SYNOPSIS

Name of Sponsor: Drugs for Neglected Diseases initiative (DNDi), Geneva Switzerland **Name of finished products:** NA **Name of the active ingredient(s):** DNDI-6148	**Individual study table Referring to part of the dossier** Ref.: Volume:	Confidential (for Authority Use Only)

Title of the study:

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 N°: DNDi-6148-01 / OP105718.DND

Principal Investigator:

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Study centre: Eurofins Optimed – 1 rue des Essarts – 38610 Gières - France.

Publication: Study results are not published at the time of writing this report

Studied period: 21 JAN 2020 (first subject enrolled) - 08 MAR 2022 (last subject last visit)

Clinical Phase: Phase I, First-in Human study

Objectives:

Primary objective:

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.

Secondary objectives:

- To determine AUC_{0-24}, AUC_{0-t}, AUC_{0-t}/D, $AUC_{0-\infty}$, $AUC_{0-\infty}/D$, 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.

Exploratory objectives:

- To determine PD effect on cardiac 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 CRP and TNFα for the last 4 subjects of cohort 160 mg, and the cohorts 220 mg, 300 mg and 380 mg.

Methodology:

This was a randomized, blinded, placebo-controlled, single centre, single ascending dose study with DNDI-6148 administered as an oral suspension in 8 cohorts with healthy male subjects.

The planned starting dose for cohort 1 was 10 mg. Doses administered in Cohorts 2 to 8 were selected following review of the emerging PK and safety data from the previous cohorts. Decision on dose escalation was taken in blinded conditions.

Each cohort followed the same study design. Subjects were screened for inclusion in the study up to 28 days before dosing. Subjects were admitted to the clinical unit on the day before dosing (Day -1) for all cohorts. Subjects were dosed in the morning of Day 1 with either DNDI-6148 or matching placebo. As a safety precaution each cohort was split into two groups: sentinels (2 subjects) and main (6 subjects). The subjects of the sentinel group (1 subject on active, 1 subject on placebo) were dosed

with an appropriate time interval between them. After review of the safety data from the 24 h post-dose period, the Principal Investigator (PI), decided 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 subject.

Number of subjects:

Planned: 64 subjects - 8 cohorts

Included: 64 subjects in 8 cohorts

Analyzed: 64 subjects were analyzed in the Included Set (IS) and Safety Set (SS). 61 subjects were analyzed in the Pharmacokinetic Set (PKS) and Pharmacodynamic Set (PDS) (3 subjects from the IS with major protocol deviations were excluded).

Diagnosis and main criteria for inclusion:

Subjects were healthy male volunteers of Caucasian origin aged between 18 and 50 years, with a body Mass Index (BMI) between 18 and 30.1 kg/m^2 (both inclusive); and non-smoker, or smoker of no more than 5 cigarettes per day.

All subjects had to be in compliance with the inclusion and exclusion criteria described in the protocol and were judged eligible for enrolment in this study based on medical and medication histories, demographic data, vital signs measurements, 12-lead ECG, a physical examination, urine drug screen, and clinical laboratory tests (hematology, hormonology, blood chemistry tests, urinalysis, human immunodeficiency virus [HIV], hepatitis C [HCV] antibodies, and hepatitis B surface [HBs] antigen).

Test product, dose, mode of administration, batch:

Name of the compound:	DNDI-6148 (DNDI-6148 arginine monohydrate)
Pharmaceutical form:	Powder for oral suspension (bottles of pre-weighted powder corresponding to two strengths of 60 mg and 600 mg DNDI-6148 free acid equivalent) Vehicle: ORA-Sweet® (INRESA Pharma)
Dose per administration:	10 mg, 20 mg, 40 mg, 80 mg, 160 mg, 220 mg, 300 mg and 380 mg (DNDI-6148 free acid equivalent)
Timing for administration:	Single oral dose administration on D1 according to randomization. The administration was performed around 8:00 a.m. in sitting position and in fasting conditions. 250 mL of tap water was administered after dosing.

Batch N°: GF18000094 (60 mg strength); GF18000096 (600 mg strength)

A 2 or 20 mg/mL suspension, for the 60 or 600 mg dose strength respectively, was prepared extemporaneously by the pharmacist prior to administration to volunteers. The powder was suspended in 30 mL ORA-Sweet® vehicle, a maximum of 24 hours prior to dosing. The volume of suspension to be administered varied from 4 to 20 mL per subject.

