott@simbecorion.com

Type(s)
Public, Scientific

Contact name
Ms Gabrielle Brill

Contact details
Simbec-Orion Clinical Pharmacology
Merthyr Tydfil Industrial Park
Cardiff Road
Merthyr Tydfil
United Kingdom
CF48 4DR
+44 (0)1443 694319
gabrielle.brill@simbecorion.com

Type(s)
Public

Contact name
Dr Clinical Trials Disclosures Group -

Contact details
Denali Therapeutics
-
United States of America
-
None provided
clinical-trials-disclosures@dnli.com

Additional identifiers

Clinical Trials Information System (CTIS)
2022-003926-38

Integrated Research Application System (IRAS)
1007175

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 1007175

Study information

Scientific Title
A drug-drug interaction study of the effect of DNL343 on midazolam pharmacokinetics in healthy participants

Study objectives
To assess the pharmacokinetics (PK) of midazolam (MDZ) in the presence and absence of DNL343

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 10/03/2023, Wales Research Ethics Committee 2 (Health and Care Research Wales, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, UK; +44 (0)2922941119; Wales.REC2@wales.nhs.uk), ref: 23/WA/0041
2. Approved 14/03/2023, MHRA (10 South Colonnade, Canary Wharf, London, E14 4PU, UK; +44 (0)20 3080 6000; info@mhra.gov.uk), ref: CTA 50398/0011/001-0001
The HRA approved the deferral of the publication of trial details. Full details were added after the deferral ended.

Study design
Fixed sequence crossover drug-drug interaction study

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Healthy volunteers

Interventions
Treatment Period 1: Single oral dose of MDZ
Treatment Period 2: Once daily oral dose of DNL343 for 14 days then coadministered with a single dose of MDZ on the 14th day

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
DNL343, midazolam (MDZ)

Primary outcome(s)
MDZ PK parameters, as measured by laboratory analysis of plasma concentrations from blood samples including, but not limited to, the following at multiple timepoints over 25 days:
1. Maximum concentration (Cmax)
2. Time to reach maximum concentration (tmax)
3. Area under the concentration-time curve from time zero to infinity (AUC∞)
4. Terminal elimination half-life (t1/2)

Key secondary outcome(s))
1. Incidence of treatment-emergent adverse events (TEAEs) and SAEs as reported by the participant continuously over 25 days:
2. MDZ metabolite PK parameters, as measured by laboratory analysis of plasma concentrations from blood samples including, but not limited to, the following at multiple timepoints over 25 days:
2.1 Maximum concentration (Cmax)
2.2 Time to reach maximum concentration (tmax)
2.3 Area under the concentration-time curve from time zero to infinity (AUC∞)
2.4 Terminal elimination half-life (t1/2)
3. DNL343 PK parameters, as measured by laboratory analysis of plasma concentrations from blood samples including, but not limited to, the following at multiple timepoints over 25 days:
3.1 AUC during a dosage interval (tau) (AUCτ)
3.2 Maximum concentration at steady state (Cmax,ss)

Completion date
09/06/2023

Eligibility

Key inclusion criteria
1. Healthy female participants of non-childbearing potential or healthy male participants between 18 and 65 years of age, inclusive
2. Body mass index (BMI) between 18.5 and 30 kg/m² and a body weight of at least 50 kg

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
65 years

Sex
All

Total final enrolment
16

Key exclusion criteria
1. Any history of hepatic, pulmonary, and/or renal disease
2. History of serious adverse reaction or serious hypersensitivity to any drug
3. History of allergy to any component of the study intervention
4. Have any surgical or medical condition affecting drug absorption (eg, gastrectomy)

Date of first enrolment
29/03/2023

Date of final enrolment
15/05/2023

Locations

Countries of recruitment
United Kingdom

Wales

Study participating centre
Simbec-Orion Clinical Pharmacology (AKA Simbec Research Ltd)
Merthyr Tydfil Industrial Park
Cardiff Road
Merthyr Tydfil
United Kingdom
CF48 4DR

Sponsor information

Organisation
Denali Therapeutics Inc.

Funder(s)

Funder type
Industry

Funder Name
Denali Therapeutics

Alternative Name(s)
DENALI, Denali Therapeutics Inc.

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study are not expected to be made available because of their high commercial sensitivity and the negligible benefit to the public of publication of results of non-therapeutic clinical trials.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		25/03/2024	09/05/2024	No	No