

STUDY PROTOCOL SYNOPSIS

STUDY TITLE:	A Phase I, Double-blind, Randomised, Single Centre, Parallel-group, Multiple-dose, Dose-escalation, Placebo-controlled Study of the Safety, Tolerability and Pharmacokinetics of DNDI-0690 after Oral Dosing in Healthy Subjects
STUDY NUMBER:	RD 777/34920 (DNDi-0690-02)
EudraCT NUMBER:	2020-003963-24
IRAS ID:	288914
INVESTIGATIONAL MEDICINAL PRODUCT(IMP):	DNDI-0690
PLANNED STUDY DOSES:	Part A: Cohort 1: 400 mg DNDI-0690 or placebo once a day for 10 days. Cohorts 2-4: DNDI-0690 dose to be confirmed after dose escalation review meeting. Part B: 3600 mg DNDI-0690 or placebo once a day for 5 days. Part C: DNDI-0690 dose to be confirmed.

SYNOPSIS

NAME OF COMPANY: Drugs for Neglected Diseases initiative (DNDi)
NAME OF INVESTIGATIONAL MEDICINAL PRODUCT: DNDI-0690
NAME OF ACTIVE INGREDIENT: nitroimidazooxazine
TITLE OF STUDY: A Phase I, Double-blind, Randomised, Single Centre, Parallel-group, Multiple-dose, Dose-escalation, Placebo-controlled Study of the Safety, Tolerability and Pharmacokinetics of DNDI-0690 after Oral Dosing in Healthy Subjects
PRINCIPAL INVESTIGATOR: ██████████
STUDY CENTRE: Simbec-Orion Clinical Pharmacology Merthyr Tydfil, CF48 4DR, UK
CLINICAL PHASE: I
<p>OBJECTIVES:</p> <p><u>Part A & B</u></p> <p>Primary Objective</p> <ul style="list-style-type: none"> To assess the safety and tolerability of DNDI-0690 after multiple oral doses in healthy subjects in fasted conditions. <p>Secondary Objective</p> <ul style="list-style-type: none"> To investigate plasma and urinary pharmacokinetics (PK) of DNDI-0690 after multiple oral doses in healthy subjects in fasted conditions. <p>Exploratory Objectives</p> <ul style="list-style-type: none"> To investigate any potential changes to renal toxicity markers in urine. To assess the effect of DNDI-0690 on Holter electrocardiogram (ECG) parameters. To compare PK bioanalysis in fixed volume dry blood spots versus PK bioanalysis in plasma samples. To investigate the metabolite profile of DNDI-0690 after multiple dosing. To assess variation of mRNA expression in full blood before and after exposure to the drug (Transcriptional Profiling). <p><u>Part C</u></p> <p>Primary Objective</p> <ul style="list-style-type: none"> To evaluate renal function (glomerular filtration rate (GFR)) before and after administration of DNDI-0690 in healthy subjects in fasted condition at maximum well tolerated dose tested in Part A or below.
<p>METHODOLOGY:</p> <p>The study will be conducted in three parts (Part A, Part B and Part C).</p> <p>Part A of the study is a single centre, double-blind, randomised, placebo-controlled, parallel-group, multiple oral dose, dose-escalation study to assess the safety, tolerability and PK of DNDI-0690 after multiple oral doses in the fasted condition in healthy male and woman of non-childbearing potential (WONCBP) subjects.</p> <p>Part B of the study is a single centre, double-blind, randomised, placebo-controlled, multiple oral dose study to assess the pharmacodynamic effect of DNDI-0690 on cardiac function after multiple oral doses at the supra-therapeutic dose in the fasted condition in healthy male and WONCBP subjects.</p>

Part C of the study is a single centre, double-blind, randomised, placebo-controlled, multiple oral dose study to evaluate the renal function (measured Glomerular Filtration Rate (mGFR)) before and after multiple oral doses in the fasted condition in healthy male and WONCBP subjects.

Part A: Multiple Ascending Dose Cohorts (Cohorts 1-4)

Part A will consist of up to 4 cohorts of 9 subjects. Subjects will be randomly assigned to receive an oral dose of active IMP (6 subjects) or matching placebo (3 subjects) for 10 days in a sequential escalating manner with a minimum of 7 days interval between two cohorts.

In Part A, each cohort will follow a sentinel dose-escalation schedule; two (2) subjects will be dosed on the first dosing day of each cohort (1 subject on active IMP and 1 subject on matching placebo). The remainder of the cohort (5 subjects on active IMP and 2 subjects on matching placebo) will be dosed a minimum of 48 hours later pending confirmation of an acceptable safety profile in the dose-leader cohort by the Principal Investigator (PI), or medically-qualified designees who are familiar with the study protocol and Investigator's Brochure (IB).

The planned starting dose for Cohort 1 is 400 mg of DNDI-0690 once a day for 10 days. Doses to be administered in Cohorts 2 to 4 will be determined based on emerging PK and safety data. The number of daily doses may be increased to 2 by implementation of a twice a day (BID) dosing regimen if the number of capsules in a single intake is raising concerns of acceptability. This decision will be made by the Safety Review Committee (SRC) prior to each cohort and will apply to all subjects within a cohort.

Dose escalation between cohorts in Part A (and between Part A and Part B) will be temporarily stopped pending evaluation of all available data if any of the following criteria are fulfilled:

- A serious adverse reaction (*i.e.*, a serious adverse event (SAE) considered at least possibly related to the IMP administration) occurs in one subject.

