STATISTICAL ANALYSIS PLAN

A Phase 1, blinded, randomized, single centre, parallel-group, single-dose, dose-escalation, placebo-controlled study of the safety, tolerability, and pharmacokinetics of DNDI-6148 after oral dosing in healthy male subjects

Protocol number:	DNDi-6148-01
Drug name:	DNDI-6148
Drug development phase:	Phase I
Sponsor's representative:	Sophie Delhomme DNDi Chemin Camille-Vidart, 15 1202 Geneva - Switzerland
Pharmacokineticist:	Sabrina Loyau PhinC Development 36, rue Victor Basch 91300 Massy - France
Statistician:	Mathieu Felices PhinC Development (same address as above)
PhInC reference:	PH18023
Version - date:	Version 2.0 – 04/04/2022

2 SIGNATURE PAGE

I herewith declare that I agree without reservation to the methods described in detail in this document:

Author: Name: Sabrina Loyau Pharmacokineticist, PhinC Development	Date: Signature:	Sabrina LOYAU 2022.04.14 18:07:38 +02'00'
Approval: Name: Mathieu Felices Biostatistician, PhinC Development	Date: Signature:	Mathieu FELICES Signature numérique de Mathieu FELICES Date : 2022.04.14 18:07:12 +02'00'
Approval: Name: Sophie Delhomme Translational Manager, DNDi	Date: Signature:	Nabila Ibnou Zekri Lassout Digitally signed by Nabila Ibnou Zekri Lassout Date: 2022.04.06 13:51:57 +02'00'
Name: Jean-Yves Gillon Head of Translational Sciences	Date: Signature:	Jean-Yves Gillon 2022.04.13 09:55:05 +02'00'

3 TABLE OF CONTENTS

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

%	Percentage
%AUCextra	Percentage of extrapolated $AUC_{0-\infty}$
ADaM	Analysis Data Model
Ae	Total amount excreted in urine
ALQ	Above limit of quantification
ANOVA	Analysis of variance
AUC	Area under the concentration curve
BLQ	Below the limit of quantification
CI	Confidence interval
CL/F	Apparent total clearance
CLr	Renal clearance
C_{max}	Maximum concentration
CRP	C-reactive protein
CRO	Clinical research organization
CV/CV%	Coefficient of variation
D	Dose
DTA	Data transfer agreement
e.g.	*exempli gratia* (for example)
Fe	Fraction of the dose excreted in urine
GM	Geometric mean
H	Hour(s)
i.e.	*id est* (that is)
k_e	Terminal plasma elimination rate-constant
Kg	Kilogram(s)
L	Liter
LOQ	Limit of quantification
M	Meter(s)
Max	Maximum value
Mg	Milligram(s)
Min	Minimum value
mL	Milliliter(s)
MRT	Mean time of drug presence in plasma
N	Number of observation/value
NC	Not calculable

NCA	Non compartment analysis
Ng	Nanogram(s)
NR	Not reported
PC	Pharmacokinetic concentration
PD	Pharmacodynamics
PK	Pharmacokinetic
PP	Pharmacokinetic parameter
r^2	Coefficient of determination
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study Data Tabulation Model
$t_{1/2}$	Terminal half-life
t_{max}	Time of occurrence of maximum concentration
TNFα	Tumor necrosis factor alpha
µM	Micromolar(s)
Vz/F	Apparent volume of distribution
vs.	*Versus*

5 HISTORY OF CHANGES

Version Number	Effective Date	Author	Summary of Changes Made
1.0	06/07/2021	S Loyau and M Felices	Initial Document
2.0	04/04/2022	S Loyau	Addition of ambulatory visit for Cohort 300 and 380 mg

6 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to give details of the methodology and conventions that will be used for the analysis of pharmacokinetic (PK) data of the Study DNDi-6148-01.

This SAP is based on Study Protocol Version 10.0 dated 21/09/2021.

The SAP ensures the credibility of all study findings by means of predefined data analysis plan before database lock.

