

# **CLINICAL STUDY PROTOCOL SYNOPSIS**

**A Phase I, Double-blind, Randomised, Single Centre,  
Parallel-group, Single-dose, Dose-escalation,  
Placebo-controlled Study of the Safety, Tolerability and  
Pharmacokinetics of DNDI-0690 after Oral Dosing in Healthy  
Subjects**

**Single Oral Dose Escalation Study of DNDI-0690 in Healthy  
Subjects**

<b>Quotient Study Number:</b>	QSC200932
<b>Sponsor Study Number:</b>	DNDi-0690-01
<b>EudraCT Number:</b>	2018-002021-35

<b>Protocol Synopsis version</b>	v3.0
<b>Protocol Synopsis date</b>	04 Sep 2019

## Synopsis

<b>Sponsor:</b> DNDi	<b>Drug Substance:</b> DNDI-0690	<b>EudraCT No.:</b> 2018-002021-35
<b>Title of Study:</b> A Phase I, Double-blind, Randomised, Single Centre, Parallel-group, Single-dose, Dose-escalation, Placebo-controlled Study of the Safety, Tolerability and Pharmacokinetics of DNDI-0690 after Oral Dosing in Healthy Subjects		
<b>Principal Investigator:</b> [REDACTED]		
<b>Study Centre:</b> Quotient Sciences, Mere Way, Ruddington Fields, Nottingham, NG11 6JS, UK		
<p><b>Objectives:</b></p> <p><b>Primary Objective:</b></p> <ul style="list-style-type: none"> <li>To assess the safety and tolerability of DNDI-0690 after single oral doses</li> </ul> <p><b>Secondary Objective:</b></p> <ul style="list-style-type: none"> <li>To investigate plasma and urinary pharmacokinetics (PK) of DNDI-0690 after single oral doses</li> </ul> <p><b>Exploratory Objectives:</b></p> <ul style="list-style-type: none"> <li>To investigate any potential changes to renal toxicity markers in plasma and urine</li> <li>To investigate the metabolite profile of DNDI-0690</li> <li>To assess the effect of DNDI-0690 on Holter ECG parameters</li> <li>To investigate the PK of DNDI-0690 after single doses in the fed versus fasted state in healthy male subjects</li> <li>To investigate the PK of DNDI-0690 after single doses in healthy women of non-childbearing potential (WONCBP) versus healthy male subjects</li> </ul>		
<p><b>Methodology:</b></p> <p>This is a single centre, double-blind, randomised, placebo-controlled, parallel-group, single oral dose, dose-escalation study in healthy male and WONCBP subjects. It is planned to enrol 8 subjects in 8 planned cohorts. Cohorts 1 to 7 will include male subjects. Cohort 8 will include WONCBP subjects. Subjects will be randomly assigned to receive a single oral dose of active investigational medicinal products (IMP) or matching placebo in a sequential escalating manner with a minimum of 7 days between dosing of each cohort.</p> <p>The planned starting dose for Cohort 1 (Regimen A) will be 10 mg. Doses to be administered in Cohorts 2 to 8 will be determined based on emerging PK and safety data.</p>		

**Study Design:**

Each cohort will follow the same study design. Subjects will be screened for inclusion in the study up to 28 days before dosing. Subjects will be admitted during the morning of the day before dosing (Day -1) for all regimens. Subjects will be dosed in the morning of Day 1 in a randomised, double-blind manner with either DNDI-0690 capsule or matching placebo. Subjects in Cohorts 1 to 6 and 8 will be dosed following a minimum overnight fast of 10 h. Subjects in Cohort 7 will be dosed after a standard high-fat breakfast. Subjects will remain onsite until 72 h post-dose. A follow-up visit will take place 7 to 10 days post-dose to ensure the ongoing wellbeing of the subjects. There will be a minimum of 7 days between dosing of each cohort.

As a safety precaution each cohort will be split into two groups: sentinel (2 subjects) and main (6 subjects). The subjects of the sentinel group (1 subject on active, 1 subject on placebo) will be dosed with an appropriate interval between them as allowed by logistics. After review of the safety data from the 24 h post-dose period, the Principal Investigator (PI), or medically-qualified designees who are familiar with the study protocol and Investigator's Brochure (IB), will decide whether to proceed with dosing the remaining subjects in the main group (5 subjects on active treatment, 1 subject on placebo) at least 24 h after the second sentinel subjects. The first subject of the main group will be dosed no earlier than 24 h after dosing of the second subject in the sentinel group.

**Number of Subjects Planned:**

It is planned to enrol 8 healthy male subjects in Cohorts 1 to 7 and 8 healthy WONCBP subjects in Cohort 8 (8 planned cohorts, 64 subjects in total). This will ensure data in 6 evaluable subjects per cohort. Subjects withdrawn due to an IMP-related adverse event (AE) will not be replaced. Subjects who are withdrawn for other reasons may be replaced as required by agreement between the PI and Sponsor to ensure sufficient evaluable subjects. Up to 2 additional subjects per cohort may be enrolled into the study. The maximum number of subjects that may be dosed is 80. An evaluable subject is defined as a subject who has sufficient PK and safety data up to 72 h post-dose or was withdrawn prior to 72 h due to an adverse event.