Or

- Severe non-serious adverse reactions (*i.e.*, severe non-serious AE considered as, at least possibly related to the IMP administration) occur in two subjects in the same cohort, independent of within or not within the same system organ class.

Or

- If two or more subjects in the preceding dose group experience any of the following:
 - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x upper limit of normal (ULN), considered clinically significant and IMP related.
 - Serum Cystatin C (Cys C) increase > 25%, confirmed after repeat assessment 24-48h apart, and considered IMP related. Baseline Cys C will be the average value of Day -2, Day -1 and Day 1 (pre-dose) Cys C levels.
 - Ratio of microalbuminuria/creatininuria >300 mg/g and considered IMP related.
 - An increase in corrected QT interval by Fridericia's formula (QTcF) value of >60 msec from baseline (average of baseline triplicate values) or an absolute QTcF >500 msec, both confirmed by repeat measurement after 20 minutes in resting position, and considered IMP related.

Or

- If one or more subjects in the preceding dose group experience:
 - An increase in troponin I concentration which is considered clinically significant by the Investigator (with reference to the change from baseline value) and considered IMP related.

Or

- If the dose in a single subject is anticipated to exceed an AUC from time of dosing to the end of the dosing interval (AUC_{0-tau}) of $\geq 100 \mu\text{g}\cdot\text{h}/\text{mL}$. These limits are based on the exposure observed at the 20

mg/kg in cynomolgus monkeys (no observed adverse effect level (NOAEL): AUC₀₋₂₄ of 101 µg*h/mL in male and 111 µg*h/mL in females).

Or

- If the dose in a single subject is anticipated to exceed a maximum concentration (C_{max}) of ≥ 8.0 µg/mL. These limits are based on the exposure observed at the 20 mg/kg in cynomolgus monkeys (NOAEL: C_{max} of 8.03 µg/mL in males and 9.03 µg/mL in females).

Dose escalation between cohorts in Part A will be limited to a maximal 3-fold increase, and 2-fold increase between Part A and Part B, depending on safety and tolerability data and predicted exposure (both AUC and C_{max}).

If any of the above criteria are fulfilled, the cases will be discussed at the SRC who could proceed with partial or full unblinding as necessary to take its decision to either dose-escalate, proceed to enlargement of the cohort, or explore a lower dose.

If any of the stopping criteria occurred in a subject receiving DNDI-0690 the trial will put on halt and further dosing can be resumed only once an appropriate substantial amendment has been submitted and received regulatory and ethical approval from the relevant ethics committee and competent authority.

Each cohort will follow the same study design including Screening Period, Treatment Period and Post-Study Follow-up. The study sequence for Part A is presented in [Figure 1](#).

Screening Period (Day -28 to Day -3):

After signing the informed consent form (ICF), Screening assessments will be performed within 28 days of the planned first dose to ensure the eligibility of subjects. Screening assessments will include:

- Medical and surgical history
- Demographic data
- Hepatitis/human immunodeficiency virus (HIV) serology
- Inclusion/Exclusion Criteria
- Weight and height
- Vein assessment
- Urine drugs of abuse (DOA) and alcohol/cotinine screen
- Physical examination (full)
- Laboratory safety tests (biochemistry, haematology, coagulation, urinalysis, urine microscopy and follicle-stimulating hormone (FSH) for post-menopausal female subjects only)
- 12-lead ECG
- Vital signs (supine systolic and diastolic blood pressure, pulse rate, and tympanic temperature)
- Adverse event (AE)
- SAE
- Prior and concomitant medication

Treatment Period (Day -2 to Day 12):

Subjects will be admitted to the clinic in the morning of Day -2 and will remain in the unit until the 48 hours post-last dose scheduled assessments and procedures have been performed (Day 12).

Day -2:

- Polymerase chain reaction (PCR) test for COVID-19
- Eligibility check
- Urine DOA and alcohol/cotinine screen
- A brief physical examination
- Laboratory safety tests (biochemistry, haematology, coagulation, urinalysis and urine microscopy)
- Troponin I
- 12-lead ECG
- Vital signs (supine systolic and diastolic blood pressure, pulse rate, and tympanic temperature)

- AE
- SAE
- Prior and concomitant medication
- Full blood sampling for transcriptional profiling (mRNA) assessment (**Only performed on Cohort 2 and Cohort 3**)

Day -1:

- Start Holter monitoring (for extraction of ECGs) at approximately 60 minutes prior to the theoretical time of Day 1 dosing (Holter will be on for at least 25 hours and can only be removed after Day 1 dosing)
- Laboratory safety test (biochemistry only for Cys C)
- AE
- SAE
- Prior and concomitant medication

Day 1:

Dose administrations of DNDI-0690 capsules or matching placebo will occur in the morning of Day 1 in a randomised, double-blind manner.

- Eligibility check: Pre-dose
- Subjects in once daily (OD) regimen will be dosed following an overnight fast of at least 10 hours.
- If a BID regimen is implemented, subjects in BID regimen will be dosed following an overnight fast of at least 10 hours for the morning dose, and 10 hours later for the afternoon dose. The afternoon dose shall be taken at least 5 hours post mid-day meal, and one hour before the dinner.

The specific instructions for Day 1 dosing apply for all dosing days.