7 STUDY OBJECTIVES

7.1 PRIMARY OBJECTIVE

The primary objective is to assess the safety and tolerability of DNDI-6148 after single oral doses administered as oral suspension of DNDI-6148 in healthy male subjects, compared to matching placebo.

7.2 SECONDARY OBJECTIVES

The secondary objectives are:

- To determine area under the concentration curve from time 0 to 24 h post-dose (AUC_{0-24}), AUC from time 0 to time of the last quantifiable concentration t (AUC_{0-t}), AUC_{0-t} divided by dose (AUC_{0-t}/D), AUC from time 0 to infinity ($AUC_{0-\infty}$), $AUC_{0-\infty}/D$, maximum concentration (C_{max}), C_{max}/D for DNDI-6148 in plasma after single oral doses, administered as oral suspension in healthy male subjects.
- To determine other PK parameters of DNDI-6148 in plasma and urine after single oral doses administered as oral suspension of DNDI-6148 in healthy male subjects.

7.3 EXPLORATORY OBJECTIVE

The exploratory objectives are:

- To determine pharmacodynamics (PD) effect on cardiologic parameters after single oral dose administered as oral suspension of DNDI-6148 in healthy male subjects.
- To identify DNDI-6148 main metabolites
- To determine pre- and post-dose plasma concentrations of C-reactive protein (CRP) and tumor necrosis factor alpha (TNFα) for the last 4 subjects of Cohort 160 mg, and the Cohorts 220 mg, 300 mg and 380 mg.

Only PK objectives are considered in this SAP

8 STUDY DESIGN

8.1 DESIGN

This is a First in Human Phase I blinded, randomized, placebo-controlled, single ascending dose study with DNDI-6148 administered as an oral suspension in healthy male volunteers. Each cohort will include 8 subjects (6 active/ 2 placebo).

Bioanalysis (in plasma and urine) will be performed in open conditions.

The administered dose will be 10 mg, 20 mg, 40 mg, 80 mg, 160 mg, 220 mg, 300 mg and 380 mg. The treatment will be administered as a single dose on Day 1.

At each dose level, subjects will be split at least in two sub-cohorts: first sub-cohort will be one subject under active, one subject on placebo (sentinel approach as recommended by European Medicine Agency). The 6 remaining subjects will be dosed after a minimum of 24 h of safety surveillance of the first 2 subjects. Decision to proceed with the administration of the 6 remaining subjects will be taken by the Investigator on the basis of biology and clinical safety data. The 6 remaining subjects can be divided in multiple subgroups. Any safety data available on previous subjects will be taken into consideration before dosing any new subject. Any concern should be shared with the Sponsor prior to next dosing.

Decision on dose escalation will be taken in blinded conditions, based on safety interim report and DNDI-6148 plasma exposure.

A screening visit will be performed within 28 days prior to the first administration, then subjects will be hospitalized for 5 days (from Day -1 morning to Day 4 morning), ambulatory visits will be done on Day 5 and Day 6 for Cohorts 160, 220, 300 and 380 mg only and on Day 8 for Cohorts 300 and 380 mg only. End of study visit will be done on Day 4 for 4 first cohorts, on Day 6 for the Cohorts 160 and 200 mg and on Day 8 for the Cohorts 300 and 380 mg.

Blood samples will be collected from all subjects for DNDI-6148 concentration measurements at the following time points: pre-dose, then 0.50, 1.00, 1.50 (only for the Cohorts 10 mg, 20 mg, 40 mg, 80 mg), 2.00, 2.50, 3.00, 4.00, 5.00*, 6.00, 9.00, 12.00, 24.00, 48.00, 72.00, 96.00*, 120.00* and 168.00** h post-dose (* only for the Cohorts 160 mg, 220 mg, 300 mg and 380 mg / ** only for the Cohorts 300 mg and 380 mg).

Furthermore, urine collection will be performed for DNDI-6148 urine concentration measurements at the following time points: pre-dose,]D1T0h – D1T12h],]D1T12h – D2T24h],]D2T24h – D3T48h] and] D3T48h – D4T72h].