Name of the compound:	DNDI-6148 - Placebo
Pharmaceutical form:	Powder for oral suspension Vehicle: ORA-Sweet® (INRESA Pharma)
Dose per administration:	NA
Timing for administration:	Single oral dose administration on D1 according to the randomization. The administration was performed around 8:00 a.m. in sitting position and in fasting conditions. 250 mL of tap water was administered after dosing.

Batch N°: GF19000082

A suspension was prepared extemporaneously by the pharmacist prior to administration to volunteers. The powder was suspended in 30 mL ORA-Sweet® vehicle, a maximum of 24 hours prior to dosing. Volume of suspension to be administered varied from 4 to 20 mL per subject.

Duration of treatment: Single oral dose administration

Duration of observation:

For the cohorts 10 mg, 20 mg, 40 mg and 80 mg:
- Screening within 28 days prior to the first administration;
- Hospitalization for 5 days (D-1 morning to D4 morning);
- End of study visit: D4.

For the cohorts 160 mg and 220 mg:
- Screening within 28 days prior to the first administration;
- Hospitalization for 5 days (D-1 morning to D4 morning);
- Ambulatory visits on D5 and D6;
- End of study visit: D6.

For the cohorts 300 mg and 380 mg:
- Screening within 28 days prior to the first administration;
- Hospitalization for 5 days (D-1 morning to D4 morning);
- Ambulatory visits on D5, D6 and D8;
- End of study visit: D8.

Expected duration = up to approximately 36 days for each subject

Reference therapy, dose, mode of administration, batch:
NA

Criteria for evaluation:

Primary evaluation criteria

Assessment of safety and tolerability of DNDI-6148 by evaluation of the following parameters:
- Adverse Events (AEs),
- Physical examination (including body weight), Clinical neurological examination,
- Vital signs,
- 12-lead ECG,
- Clinical laboratory (including serum chemistry, hematology, hormonology and urinalysis).
- Psychological and cognitive examination (evaluated by Columbia-Suicide Severity Rating Scale (CSSR-S) and Bond & Lader questionnaires).

Secondary evaluation criteria: *Pharmacokinetic evaluation*

For PK **in plasma**, the following parameters were 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, $AUC_{0-\infty}/D$, Cmax/D, tmax, t1/2, MRT, CL/F, Vz/F
  - ke, %AUCextra;

The following parameters were calculated from **urine** data for DNDI-6148:
- 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,
- CL_r The renal clearance of DNDI-6148.

Exploratory evaluation criteria

- *Exploratory Pharmacodynamic evaluation*

  The following cardiac pharmacodynamic parameters of DNDI-6148 were analyzed:
  - RR, HR, PR, QRS, QT, QTcF, QTcB, ΔHR, ΔRR, ΔPR, ΔQRS, ΔQT, ΔQTcF and ΔQTcB.

- *Exploratory identification of DNDI-6148 metabolites*

- *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.*

Statistical methods

Analysis populations:

Populations to be defined regarding populations defined in SAP.

- **Included set (IS):** All randomized subjects of the study were included in this population.
- **Pharmacokinetic set (PKS):** Subjects from the IS without protocol deviations or with violations thought not to significantly affect the pharmacokinetic analysis were included in this population.
- **Pharmacodynamic set (PDS):** Subjects from the IS without protocol deviations or with violations thought not to significantly affect the pharmacodynamic analysis were included in this population.
- **Safety set (SS):** Subjects from the IS who received at least one study treatment dose were included in this population.

Three subjects with major deviations (see Section 10.2.1) were excluded from the PKS and PDS (N=61).

Safety parameters:

AEs:

AEs were individually listed per subject number, presenting assigned dose group, verbatim, MedDRA Primary System Organ Class (SOC), MedDRA Preferred Term (PT), treatment-emergence (TEAEs or not), date and time of onset, date and time of the study drug administration before AE, duration, time from onset since last study drug administration, frequency, severity and seriousness, relationship to study drug, the required action taken, outcome. The non-treatment emergent events (or pre-dose events) were summarised by SOC and PT for the SS. The treatment emergent AEs (TEAEs) were summarised by Primary SOC, PT, by dose group and overall, for the SS to describe the evaluation of the number of TEAEs and the number of subjects reporting these TEAEs.