The following procedures will be performed on **Day 1:**

- Laboratory safety test (biochemistry only for Cys C): Pre-dose
- End Holter after morning dosing
- 12-lead ECG: Pre-morning dose (in triplicate) and 4 h post-morning dose (single)
- Vital signs (supine systolic and diastolic blood pressure, pulse rate and tympanic temperature):
Pre-morning dose
- AE
- SAE
- Prior and concomitant medication
- PK plasma sample for DNDI-0690 and metabolite: Pre-morning dose and 0.5, 1, 2, 3, 3.5, 4, 6, 9, 12 h post-morning dose
- DBS (Dried Blood Spot) samples for DNDI-0690: Pre-morning dose, 0.5, 1 and 2 h post-morning dose
- PK urine samples for DNDI-0690: Pre-morning dose and [0-24] h post morning dose
- Urine samples for exploratory biomarkers: Pre-morning dose

Day 2:

- Eligibility check: Pre-dose
- Dosing
- Laboratory safety tests (biochemistry, haematology, coagulation, urinalysis, urine microscopy): Pre-morning dose
- AE
- SAE
- Prior and Concomitant Medication
- PK plasma sample for DNDI-0690 and metabolite: Pre-morning dose
- Urine samples for exploratory biomarkers: Pre-morning dose

Day 3, Day 5, Day 6, Day 8 and Day 9:

- Eligibility check: Pre-dose
- Dosing
- AE
- SAE
- Prior and Concomitant Medication
- PK plasma sample for DNDI-0690 and metabolite: Pre-morning dose

Day 4 and Day 7:

- Eligibility check: Pre-dose
- Dosing
- A brief physical examination
- Laboratory safety tests (biochemistry, haematology, coagulation, urinalysis, urine microscopy): Pre-morning dose
- 12-lead ECG: Pre-morning dose and 4 h post-morning dose
- Vital signs (supine systolic and diastolic blood pressure, pulse rate, and tympanic temperature)
- AE
- SAE
- Prior and concomitant medication
- PK plasma sample for DNDI-0690 and metabolite: Pre-morning dose
- PK urine samples for DNDI-0690:[0-24] h post-morning dose
- Urine samples for exploratory biomarkers: Pre-morning dose

Day 10:

On Day 10, only a morning dose will be administered.

- Start Holter monitoring (for extraction of ECGs) at approximately 60 minutes prior to dosing (Holter will be on for at least 25 hours and can only be removed after 24 h post-last dose PK blood samples are collected)
- Eligibility check: Pre-dose
- Dosing (morning only on Day 10, even if BID regimen implemented)
- Laboratory safety tests (biochemistry, haematology, coagulation, urinalysis, urine microscopy): Pre-dose
- Troponin I: Pre-dose
- 12-lead ECG: Pre-dose and 4 h post-dose
- Vital signs (supine systolic and diastolic blood pressure, pulse rate and tympanic temperature): Pre-dose
- AE
- SAE
- Prior and concomitant medication
- PK plasma sample for DNDI-0690 and metabolite: Pre-dose and 0.5, 1, 2, 3, 3.5, 4, 6, 9, 12 h post-dose
- DBS samples for DNDI-0690: Pre-dose and 0.5, 1, 2, 3, 3.5, 4, 6, 9, 12 h post-dose
- PK urine samples for DNDI-0690:[0-24] h post-dose
- Urine samples for exploratory biomarkers: Pre-dose
- Full blood sampling for transcriptional profiling (mRNA) assessment (**Only performed on Cohort 2 and Cohort 3**)

Day 11:

- End Holter after 24 h PK sample
- AE
- SAE
- Prior and concomitant medication
- PK plasma sample for DNDI-0690 and metabolite: 24 h post-last dose
- DBS samples for DNDI-0690: 24 h post-last dose

Day 12:

- A brief physical examination
- Weight
- Laboratory safety tests (biochemistry, haematology, coagulation, urinalysis, urine microscopy)
- 12-lead ECG
- Vital signs (supine systolic and diastolic blood pressure, pulse rate, and tympanic temperature)
- AE
- SAE
- Prior and concomitant medication
- PK plasma sample for DNDI-0690 and metabolite: 48 h post-last dose
- DBS samples for DNDI-0690: 48 h post-last dose

If all assessments are satisfactory to the PI (or deputy), subjects will be discharged from clinic after all Day 12 procedures are completed. In case of Clinically Significant laboratory results on Day 12, the volunteer will be given an appointment for an unscheduled control visit.

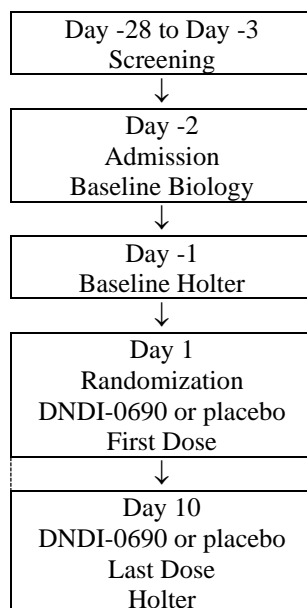
Post Study Follow-up (Day 24 to Day 28):

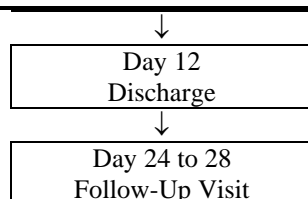
A post study follow-up visit will take place 14 to 18 days after last dose (Day 24 to Day 28) to ensure the ongoing wellbeing of the subjects.