8.2 STUDY ENDPOINTS

8.2.1 Primary endpoint

Assessment of safety and tolerability of DNDI-6148 by evaluation of following parameters: adverse events, physical examination (including body weight), clinical neurological examination, vital signs, 12-lead electrocardiogram, clinical laboratory (including serum chemistry, hematology, hormonology and urinalysis), psychological and cognitive examination (Columbia-Suicide Severity Rating Scale and Bond and Lader questionnaires).

8.2.2 Secondary endpoints

PK evaluation

For PK in plasma, the recording of following parameters will be analyzed:

- Main DNDI-6148 PK parameters: $AUC_{0-\infty}$, C_{max}
- Other DNDI-6148 PK parameters:
    - AUC_{0-24}, AUC_{0-t}, AUC_{0-t}/D, $AUC_{0-\infty}/D$, C_{max}/D, time of C_{max} (t_{max}), terminal elimination half-life ($t_{1/2}$), mean time of drug presence in plasma (MRT), apparent clearance (CL/F), apparent volume of distribution (Vz/F)
    - terminal elimination rate-constant (k_e), percentage of AUC extrapolated (%AUCextra)

The following parameters will be calculated from urine data for DNDI-6148: total amount excreted over 24 h and 72 h (Ae_{0-t} with t = 24 or 72), fraction of the dose excreted in urine over 24 h and 72 h (fe), and renal clearance of DNDI-6148 (CLr).

8.2.3 Exploratory endpoints

- PD evaluation: The cardiological pharmacodynamics parameters of DNDI-6148 will be analyzed.
- Identification of metabolites: exploratory identification of DNDI-6148 metabolites.
- Exploratory plasma concentrations: exploratory evaluation of plasma concentrations of CRP and TNFα, pre- and post-dose for the last 4 subjects of Cohort 160 mg, and the Cohorts 220 mg, 300 mg and 380 mg.

Only PK evaluation (i.e. secondary endpoints) are considered in this SAP

9 STUDY POPULATION

9.1 JUSTIFICATION FOR THE NUMBER OF SUBJECTS PLANNED

No formal calculation was performed. It has been decided to include 8 subjects (6 active and 2 placebo) within each treatment group, which, given the exploratory nature of the trial, is considered as a sufficient number of subjects.

9.2 DISPOSITION OF SUBJECTS

The study will be performed on up to 64 healthy Caucasian male subjects in good general condition, aged 18 to 50 inclusive and with body mass index between 18 and 30.1 kg/m^2 inclusive, who met all the inclusion criteria and none of the exclusion criteria presented in Sections 4.1 and 4.2 of the study protocol. All subjects had to give their written informed consent at selection visit and still willing to perform the trial. A subject who prematurely ends his study period (for reasons unrelated to the investigational product) after the start of the baseline period and who received product/treatment will be replaced.

A listing of discontinued subject, including reasons for discontinuation, should be provided to PhinC by the Sponsor.

9.3 PROTOCOL DEVIATIONS

Protocol deviations will be assessed during the blind review of the data base and documented in the data review minutes.

The following protocol deviations will be specifically assessed:

- Unfulfilled inclusion and/or exclusion criteria
- Unauthorized previous and concomitant medications
- Treatment compliance
- Missing values for the endpoints

All decision concerning a potential withdrawal of a subject from a population of analysis due to protocol deviations will be discussed with the Sponsor before unblinding.

If necessary, the last version of this SAP will be updated accordingly.

9.4 ANALYSIS SETS

The manner of dealing with irregularities regarding the below definition will be deferred until the data review meeting after which analysis sets will be completely defined.

9.4.1 PK analysis set

The PK analysis set will include all subjects receiving DNDI-6148 as planned in the protocol, completing the study and who did not have any protocol deviation or events implying a bias for the PK evaluation.