Physical examination, neurological examination, ECGs, vital signs and questionnaires:

Physical examination, neurological examinations, ECGs, vital signs, and questionnaires (C- SSRS, Bond and Lader VAS) recorded during the study were individually listed and quantitative parameters were summarised by using descriptive statistics. For vital signs and ECG parameters, all values recorded during the study were individually listed and flagged for abnormalities and for clinical significance (assessed by investigator). In addition, values, and abnormalities (not clinically significant and clinically significant) were described by dose group and overall, at screening, study baseline (D-1, or D1 predose), each evaluation under treatment phase, ambulatory visits (as applicable) and at the end of the study. Change between the value at baseline and the value at each evaluation under treatment phase, ambulatory visits (as applicable) and at end of study visit was described for each parameter by dose group and overall.

Laboratory parameters:

All laboratory values recorded during the study were individually listed and flagged for values outside reference ranges and for clinical significance (assessed by investigator). Quantitative parameters were summarized by descriptive statistics. Values, position according to laboratory range and clinical significance assessment were described at screening, D-1 (baseline) and at D2, D4, D6 (only for the cohorts 160 mg, 220 mg, 300 mg and 380 mg) and D8 (only for the cohorts 300 mg and 380 mg) by dose group and overall. Changes between the value at baseline and the value at post-dose visits were described for each parameter by dose group and overall. All quantitative and qualitative urinary test results were listed, sorted by dose group, visit and subject.

Pharmacokinetic parameters:

Plasma concentrations were summarized by dose level and time point. The derived PK parameters were listed by subject and summarized by dose level.

In addition, the hypothesis that AUC and C_{max} are dose proportional was formally tested using a power model approach.

Pharmacodynamic parameters:

ECG parameters were summarized by dose level and time point on actual values and changes from baseline.

Placebo corrected changes from baseline ΔΔ were calculated with their 90% CI for each dose level and time point and displayed.

Subjects meeting predefined criteria for ECG parameter abnormality and results of the ECG morphological analysis were summarized by dose level using count and percentage.

An optional post hoc concentration-response analysis between ΔQTcF and DNDI-6148 concentrations was performed on ECG data issued from Holter extraction. ΔΔQTcF with 90% CI was estimated from the model at C_{max} (the geometric mean in each cohort) for each dose level.

Exploratory parameters:

For CRP and TNFα, values, position (in the normal range or not) according to available laboratory range and clinical assessment (if outside of the normal range, if relevant a clinical assessment could be done) were described at D1 pre-dose and at T6h post-dose for the last 4 subjects of the cohort 160 mg, and the cohorts 220 mg, 300 mg and 380 mg by dose group and overall.

Change between the baseline value and the post-dose value were described for each parameter by dose group and overall.

SUMMARY - CONCLUSIONS:

POPULATION / STUDY OUTCOME:

A total of 129 subjects were screened, and 64 of these subjects were randomized in the study. None of the subjects were withdrawn from the study. Three subjects had a major deviation (urine sample at D2 was added into the citric acid container 33 min after collection instead of 5 minutes as planned in the protocol) and were excluded from PK and PD populations (see Section 10.2 for protocol deviations and 10.3 for analysis sets definitions).

In the randomized population (N = 64):

- 100% were Caucasian male volunteers.
- The age ranged from 18 to 50 years with a mean of 35.05 ± 10.35 (SD) years.
- The BMI ranged from 18.5 to 29.8 kg/m² with a mean of 23.64 ± 2.88 (SD) kg/m².

SAFETY RESULTS

All randomized subjects completed the full dosing regimen and received DNDI-6148 10 mg to 380 mg or placebo as single dose as scheduled in the protocol.

There were no deaths, no serious and no severe AEs reported during the study, and 13 randomized subjects (20.3%) experienced 16 AEs. Out of the 16 AEs, only 13 AEs (in 11 subjects) occurred after treatment initiation (treatment emergent AEs: TEAEs) (see Tables 14.3.1.1.1 and 14.3.1.1.2 in Section 14.3.1).

TEAEs were presented by SOC and PT and for each, are reported as number of subjects reporting it:

	DNDI-6148 10mg (N=6)		**DNDI-6148 20mg (N=6)**		**DNDI-6148 40mg (N=6)**		**DNDI-6148 80mg (N=6)**		**DNDI-6148 160mg (N=6)**	
	n%[1]	**E[2]**	**n%[1]**	**E[2]**	**n%[1]**	**E[2]**	**n%[1]**	**E[2]**	**n%[1]**	**E[2]**
Total TEAEs	**1 (16.7%)**	**1**	**2 (33.3%)**	**2**	**2 (33.3%)**	**3**	**0**		**1 (16.7%)**	**1**
Gastrointestinal disorders	***0***		***1 (16.7%)***	***1***	***1 (16.7%)***	***1***	*0*		*0*	
Abdominal pain	0		**1 (16.7%)**	**1**	0		0		0	
Diarrhoea	0		0		0		0		0	
Nausea	0		0		**1 (16.7%)**	**1**	0		0	
General disorders and administration site conditions	***0***		*0*		*0*		*0*		*0*	
Fatigue	0		0		0		0		0	
Medical device site reaction	0		0		0		0		0	
Musculoskeletal and connective tissue disorders	***0***		***1 (16.7%)***	***1***	***1 (16.7%)***	***1***	*0*		*0*	
Arthralgia	0		0		0		0		0	
Back pain	0		0		**1 (16.7%)**	**1**	0		0	

Pain in extremity	0		**1 (16.7%)**	**1**	0		0		0	
Nervous system disorders	***1 (16.7%)***	***1***	*0*		***1 (16.7%)***	***1***	*0*		***1 (16.7%)***	***1***
Dizziness postural	0		0		0		0		**1 (16.7%)**	**1**
Headache	**1 (16.7%)**	**1**	0		**1 (16.7%)**	**1**	0		0	

N: Number of subjects randomized in the treatment group
(1) n % : Number of subjects and percentage (Percentages are computed using N provided in the Column header)
(2) E : Number of events

Source: Table 14.3.1.2.1

	DNDI-6148 220mg (N=6)		**DNDI-6148 300mg (N=6)**		**DNDI-6148 380mg (N=6)**		**Placebo (N=16)**		**Overall (N=64)**	
	n%[1]	**E[2]**	**n%[1]**	**E[2]**	**n%[1]**	**E[2]**	**n%[1]**	**E[2]**	**n%[1]**	**E[2]**
Total TEAEs	**0**		**2 (33.3%)**	**3**	**0**		**3 (18.8%)**	**3**	**11 (17.2%)**	**13**
Gastrointestinal disorders	*0*		*0*		*0*		***1 (6.3%)***	***1***	***3 (4.7%)***	***3***
Abdominal pain	0		0		0		0		**1 (1.6%)**	**1**
Diarrhoea	0		0		0		**1 (6.3%)**	**1**	**1 (1.6%)**	**1**
Nausea	0		0		0		0		**1 (1.6%)**	**1**
General disorders and administration site conditions	*0*		***1 (16.7%)***	***1***	*0*		***1 (6.3%)***	***1***	***2 (3.1%)***	***2***
Fatigue	0		**1 (16.7%)**	**1**	0		0		**1 (1.6%)**	**1**
Medical device site reaction	0		0		0		**1 (6.3%)**	**1**	**1 (1.6%)**	**1**
Musculoskeletal and connective tissue disorders	*0*		***2 (33.3%)***	***2***	*0*		*0*		***4 (6.3%)***	***4***
Arthralgia	0		**2 (33.3%)**	**2**	0		0		**2 (3.1%)**	**2**
Back pain	0		0		0		0		**1 (1.6%)**	**1**
Pain in extremity	0		0		0		0		**1 (1.6%)**	**1**
Nervous system disorders	*0*		*0*		*0*		***1 (6.3%)***	***1***	***4 (6.3%)***	***4***
Dizziness postural	0		0		0		0		**1 (1.6%)**	**1**
Headache	0		0		0		**1 (6.3%)**	**1**	**3 (4.7%)**	**3**

N: Number of subjects randomized in the treatment group
(1) n % : Number of subjects and percentage (Percentages are computed using N provided in the Column header)
(2) E : Number of events

Source: Table 14.3.1.2.2

Of the 13 TEAEs observed:

- 11 TEAEs were mild and 2 were of moderate intensity (see Table 14.3.1.4.2, in Section 14.3.1).
- Only 4 TEAEs were assessed as related to the DNDI-6148 (Adverse Drug Reaction - ADR): 1 AE of abdominal pain experienced by 1 subject dosed with DNDI-6148 20 mg; 1 AE of nausea and 1 AE of headache experienced by 1 subject dosed with DNDI-6148 40 mg; 1 AE of dizziness postural experienced by 1 subject dosed with DNDI-6148 160 mg.
- One TEAE was assessed as related to the placebo: 1 AE of diarrhoea.
- All TEAEs resolved during the course of the study.
- None of these TEAEs resulted in any subject withdrawal.

See Tables 14.3.1.1.1 and 14.3.1.1.2 in Section 14.3.1 for detailed description.