- A brief physical examination
- Laboratory safety tests (biochemistry, haematology, coagulation, urinalysis, urine microscopy)
- Vital signs (supine systolic and diastolic blood pressure, pulse rate, and tympanic temperature)
- AE
- SAE
- Prior and concomitant medication

If all follow-up assessments are satisfactory to the PI (or deputy), the subject will be discharged from the study at the discretion of the PI/deputy. If any AEs are ongoing, or any assessments are not satisfactory, subjects may be recalled to the unit for follow-up assessments until the PI/deputy is satisfied the subject may be discharged from the study. Subjects will be advised to return or contact the unit at any time if they think they may be experiencing any AEs.

Figure 1 Study Sequence Part A





Part B: Cardiac pharmacodynamic assessment (Cohort 5 - Optional)

Part B will consist of 1 cohort of 9 subjects. Subjects will be randomly assigned to receive an oral dose of active IMP (6 subjects) or matching placebo (3 subjects) for 5 days. Part B will only be implemented if the SRC considers it safe and appropriate to proceed with a maximum considered dose of 3600 mg. This cohort is thus considered optional.

Subjects in Part B will follow a sentinel schedule; two (2) subjects will be dosed on the first dosing day (1 subject on active IMP and 1 subject on matching placebo). The remainder of the cohort (5 subjects on active IMP and 2 subjects on matching placebo) will be dosed a minimum of at least 48 hours later pending confirmation of an acceptable safety profile in the dose-leader cohort by the PI, or medically-qualified designees who are familiar with the study protocol and IB.

The study sequence for Part B is presented in [Figure 2](#).

Screening Period (Day -28 to Day -3):

- Screening procedures are identical to Part A.

Treatment Period (Day -2 to Day 7):

Subjects will be admitted to the clinic in the morning of Day -2 and will remain in the unit until 48 h post-last dose scheduled assessments and procedures have been performed (Day 7).

Day -2: Same procedures as Day -2 of Part A.

Day -1: Same procedures as Day -1 of Part A.

Day 1 to Day 4: Same procedures as Day 1 to Day 4 procedures of Part A, except no Day 4 PK urine samples for DNDI-0690 are required.

Day 5:

On Day 5, the last dose will be administered.

- Start Holter monitoring (for extraction of ECGs) at approximately 60 minutes prior to dosing (Holter will be on for at least 25 hours and can only be removed after 24 h post-last dose PK blood samples are collected)
- Eligibility check: Pre-dose
- Dosing
- Laboratory safety tests (biochemistry, haematology, coagulation, urinalysis, urine microscopy): Pre-dose
- Troponin I: Pre-dose
- 12-lead ECG: Pre-dose and 4 h post-dose
- Vital signs (supine systolic and diastolic blood pressure, pulse rate and tympanic temperature): Pre-dose
- AE
- SAE
- Prior and concomitant medication
- PK plasma sample for DNDI-0690 and metabolite: Pre-dose and 0.5, 1, 2, 3, 3.5, 4, 6, 9, 12 h post-dose
- DBS samples for DNDI-0690: Pre-dose and 0.5, 1, 2, 3, 3.5, 4, 6, 9, 12 h post-dose
- PK urine samples for DNDI-0690:[0-24] h post-dose
- Urine samples for exploratory biomarkers: Pre-dose

Day 6:

- End Holter after 24 h PK sample
- AE
- SAE
- Prior and concomitant medication
- PK plasma sample for DNDI-0690 and metabolite: 24 h post-last dose
- DBS samples for DNDI-0690: 24 h post-last dose

Day 7:

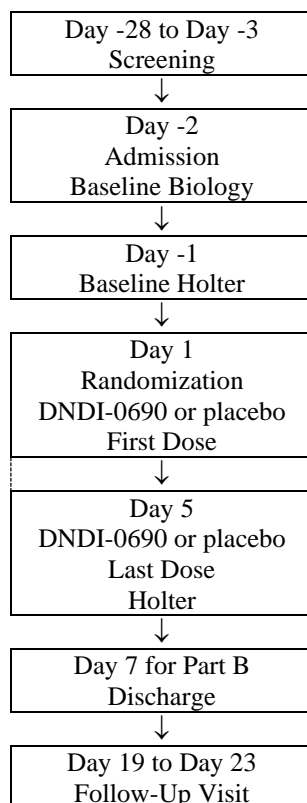
- A brief physical examination
- Weight
- Laboratory safety tests (biochemistry, haematology, coagulation, urinalysis, urine microscopy)
- 12-lead ECG
- Vital signs (supine systolic and diastolic blood pressure, pulse rate, and tympanic temperature)
- AE
- SAE
- Prior and concomitant medication
- PK plasma sample for DNDI-0690 and metabolite: 48 h post-last dose
- DBS samples for DNDI-0690: 48 h post-last dose

If all assessments are satisfactory to the PI (or deputy), subjects will be discharged from the clinic after all Day 7 procedures are completed.

Post Study Follow-up (Day 19 to Day 23):

- Post study follow-up procedures are identical to Part A.

Figure 2 Study Sequence Part B



Part C: Measured Glomerular Filtration Rate (mGFR) Cohort (Cohort 6)

Part C will consist of 1 cohort of 9 subjects.