10 PRESENTATION OF RESULTS

10.1 GENERAL SPECIFICATION

The PK statistical outputs will be generated according to PhinC template for statistical appendices of the report.

The appendix containing the individual data listings will be generated in Word format. The summary tables will be generated as Rich Text Format files (rtf) from SAS® or in Word format. Specific tables may be generated apart this document for direct insertion in the report.

General layout of tables will be similar to the shell examples provided Section 15 of this SAP.

10.2 GENERAL RULES FOR STUDY DATA

10.2.1 General rules

All data recorded during the course of the study or derived during the programming phase will be presented in the individual data listings.

All listings will be presented sorted by dose level, subject number, and time point (using 24 hour clock).

Individual concentrations will be presented with the same number of significant digits or decimals as raw data. If format is not homogeneous, concentrations will be presented with 2 decimals. Individual PK parameters will be presented with the same number of significant digits or decimals as raw data or with 2 decimals (for k_e additional decimals could be added). Descriptive statistics will be presented with the same number of significant digits or decimals as the individual data except for coefficient of variation (CV%), which will be presented with only one decimal.

10.2.2 Handling of drop-outs and missing data

Missing data will not be replaced, descriptive statistics and statistical analysis will be performed on the basis of the available data only.

In case of missing actual time of sampling, the scheduled time will be used for derivation of PK parameters.

Specific rules to deal with concentrations below or above the limit of quantification are defined in Section 11.1.

All data recorded on discontinued subjects will be listed. For PK, PK parameters will be derived if data are available.

11 PHARMACOKINETIC ANALYSIS

PK parameters of DNDI-6148 will be calculated using non-compartmental methods. Derivation of PK parameters will be carried out by PhinC Development using Phoenix WinNonlin® (Version Phoenix 8.1 or higher – Certara – Princeton – – USA).

For final analysis, after database lock, data (concentrations, EX, PK and DM) will be transferred to PhinC Development by Eurofins Optimed according to predefine format.

11.1 PHARMACOKINETIC ENDPOINTS

For the calculation of the PK parameters and characteristics the following rules were applied:

- All the plasma concentrations validated by the bioanalytical laboratory and provided to the pharmacokineticist will be used for the PK analysis.
- The actual PK blood sampling time points will be used except for interim analyses.
- At time points in the lag-time between time zero and the first concentration equal or above limit of quantification (LOQ), concentrations below the LOQ (BLQ) will be set to zero (0).
- Concentrations BLQ between 2 concentrations equal or above LOQ will be considered as missing.
- Trailing concentrations (at time point between time of last measurable concentrations and time of last blood sample) BLQ will be not used in calculations.
- For plasma concentration above the upper limit of quantification and reported as above limit of quantification (ALQ) in the final plasma concentration tables, ALQ will be considered as missing.
- Not reported (NR) concentration will be excluded from the PK analysis.

In plasma, the following PK parameters of DNDI-6148, will be derived for each subject receiving the active treatment on Day 1:

C_{max} The observed maximum concentration in plasma measured in a subject after dosing identified by inspection of the plasma drug concentration *versus* (*vs*.) time data by Phoenix WinNonlin®.

C_{max}/D C_{max} divided by dose.

t_{max} The time at which C_{max} is apparent, identified by inspection of the plasma drug concentration *vs.* time data by Phoenix WinNonlin®.

k_e The terminal plasma elimination rate-constant will be estimated from log-linear regression analysis of the terminal phase of the plasma concentration-time profile. The number of points included in the terminal phase was determined by visual inspection of the semi-log plots of the plasma concentration-time profiles. A minimum of 3 data points, including the last measured data point and excluding C_{max}, should be available for the regression.

r^2 The coefficient of determination for the goodness of the fit of the regression line through the data points (r^2) must be 0.90 or higher, for the value to be considered reliable. No AUC extrapolation or determination of derived parameters will be performed with unreliable elimination rate constants (hence, considered as not calculable – NC)

$t_{½}$ The apparent terminal elimination half-life will be calculated as $\ln 2/k_e$, where k_e is the elimination rate constant as defined above.