**Duration of Study:**

Subjects will receive a single dose administration on one occasion. The estimated time from screening until the follow-up visit is approximately up to 6 weeks.

**Main Inclusion Criteria:**

Healthy males aged 18 to 55 years (Cohorts 1 to 7)  
Healthy WONCBP aged 18 to 60 years (Cohort 8)  
Body mass index (BMI) 18.0 to 30.1 kg/m<sup>2</sup>.

**Investigational Medicinal Product, Dose and Mode of Administration:**

The following IMPs will be used in this clinical study:

Regimen	IMP Name	Unit Strength <sup>a</sup>	Route of Administration
A to H	DNDI-0690 capsule or matching placebo	10 mg or 100 mg or 200 mg	Oral Administration, Cohorts 1 to 6 and 8: Fasted Cohort 7: Fed

<sup>a</sup> DNDI-0690 capsule strengths are displayed as free drug equivalent.

**Pharmacokinetic Assessments:**

Blood samples for PK analysis will be collected at regular time points. The plasma concentration data for DNDI-0690 provided by SGS Belgium will be analysed by Quotient Sciences using Phoenix WinNonlin 8.0 or a more recent version (Certara USA, Inc., USA).

Plasma concentration data will be tabulated and plotted for each subject for whom DNDI-0690 concentrations are quantifiable. PK analysis of the concentration time data obtained will be performed using appropriate non-compartmental techniques to obtain estimates of the following PK parameters, where possible:

- **T<sub>max</sub>**: the elapsed time from dosing at which C<sub>max</sub> was apparent
- **C<sub>max</sub>**: the maximum observed concentration
- **C<sub>max/D</sub>**: the maximum observed concentration normalised for dose
- **C<sub>max, norm</sub>**: the maximum observed concentration normalised for dose and body weight
- **AUC<sub>(0-24)</sub>**: area under the curve from 0 time to 24h
- **AUC<sub>(0-t)</sub>**: area under the curve from 0 time to last measurable concentration
- **AUC<sub>(0-t), norm</sub>**: area under the curve from 0 time to last measurable concentration normalised for dose and body weight
- **AUC<sub>(0-inf)</sub>**: area under the curve from 0 time extrapolated to infinity
- **AUC<sub>(0-inf)/D</sub>**: area under the curve from 0 time extrapolated to infinity normalised for dose
- **AUC<sub>(0-inf), norm</sub>**: area under the curve from 0 time extrapolated to infinity normalised for dose and body weight
- **AUC<sub>t-inf</sub>**: percentage of AUC<sub>(0-inf)</sub> extrapolated beyond last measured time point
- **Points terminal**: the number of points used to determine the elimination half-life
- **T<sub>1/2</sub>**: the apparent elimination half-life
- **C<sub>1/F</sub>**: apparent plasma clearance after oral administration
- **V<sub>Z/F</sub>**: apparent volume of distribution based on area for oral dose
- **MRT**: mean residence time
- **lambda-z**: the slope of the apparent elimination phase

The urine concentration data for DNDI0690 will be analysed for the following PK parameters:

- **Ae**: amount excreted
- **Fe**: fraction of dose excreted
- **CLr**: renal clearance

**Safety Assessments:**

The safety assessments to be conducted are:

- AEs
- Clinical chemistry, haematology, coagulation and urinalysis assessments, especially renal function parameters.
- Physical Examinations
- 12-lead electrocardiograms (ECGs)

- Vital signs
- Troponin I

**Exploratory Assessments**

- Holter extracted ECGs
- Urine sampling for Drug-related Renal Injury Exploratory Biomarkers

**Statistical Methodology:**

Descriptive summaries of baseline, PK and safety data will be presented including changes from baseline as appropriate.

Dose proportionality will be assessed across dose groups (assuming same prandial status and gender) using the power model. The power model will be applied separately to the  $\ln(\text{AUC})$  and  $\ln(\text{C}_{\text{max}})$  values. A point estimate and its 90% confidence interval will be calculated for the population mean slope together with the acceptance range.

Further statistical analyses of PK parameters  $\text{AUC}_{(0-t)}$ ,  $\text{AUC}_{(0-\text{inf})}$  and  $\text{C}_{\text{max}}$  will be performed to examine the effect of food in males (comparing fed and fasted cohorts at same dose level) and the effect of gender (comparing male and female cohorts at same dose level).

**Sample Size and Power:**

The study is exploratory and no formal sample size calculation has been made. Based on experience from previous studies of a similar design, a total of 8 subjects are to be enrolled per cohort and a minimum of 6 evaluable subjects per cohort are considered sufficient.