- Subjects will be administered DNDI-0690 or placebo once daily for 10 days at a dose level that is either at or below the highest well tolerated dose of DNDI-0690 as evaluated in the Part A dose escalating cohorts. The dose will be decided by the SRC after reviewing data from Part A. As this dose will already have been explored, no sentinel group will be implemented in this cohort.
- All subjects will receive 5 mL of iohexol solution (300 mg/mL iodine) intravenously on Day -1, Day 10, and optionally Day 24-28 that will be flushed with 10 mL of normal saline solution. On Day -1, iohexol will be administered at the same time as expected dosing of the study drug or placebo on Day 10. On Day 10, iohexol will be administered immediately after dosing of study drug or placebo.

The study sequence for Part C is presented in [Figure 3](#).

Screening Period (Day -28 to Day -3):

- Screening procedures are identical to Part A.

Treatment Period (Day -2 to Day 12):

Day -2: Same procedures as Day -2 of Part A, except an additional vein assessment.

Day -1:

- Laboratory safety test (biochemistry only for Cys C): Pre-iohexol dose
- All subjects will receive 5 ml of iohexol solution (300 mg/mL iodine) intravenously on Day -1 at the expected time of dosing of study drug DNDI-0690 or placebo on Day 10.
- A brief physical examination
- 12-lead ECG: Pre-iohexol dose
- Vital signs (supine systolic and diastolic blood pressure, pulse rate, and tympanic temperature): Pre-iohexol dose
- AE
- SAE
- Prior and concomitant medication
- Plasma samples for iohexol: Pre-iohexol dose, 1, 2, 3, 4 and 5 h post-iohexol dose
- Urine samples for iohexol: Pre-iohexol dose, [0-1], [1-2], [2-3], [3-4] and [4-5] h post-iohexol dose (240 mL water to be taken after each urine PK sampling timepoint to ensure the capability of the volunteer to provide urine samples during each collection period).

Day 1:

Dose administrations of DNDI-0690 capsule or matching placebo will occur on the morning of Day 1 in a randomised, double-blind manner following an overnight fast of at least 10 hours.

- Eligibility check: Pre-dose
- Laboratory safety test (biochemistry only for Cystatin C and Troponin I): Pre-morning dose
- 12-lead ECG: Pre-morning dose (in triplicate) and 4 h post-morning dose (single)
- Vital signs (supine systolic and diastolic blood pressure, pulse rate and tympanic temperature): Pre-morning dose
- AE
- SAE
- Prior and concomitant medication
- PK plasma sample for DNDI-0690 and metabolite: Pre-morning dose
- Urine samples for exploratory biomarkers: Pre-morning dose

Day 2:

- Eligibility check: Pre-dose
- Dosing

- Laboratory safety tests (biochemistry, haematology, coagulation, urinalysis, urine microscopy): Pre-morning dose
- AE
- SAE
- Prior and Concomitant Medication
- PK plasma sample for DNDI-0690 and metabolite: Pre-morning dose
- Urine samples for exploratory biomarkers: Pre-morning dose

Day 3, Day 5, Day 6, Day 8 and Day 9:

- Eligibility check: Pre-dose
- Dosing
- AE
- SAE
- Prior and Concomitant Medication

Day 4 and Day 7:

- Eligibility check: Pre-dose
- Dosing
- A brief physical examination
- Laboratory safety tests (biochemistry, haematology, coagulation, urinalysis, urine microscopy): Pre-morning dose
- 12-lead ECG: Pre-morning dose, 4h post-morning dose
- Vital signs (supine systolic and diastolic blood pressure, pulse rate, and tympanic temperature): Pre-morning dose
- AE
- SAE
- Prior and concomitant medication
- PK plasma sample for DNDI-0690 and metabolite: Pre-morning dose
- Urine samples for exploratory biomarkers: Pre-morning dose

Day 10:

On Day 10, DNDI-0690 (6 subjects) or matching placebo (3 subjects) will be administered in the morning only. 5 ml of iohexol solution (300mg/mL iodine) will be administered intravenously immediately after dosing of DNDI-0690.

- Eligibility check: Pre-dose
- Laboratory safety tests (biochemistry, haematology, coagulation, urinalysis, urine microscopy): Pre-dose
- Troponin I: Pre-dose
- 12-lead ECG: Pre-dose and 4 h post-dose
- Vital signs (supine systolic and diastolic blood pressure, pulse rate and tympanic temperature): Pre-dose
- AE
- SAE
- Prior and concomitant medication
- PK plasma sample for DNDI-0690 and metabolite: Pre-dose and, 0.5, 1, 2, 3, 4, 6, and 9 h post-dose
- Plasma samples for iohexol: Pre-iohexol dose, 1, 2, 3, 4 and 5 h post-iohexol dose
- Urine samples for exploratory biomarkers: Pre-dose
- Urine sample for iohexol: Pre-iohexol dose, [0-1], [1-2], [2-3], [3-4] and [4-5]h post-iohexol dose (minimum 240 mL water to be taken after each urine PK sampling timepoint to ensure the capability of the volunteer to provide urine samples during each collection period. No extra water is required for 0-1 h collection period as 240 mL will be taken with DNDI-0690 or placebo dosing)

Day 11:

- AE
- SAE
- Prior and concomitant medication
- PK plasma sample for DNDI-0690 and metabolite: 24 h post-last dose

Day 12:

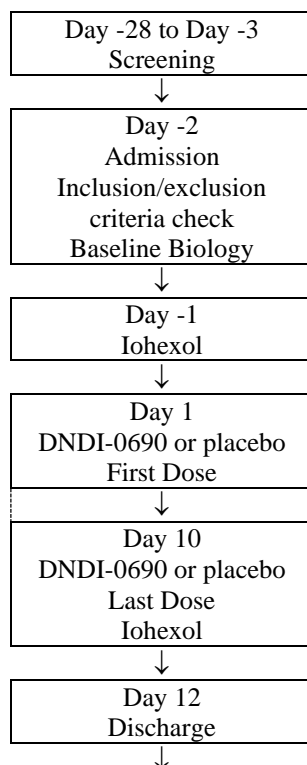
- A brief physical examination
- Weight
- Laboratory safety tests (biochemistry, haematology, coagulation, urinalysis, urine microscopy)
- 12-lead ECG
- Vital signs (supine systolic and diastolic blood pressure, pulse rate, and tympanic temperature)
- AE
- SAE
- Prior and concomitant medication
- PK plasma sample for DNDI-0690 and metabolite: 48 h post-last dose

If all assessments are satisfactory to the PI (or deputy), subjects will be discharged from clinic after all Day 12 procedures are completed.

Post Study Follow-up (Day 24 to Day 28):

- Post study follow-up procedures are identical to Part A.
- Optional iohexol dosing at the time of the follow-up visit, plasma and urine samples for iohexol may be taken if results from previous timepoints of mGFR calculation showed abnormal results.
 - Plasma samples for iohexol: Pre-iohexol dose, 1, 2, 3, 4 and 5 h post-iohexol dose
 - Urine samples for iohexol: Pre-iohexol dose, [0-1], [1-2], [2-3], [3-4] and [4-5]h post-iohexol dose (240 mL water to be taken after each urine PK sampling timepoint to ensure the capability of the volunteer to provide urine samples during each collection period)

Figure 3 Study Sequence Part C



Day 24 to 28
Follow-Up Visit
Iohexol (only if
abnormal mGFR at D10
assessment)

NUMBER OF SUBJECTS:

Part A: Up to 4 cohorts of 9 subjects

Part B: 9 subjects (Optional)

Part C: 9 subjects

MAIN INCLUSION CRITERIA:

1. Healthy males or healthy women of non-childbearing potential (WONCBP) between 18 and 55 years of age inclusive at the time of signing informed consent
2. Female subject of non-childbearing potential. WONCBP is defined as women who are postmenopausal or permanently sterilised (permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy).
3. Female post-menopausal state is defined as no menses for 12 months without an alternative medical cause and confirmed by a serum FSH result of ≥ 40 IU/L at Screening.
4. Male subject (and subject's partner of childbearing potential) must use condom and also willing to use a highly effective method of contraception or 2 effective methods of contraception (see [Section Error! Reference source not found.](#)), if applicable (unless anatomically sterile or where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the subject) from first dose until 3 months after last dose of IMP.
5. Body mass index (BMI) of 18.0 to 30.1 kg/m² as measured at Screening and body weight ≥ 60 kg (BMI = body weight (kg) / [height (m)]²).
6. No clinically significant abnormal test results for serum biochemistry, haematology and/or urine analyses within 28 days before the first dose administration of the IMP.
7. Subject with a negative urinary drugs of abuse (DOA) screen (including alcohol and cotinine) test results, determined within 28 days before the first dose administration of the IMP (N.B.: A positive test result may be repeated at the Investigator's discretion).
8. Subject with negative human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (HCV Ab) test results at Screening.
9. General good physical health determined by medical and surgical history, physical examination, 12-lead ECG, vital signs and clinical laboratory tests.
10. Normal blood pressure: Systolic blood pressure between ≥ 90 and ≤ 140 mmHg, Diastolic blood pressure ≤ 90 mmHg, measured after 10 min rest in supine position at Screening, admission and pre-dose.
11. A resting heart rate (HR) between ≥ 50 and ≤ 100 bpm measured after 10 min rest in supine position at Screening, admission and pre-dose.
12. ECG recording without clinically significant abnormality, including QTcF measure of ≤ 450 msec at Screening, admission and pre-dose,
13. No febrile seizures or infectious illness for at least 7 days prior to first administration of the IMP (Day 1).
14. Must agree to adhere to the contraception requirements and the life-style restrictions.
15. Subject must be available to complete the study (including all follow up visits).
16. Subject must satisfy an Investigator about his/her fitness to participate in the study.
17. Subject must provide written informed consent to participate in the study.

MAIN EXCLUSION CRITERIA:

1. Subjects who have received any IMP in a clinical research study within 90 days prior to Day 1.
2. Subjects who are study site employees, or immediate family members of a study site or sponsor employee.
3. Subjects who have previously been enrolled in this study and/or have received DNDI 0690 previously
4. History of any drug or alcohol abuse in the past 2 years.
5. Demonstrating excess in caffeine/xanthine consumption (more than 6 cups of coffee or equivalent a day).
6. Regular alcohol consumption in males >21 units per week and females >14 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 Units = 125 mL glass of wine, depending on type). As confirmed by a positive urine alcohol test at Screening or admission.
7. Current smokers or those who have smoked within the last 12 months with a positive cotinine result at Screening and Admission.
8. Current users of cigarette replacements (*i.e.* e-cigarettes, nicotine patches or gums) and those who have used these products within the last 12 months.
9. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the Investigator or delegate at Screening.
10. Clinically significant abnormal biochemistry, haematology, coagulation or urinalysis as judged by the Investigator or AST/ALT/total bilirubin/gamma glutamyl transpeptidase [GGT]/ALP/creatinine > 1.2 ULN. Subjects with Gilbert's syndrome are allowed.
11. Positive PCR COVID-19 test at admission.
12. Evidence of renal impairment at Screening or admission, as indicated by an estimated Glomerular Filtration Rate (GFR) <80 mL/min/1.73m² using the CKD-EPI equation.
13. History of clinically significant cardiovascular, renal, hepatic, neurological (especially seizures), immunological, psychiatric, myopathies, bleeding tendency, respiratory and particularly gastrointestinal (GI) disease, especially peptic ulceration and chronic gastritis, GI bleeding, ulcerative colitis, Crohn's Disease or Irritable Bowel Syndrome, as judged by the Investigator.
14. History of additional risk factors for Torsades des Pointe (*i.e.* heart failure, hypokalaemia, family history of long QT syndrome).
15. Rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency.
16. Any relevant GI complaints within 7 days of dosing.
17. Serious adverse reaction or clinically relevant hypersensitivity to any drug or the formulation excipients (Hydromellose [HPMC], sodium lauryl sulphate [SLS], sucrose, croscarmellose sodium and magnesium stearate).
18. Presence or history of clinically significant allergy requiring treatment (including asthma, urticaria, clinically significant allergic rash or other severe allergic diathesis), as judged by the Investigator. Hay fever is allowed unless it is active.
19. Donation or loss of greater than 500 mL of blood within the previous 3 months or more than 100 mL within 30 days prior to signature of informed consent.
20. Subjects who are taking, or have taken, any prescribed or over-the-counter drug (including anti-acid drugs) or vitamins/herbal remedies (*i.e.* St. John's Wort and others which are known to interfere with the CYP3A4 and P-gp metabolic pathways) or hormone replacement therapy (HRT) or any drug known to modify the MATE-1/OCT-2 renal transporters (such as, for example, cimetidine, ritonavir, trimethoprim, cisplatin) or any medication with a possibility of interaction with IMP (such as COVID-19 vaccination) in the 28 days before IMP administration (or 5 half-lives of the taken drug, whichever is longer) and plan to do so during the course of study. Administration of up to 4 g of paracetamol per day within 7 days of IMP administration is allowed.
21. Surgery within 12 weeks prior to Screening, with the exception of appendectomy.
22. Any surgery (*i.e.* gastric bypass) or medical condition that may affect absorption of orally administered drugs.
23. Failure to satisfy the Investigator of fitness to participate for any other reason.
24. Breastfeeding and lactating females.

Additional Exclusion Criteria for Part C

25. Hypersensitivity to iohexol or any of its excipients or to iodine, history of allergic reaction to iohexol, iodine or other contrast media, including cutaneous adverse reactions.
26. Manifest thyrotoxicosis.

IMP ADMINISTRATION

Capsules of DNDI-0690 100mg and 200 mg have been chosen as the formulation for this study. The number of capsules to be administered will vary depending on the dose selected by the SRC upon review of data (safety and PK) from the previous cohort.

Table 1 Description of DNDI-0690 doses

Part A	Dose		Increase from the previous dose
	mg	mg/kg/day*	
Cohort 1	400 OD	5.7	
Cohort 2	To be decided	To be decided	2 to 3 times and/or change from OD to BID
Cohort 3	To be decided	To be decided	2 to 3 times and/or change from OD to BID
Cohort 4	To be decided	To be decided	2 to 3 times and/or change from OD to BID
Part B	maximum of 3600	maximum of 51.5	
Part C	To be decided	To be decided	Highest dose tested in Part A and well tolerated, or below

* assuming a 70-kg person

Part C

Non-IMP (NIMP): Iohexol solution (300mg/mL iodine). 5 ml of iohexol solution (300mg/mL iodine) will be administered intravenously on Day -1 and Day 10.

Precautions for use as per iohexol summary of product characteristics (SmPC) will be respected [\[Error! Reference source not found.\]](#).

STUDY VARIABLES/ENDPOINTS:

Primary Endpoints

Safety parameters (changes in vital signs, ECG, safety laboratory parameters with special focus on renal function parameters, *i.e.*, serum creatinine, blood urea nitrogen (BUN), and serum Cys C), and frequency and severity of observed treatment-emergent adverse events (TEAEs).

Secondary Endpoints

- Measurement of the following PK parameters:
 - Day 1:
 - Main: C_{max} , $C_{max/D}$, AUC_{0-24} , $AUC_{0-24/D}$
 - Exploratory: $AUC_{0-24, norm}$, $C_{max, norm}$, T_{max} , MRT_{last}
 - Day 10:
 - Main: AUC_{0-inf} , $AUC_{0-inf/D}$, AUC_{0-24} , $AUC_{0-24/D}$, $C_{max, ss}$, $C_{max, ss/D}$, $C_{min SS}$
 - Exploratory: $AUC_{0-inf, norm}$, $AUC_{0-24, norm}$, AUC_{last} , $AUC_{last/D}$, $AUC_{last, norm}$, $C_{max, ss, norm}$, T_{max} , $t_{1/2}$, Cl/F , $\lambda\text{-}z$, MRT_{last} , Vz/F , CL_{ss}/F and points terminal for DNDI-0690.
- Optional: if BID dosing, AUC_{0-10} , $AUC_{0-10/D}$, $AUC_{0-10, norm}$ will be added on Day 1 and Day 10
- AUC_{t-inf} , % AUC_{extra}
- Accumulation ratios $RA(C_{max})$ and $RA(AUC_{0-tau})$ will be calculated
- $C_{through}$ will be derived from the concentration data (Days 2-10 for Part A, days 2-5 for Part B and days 2/4/7/10 for Part C).