AUC_{0-24} The area under the concentration-time curve from time zero (pre-dose) to 24 h post-dose will be calculated using a linear trapezoidal method. The AUC will be only calculated if there is at least 3 concentrations above LOQ.

AUC_{0-t} The area under the concentration-time curve from time zero (pre-dose) to the time of last quantifiable concentration will be calculated using a linear trapezoidal method. The AUC will be only calculated if there is at least 3 concentrations above LOQ.

AUC_{0-t}/D AUC_{0-t} divided by dose.

$AUC_{0-\infty}$ The AUC from time 0 to infinity was calculated as $AUC_{0-\infty} = AUC_{0-t} + AUC_{t-\infty}$, where AUC_{0-t} is the area under the concentration-time curve from time zero (pre dose) to the time of last quantifiable concentration calculated using a log-linear trapezoidal method and $AUC_{t-\infty} = Ct/k_e$, where Ct is the measured concentration at time of the last quantifiable concentration t. The AUC will be only calculated if there is at least 3 concentrations above LOQ. The extrapolated part of $AUC_{0-\infty}$ must be < 20% for the value be considered as reliable.

$\%AUC_{extra}$ Percentage of extrapolated $AUC_{0-\infty}$.

$AUC_{0-\infty}$/D $AUC_{0-\infty}$ divided by dose.

MRT Mean time of drug presence in plasma will be calculated using the formula:

MRT = $AUMC_{0-\infty}$/ $AUC_{0-\infty}$ where AUMC is the area under the concentration time curve*time.

CL/F The apparent volume of the central compartment cleared of drug per unit time was estimated using the formula: CL/F = Dose / $AUC_{0-\infty}$.

Vz/F The apparent volume of distribution based on the terminal elimination phase. The estimate does not account for the bioavailability (F, as a fraction of 1) and is therefore nominally divided by this value when drug is given via extravascular routes. Vd/F=CL/F / k_e.

In urine, the following PK parameters of DNDI-6148 will be derived:

Ae_{0-t} Total amount excreted over 24 h and 72 h (*i.e.* t = 24 or 72).

fe The fraction of the dose excreted in urine over 24 h and 72 h (Ae_{0-t}/Dose x 100%).

CLr The renal clearance of DNDI-6148 (Ae_{0-t}/AUC_{0-t}).

11.2 POPULATIONS ANALYZED

The PK analysis will be performed on the PK analysis set.

11.3 STATISTICAL METHODS

The PK statistical analysis will be carried out by PhinC Development using the SAS® package (release 9.4) or using Phoenix WinNonlin® Version 8.1 or higher.

11.3.1 Descriptive statistics

Individual plasma concentrations will be presented by dose level and time point using theoretical blood sampling times. Descriptive statistics of plasma concentrations will be presented as N, mean and standard deviation (SD) and will be calculated if at least 2/3 of the plasma values per time-point will be above LOQ. For descriptive statistics calculations, concentrations BLQ will be set to zero (0) before the first concentration equal or above LOQ and considered as missing after.

Individual urine concentrations will be presented by dose level and time point. No descriptive statistics will be done on urine concentrations.

Individual plasma and urine PK parameters will be presented by dose level. Descriptive statistics of PK parameters will be presented as N, mean, SD, CV%, median, minimum (Min) and maximum (Max) values and geometric mean (GM).

Examples of listing and tables for PK data are presented in Section 15.1.

A measured plasma drug concentration *vs.* actual time curves will be produced in graphic for each subject on both linear/linear and log/linear scales. Mean plasma drug concentration *vs*. time curves will be produced for each dose level using theoretical blood sampling times.

11.3.2 Dose proportionality

The hypothesis that $AUC_{0-\infty}$ and C_{max} are dose proportional will be formally tested using a power model approach. $AUC_{0-\infty}$ and C_{max} values, for all dose levels, will be analyzed for dose proportionality using analysis of variance (ANOVA) techniques.