No clinically relevant findings or significant abnormalities were observed in clinical examination, biological parameters, vital signs or ECG parameters.

PHARMACOKINETIC RESULTS

Plasma concentrations

Visual inspection of the arithmetic mean profiles revealed similar patterns following administration of DNDI-6148 across all dose levels. DNDI-6148 exposure increased linearly with doses, the dose proportionality analysis led to a power estimate around 0.85 for C_{max} and AUC_{0-24}.

Arithmetic mean DNDI-6148 plasma concentrations vs. nominal time by dose level after single oral administration of DNDI-6148 from 10 mg to 380 mg (reported as linear and Log scales)

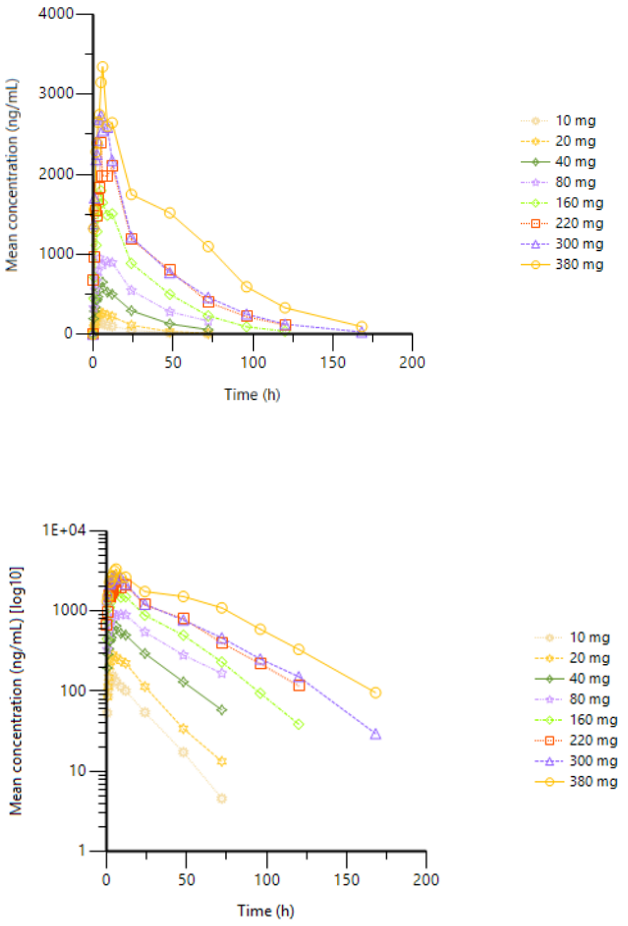

Fig 1 and 2 of PK report (Appendix 16.4.1)
Source: Table 11.1.1 - 1 and Table 11.1.1 - 2 (Appendix 16.4.1)

Plasma PK parameters

Summary of main PK parameters after single oral administration of DNDI-6148

Dose level (mg)		t_{max}* (h)	C_{max} (ng/mL)	AUC_{0-24} (h*ng/mL)	AUC_{0-72} (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**	6	6	6	6	6	6	6	6	6	6
	Mean	4.00	156	2362.26	3491.84	3491.84	3588.24	12.80	2.97	53.32	19.27
	CV%	3.00-4.05	15.2	18.3	29.7	29.7	31.8	19.0	23.8	17.9	20.1
	GM	3.82	155	2332.46	3385.11	3385.11	3464.67	12.63	2.89	52.60	18.98
20	**N**	6	6	6	6	6	6	6	6	6	6
	Mean	4.00	296	4759.33	7112.76	7112.78	7436.58	14.72	2.84	57.72	21.24
	CV%	4.00-9.00	17.1	13.5	21.4	21.4	24.2	22.8	27.2	11.7	25.3
	GM	4.58	292	4717.87	6965.69	6965.72	7245.45	14.42	2.76	57.41	20.72
40	**N**	6	6	6	6	6	6	6	6	6	6
	Mean	6.00	675	10775.06	18171.16	18172.43	20002.76	19.92	2.35	63.44	28.32
	CV%	4.00-6.00	35.3	30.0	35.4	35.4	37.5	21.6	48.3	34.3	19.6
	GM	5.24	642	10322.19	17053.40	17054.67	18598.57	19.54	2.15	60.61	27.85
80	**N**	6	6	6	6	6	6	6	6	6	6
	Mean	9.00	1020	18303.52	33681.72	33682.32	42685.67	25.42	2.51	71.12	36.76