- Measurement of the urine PK parameters Ae, Ae% and CLr for DNDI-0690.
- Glomerular filtration rate measurement (mGFR) following evaluation of plasma clearance of iohexol before and under exposure to DNDI-0690

Exploratory Endpoints

- Changes in clinical early renal toxicity biomarkers in urine: Cystatin C (Cys C), Kidney Injury Molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL) and other renal biomarkers.
- Analysis of Holter extracted ECGs for the following parameters: RR, heart rate (HR), PR, QRS, QT, corrected QT interval by Fridericia's formula (QTcF), corrected QT interval by Bazett's formula (QTcB), Δ HR, Δ RR, Δ PR, Δ QRS, Δ QT, Δ QTcF and Δ QTcB.
- Measurement of drug concentration in dry blood spots for comparison with matching plasma samples
- Variation of mRNA expression in blood sample before and after exposure to the drug (Transcriptional Profiling)
- Exploration of metabolism after multiple dose exposure

STATISTICAL METHODS:

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

All safety data will be listed, in addition:

- **AEs:** All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (the most up to date version that is available at the time of database build will be used and will be listed in the data management plan (DMP)). The MedDRA dictionary will not be updated during the course of the study. Only TEAEs, *i.e.*, existing conditions that worsen or events that occur during the course of the study after administration of IMP, will be included within the summary tables.
- **Laboratory Safety:** Biochemistry, haematology, coagulation, and urinalysis parameters will be listed with any out of normal range values flagged. Laboratory test results which are out of normal range will also be presented separately along with normal reference ranges. Descriptive statistics (N, n, mean, SD, minimum, median and maximum) of absolute and change from baseline (Day -2) values at each protocol-defined time point will be tabulated.
- **Vital Signs:** Vital signs parameters will be listed with any out of normal range values flagged. Descriptive statistics (N, n, mean, standard deviation (SD), minimum, median and maximum) of absolute and change from baseline (Day 1 Pre-dose) values at each time point will be tabulated.
- **12 Lead ECG:** 12 Lead ECG parameters will be listed with any out of normal range values flagged. Descriptive statistics (N, n, mean, SD, minimum, median and maximum) of absolute and change from baseline (Day 1 Pre-dose) values at each time point will be tabulated. Additionally, the frequency (number and % of subjects) for absolute and change from baseline QTcB and QTcF values will be summarised.

Dose Proportionality/Independence (Part A and Part B)

For Day 1 and Day 10 (Part A) or Day 1 and Day 5 (Part B), dose proportionality will be assessed by performing a regression analysis of the log-transformed C_{max} , AUC_{0-t} and AUC_{0-inf} (Day 10 for Part A and Day 5 for Part B only) values versus the log-transformed dose using the power model with a fixed effect for log(dose). For each parameter a point estimate and 95 % confidence interval (CI) will be calculated for the slope of the regression line.

For Day 10 for Part A and Day 5 for Part B, dose independence will be assessed for $t_{1/2}$ and CL/F by performing a regression analysis of the untransformed parameters versus dose with a fixed effect for dose. For each parameter a point estimate and corresponding 95 % CI will be calculated for the slope of the regression line.

Steady State (Part A and Part B)

For each dose level, log-transformed trough concentration levels at pre-dose each day (Day 2 to Day 10 for Part A and Day 2 to Day 5 for Part B) will be subjected to a mixed effects analysis of variance (ANOVA) with study day as a fixed effect and subject as a random effect in order to establish whether and when steady state has been attained for each dose level. Back-transformed ratios for the comparisons of each consecutive day (*i.e.* Day 3/Day 2) will be presented along with corresponding 90 % CI.

Accumulation (Part A and Part B)

For each dose level, log-transformed C_{max} and AUC_{0-t} values on Day 1 and Day 10 for Part A or Day 1 to Day 5 for Part B will be subjected to an ANOVA with study day as a fixed effect and subject as a random effect. For comparison point estimates and 90 % CI for the difference between Day 10 (Part A) or Day 5 (Part B) and Day 1 will be constructed using the residual mean square error obtained from the ANOVA for each dose level. The point and interval estimates will then be back transformed to give estimates of the ratios of the geometric least squares means and corresponding 90 % CI.

Measured glomerular filtration rate (mGFR) will be calculated following evaluation of plasma clearance of iohexol before and under exposure to DNDI-0690. mGFR data will be descriptively analysed together with their 95% confidence intervals.

Details on the statistical analyses will be presented in the statistical analysis plan (SAP), which will be finalized and signed before unblinding the study.

DURATION OF STUDY:

Screening will occur within 28 days before admission to the research unit prior to DNDI-0690 dosing.

Multiple oral administration per subject OD or BID for 10 days (Part A and Part C) or OD for 5 days (Part B).

Duration of clinical phase by subject will be approximately 2 months.