Data will be fitted to the following model:

$$\log(\text{AUC or } C_{max}) = \mu + [\beta \times \log(\text{Dose})]$$

This is usually referred to as a power model because after exponentiation:

$$\text{AUC or } C_{max} = \alpha \times \text{Dose}^{\beta}$$

Prior to the analysis, the assumption of a linear relationship between the log AUC (C_{max}) and log-dose will be tested using ANOVA by partitioning the sums of squares for treatments into those for linearity and departures from linearity. If the departures from linearity are significant then the hypothesis of dose proportionality is rejected and the power model analysis will not be performed.

In case, $AUC_{0-\infty}$ could not be considered as reliable in a majority of subjects (*e.g*. too large percentage of extrapolation, poor quality of k_e determination), dose proportionality assessment will be performed on AUC_{0-t} values.

The estimate obtained for β is a measure of dose proportionality. The estimate of β together with its 90% confidence interval (CI) (β_l, β_u) will be presented to quantify the degree of non-proportionality.

The dose proportionality will be confirmed if the 90% CI of β (β_l, β_u) is contained completely within the following critical region (referred as Smith[1] region):

$$[\Theta_L;\Theta_H] = \left[1+\frac{\log(0.8)}{\log(r)};1+\frac{\log(1.25)}{\log(r)}\right]$$

where *r*, defined as the dose ratio, is equal to h/l , *h* being the highest dose and *l* the lowest dose.

The use of Smith region, based on bioequivalence default values (0.8; 1.25) is reasonable for dose levels only a doubling apart but could be impractically strict and conservative (low power to demonstrate acceptable proportionality) when applied over a wide dose range. In case of the final dose ratio *r* would be much greater than 2, the critical region proposed by Hummel [2], replacing 0.8 and 1.25 by 0.5 and 2, respectively, will be also presented for supportive assessments.

In this decision rule, the dose proportionality will be analyzed as an equivalence problem. If the 90% CI is excluded completely from the critical region $[\Theta_L;\Theta_H]$ defined here above, the hypothesis of dose proportionality is rejected. If the 90% CI of β includes the lower or the upper bound of the critical region, no conclusion can be done on dose proportionality. The proportionality will be tested at a 5% significance level.

The calculation of the increase in $AUC_{0-\infty}$ and C_{max} for a two-fold increase in dose will be performed using a power model as followed (assuming that $dose_2 = 2 \times dose_1$):

$$\frac{AUC_{0-\infty}(Dose_2)}{AUC_{0-\infty}(Dose_1)} = \frac{\alpha \times Dose_2^{\beta}}{\alpha \times Dose_1^{\beta}} = 2^{\beta}$$

Therefore, the ratio of AUC and C_{max} between $dose_2$ and $dose_1$ will be equal to 2^{β}. In the same way, the 90%CI for the ratio will be obtained by substituting β_l and β_u by $2^{\beta l}$ and $2^{\beta u}$.

Assessment of the dose proportionality will be performed on the complete dose range. In case of departures from linearity or of negative conclusion of dose proportionality on the complete dose range, further investigation using the same methodology might be done on a restrained dose range.

The individual AUC and C_{max} values will be presented graphically by dose level. The mean AUC values along with the standard deviation from the mean will be also displayed graphically by dose level.

12 INTERIM ANALYSIS

Interim PK analyses on blinded data are planned after the end of each cohort. These interim analyses are planned to be used as supportive information during each dose escalation review meeting to decide to go to the next dose level.

The interim PK analyses will be performed on re-labelled data to maintain the blinding condition of the study and will include derivation of the following plasma PK parameters (t_{lag}, C_{max}, t_{max}, k_e, $t_{½}$, AUC_{0-24}, AUC_{0-t}, $AUC_{0-\infty}$, CL/F, Vd/F) as well as corresponding descriptive statistics as described in Section 11.3.1.

13 SOFTWARE USED

PK parameters derivations will be performed using Phoenix WinNonlin® 8.1 or higher.

All listings, tables, plots, and statistical analysis will be performed using Phoenix WinNonlin® Version 8.1 or higher or SAS® software version 9.4 or higher.

14 STRUCTURE OF APPENDICES/DELIVERY

14.1 TABLES

- **Plasma concentrations**
  - Descriptive statistics for DNDI-6148 plasma concentrations after single oral administration of DNDI-6148 from 10 to 80 mg
  - Descriptive statistics for DNDI-6148 plasma concentrations after single oral administration of DNDI-6148 from 160 to <x> (last dose) mg
- **PK parameters**
  - Descriptive statistics for PK parameters of DNDI-6148 in plasma after single oral administration of DNDI-6148 by dose level
  - Descriptive statistics for PK parameters of DNDI-6148 in urine after single oral administration of DNDI-6148 by dose level

14.2 FIGURES

- **Mean PK profiles**
  - Mean DNDI-6148 plasma concentrations *vs*. nominal time after single oral administration of DNDI-6148 - lin/lin and log/lin scales ***(1 figure with all dose levels)***
- **Individual PK profiles**
  - Individual DNDI-6148 plasma concentrations *vs.* actual time after single oral administration of DNDI-6148 <x> mg - lin/lin and log/lin scales ***(1 figure by dose level with all the subjects: spaghetti plots)***
  - Individual DNDI-6148 plasma concentrations *vs.* actual time by subject after single oral administration of DNDI-6148 - lin/lin and log/lin scales ***(1 figure by subject)***

Note: mean plasma concentrations vs. time in lin/lin and log/lin scales will be presented as in-text figure.

14.3 LISTINGS

- **Concentrations**
  - Individual DNDI-6148 plasma concentrations after single oral administration of DNDI-6148 <x> mg
  - Individual DNDI-6148 urine concentrations after single oral administration of DNDI-6148 <x> mg
- **PK parameters**
  - Individual DNDI-6148 plasma PK parameters after single oral administration of DNDI-6148 <x> mg
  - Individual DNDI-6148 urine PK parameters after single oral administration of DNDI-6148 <x> mg

15 EXAMPLE OF TABLES

The aim of this section is to provide an overview of the different kind of tables which will be generated. All cases will not be taken into account, but the layout of all tables will be homogenous with those provided in this section.

15.1 APPENDICES

Table 1 Descriptive statistics for DNDI-6148 plasma concentrations after single oral administration of DNDI-6148 from 10 to 80 mg

Dose level (mg)	10			20			40			80		
Time (h)	N	Mean (ng/mL)	SD (ng/mL)	N	Mean (ng/mL)	SD (ng/mL)	N	Mean (ng/mL)	SD (ng/mL)	N	Mean (ng/mL)	SD (ng/mL)
Pre-dose	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
0.5	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
1	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
1.5	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
2	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
2.5	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
3	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
4	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
6	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
9	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
12	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
24	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
48	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
72	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

Mean corresponds to arithmetic mean

Table 2 Descriptive statistics for DNDI-6148 plasma concentrations after single oral administration of DNDI-6148 from 160 to 380 mg

Dose level (mg)	160			220			300			380		
Time (h)	N	Mean (ng/mL)	SD (ng/mL)	N	Mean (ng/mL)	SD (ng/mL)	N	Mean (ng/mL)	SD (ng/mL)	N	Mean (ng/mL)	SD (ng/mL)
Pre-dose	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
0.5	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
1	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
2	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
2.5	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
3	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
4	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
5	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
6	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
9	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
12	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
24	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
48	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
72	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
96	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
120	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
168	-	-	-	-	-	-	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

Mean corresponds to arithmetic mean

Table to be adapted according to the dose levels administered

Table 3 Descriptive statistics for PK parameters of DNDI-6148 in plasma after single oral administration of DNDI-6148 by dose level

Dose level (mg)		t_{max} (h)	C_{max} (ng/mL)	AUC_{0-24} (h.ng/mL)	AUC_{0-t} (h.ng/mL)	$AUC_{0-\infty}$ (h.ng/mL)	k_e (h^{-1})	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	MRT (h)	C_{max}/D (ng/mL/mg)	AUC_{0-t}/D (h.ng/mL/mg)	$AUC_{0-\infty}$/D (h.ng/mL/mg)
10	N	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Min	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Max	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	CV%	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	GM	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
20	N	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Min	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Max	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	CV%	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	GM	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

Table to be repeated for all dose levels

Table 4 - Descriptive statistics for PK parameters of DNDI-6148 in urine after single oral administration of DNDI-6148 by dose level

Dose level (mg)		Ae_{0-24} (unit)	Ae_{0-72} (unit)	fe_{0-24} (%)	fe_{0-24} (%)	CLr (unit)
10	N	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Min	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Max	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	CV%	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	GM	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
20	N	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Min	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Max	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	CV%	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	GM	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
…	N	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Min	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Max	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	CV%	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	GM	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

Table to be repeated for all dose levels

Table 5 Individual DNDI-6148 plasma concentrations after single oral administration of DNDI-6148 10 mg

	Dose level (mg)					
	10					
	Subject No.					
	X	X	X	X	X	X
Time (h)	Concentrations (ng/mL)					
0	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
0.5	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
1	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
1.5	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
2	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
2.5	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
3	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
4	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
6	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
9	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
12	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
24	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
48	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
72	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

Table to be repeated and adapted for each dose level

Table 6 Individual DNDI-6148 urine concentrations after single oral administration of DNDI-6148 10 mg

	Dose level (mg)					
	10					
	Subject No.					
	X	X	X	X	X	X
Time interval (h)	Concentration (ng/mL)					
0	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
]0-12]	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
]12-24]	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
]24-48]	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
]48-72]	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX

Table to be repeated and adapted for each dose level

Table 7 Individual DNDI-6148 plasma PK parameters after single oral administration of DNDI-6148 10 mg

Dose level (mg)	Subject No.	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-24} (h.ng/mL)	AUC_{0-t} (h.ng/mL)	$AUC_{0-\infty}$ (h.ng/mL)	k_e (h^{-1})	$t_{1/2}$ (h)	%AUCextra (%)	r^2	CL/F (L/h)	Vz/F (L)	MRT (h)	C_{max}/D (ng/mL/mg)	AUC_{0-t}/D (h.ng/mL/mg)	$AUC_{0-\infty}$/D (h.ng/mL/mg)
10	x	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	x	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	x	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	x	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	x	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	x	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

Table to be repeated and adapted for each dose level

Table 8 - Individual PK parameters of DNDI-6148 in urine after single oral administration of DNDI-6148 10 mg

Dose level (mg)	Subject No.	Ae_{0-24} (unit)	Ae_{0-72} (unit)	fe_{0-24} (%)	fe_{0-24} (%)	CLr (unit)
10	x	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	x	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	x	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	x	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	x	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	x	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

Table to be repeated and adapted for each dose level

15.2 IN-TEXT TABLES

Table 9 Summary statistics of <Analyte> PK parameters

Dose level (mg)		t_{max}* (h)	C_{max} (ng/mL)	AUC_{0-24} (h.ng/mL)	AUC_{0-t} (h.ng/mL)	$AUC_{0-\infty}$ (h.ng/mL)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	MRT (h)
10	N	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	CV%	xx.xx-xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	GM	-	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
20	N	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	CV%	xx.xx-xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	GM	-	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
…	N	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	CV%	xx.xx-xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	GM	-	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
…	N	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	CV%	xx.xx-xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	GM	-	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

* Median and min-max

16 REFERENCE LIST

[1] Smith BP, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT, Forgue ST (2000) Confidence interval criteria for assessment of dose proportionality. Pharm Res 17(10):1278–1283.

[2] Hummel J, McKendrick S, Brindley C, et al. Exploratory assessment of dose proportionality: review of current approaches and proposal for a practical criterion. Pharm Stat 2009; 8: 38–49