	CV%	4.00-12.20	14.8	19.4	40.8	40.8	57.2	56.7	56.3	21.5	59.1
	GM	7.58	1010	17991.12	31196.85	31197.36	36867.24	22.30	2.17	69.82	31.72
160	**N**	6	6	6	6	6	6	6	6	6	6
	Mean	5.00	1830	31135.36	56566.54	62062.86	63224.91	17.47	2.83	67.98	30.56
	CV%	5.00-6.00	11.1	18.4	26.3	28.6	29.8	25.4	44.3	33.3	21.1
	GM	5.15	1820	30619.53	54460.01	59332.68	60276.25	17.06	2.65	65.34	29.95
220	**N**	6	6	6	6	6	6	6	6	6	6
	Mean	5.50	2510	41262.13	79586.18	91070.32	96466.84	24.16	2.55	81.28	38.60
	CV%	3.00-9.00	44.9	32.6	29.2	34.2	40.3	36.1	33.6	14.2	31.0
	GM	5.55	2290	39064.53	76773.05	87033.75	90928.22	23.08	2.42	80.57	37.22
300	**N**	6	6	6	6	6	6	6	6	6	6
	Mean	5.00	3070	48434.30	87121.96	103997.26	105078.91	21.67	3.28	97.66	35.99
	CV%	4.00-9.00	32.5	26.9	29.5	31.2	31.7	26.3	50.6	42.9	33.1
	GM	5.13	2960	46877.32	83186.30	98278.70	99148.89	21.06	3.03	91.91	33.95
380	**N**	6	6	6	6	6	6	6	6	6	6
	Mean	5.50	3610	57412.47	128006.47	169547.67	173690.29	25.40	2.26	79.71	49.15
	CV%	4.00-6.00	28.7	13.6	11.9	18.6	20.4	26.3	20.0	10.2	22.8
	GM	5.28	3490	56954.87	127270.30	167111.69	170708.80	24.71	2.23	79.36	48.11

* Median and Min-Max are presented instead of Mean and CV%, respectively
Tables 1 and 2 of PK report (Appendix 16.4.1)
Source: Table 11.1.2 - 1 and Table 11.1.2 - 16

Summary of descriptive statistics of DNDI-6148 dose normalized PK parameters after single oral administration of DNDI-6148 from 10 mg to 380 mg

Dose level (mg)		**C_{max}/D (ng/mL/mg)**	**AUC_{0-t}/D (h*ng/mL/mg)**	**$AUC_{0-\infty}$/D (h*ng/mL/mg)**
10	**N**	6	6	6
	Mean	15.62	349.18	358.82
	CV%	15.2	29.7	31.8
	GM	15.47	338.51	346.47
20	**N**	6	6	6
	Mean	14.79	355.64	371.83
	CV%	17.1	21.4	24.2
	GM	14.59	348.29	362.27
40	**N**	6	6	6
	Mean	16.87	454.31	500.07
	CV%	35.3	35.4	37.5
	GM	16.06	426.37	464.96
80	**N**	6	6	6
	Mean	12.76	421.03	533.57
	CV%	14.8	40.8	57.2
	GM	12.64	389.97	460.84
160	**N**	6	6	6
	Mean	11.41	387.89	395.16
	CV%	11.1	28.6	29.8
	GM	11.35	370.83	376.73
220	**N**	6	6	6
	Mean	11.42	413.96	438.49
	CV%	44.9	34.2	40.3
	GM	10.39	395.61	413.31
300	**N**	6	6	6
	Mean	10.25	346.66	350.26
	CV%	32.5	31.2	31.7
	GM	9.86	327.60	330.50
380	**N**	6	6	6
	Mean	9.49	446.18	457.08
	CV%	28.7	18.6	20.4
	GM	9.18	439.77	449.23

Table 3 of PK report (Appendix 16.4.1)
Source: Table 11.1.2 - 2 and Table 11.1.2 - 16

Urine

Summary of descriptive statistics of DNDI-6148 PK parameters in urine after single oral administration of DNDI-6148 from 10 mg to 380 mg

Dose level (mg)		Ae_{0-24} (ng)	fe_{0-24} (%)	Ae_{0-72} (ng)	fe_{0-72} (%)	CLr (L/h)
10	**N**	6	6	6	6	6
	Mean	14125.47	0.14	14125.47	0.14	0.0043
	CV%	80.7	80.7	80.7	80.7	85.2
	GM	NC	NC	NC	NC	NC
20	**N**	6	6	6	6	6
	Mean	28681.53	0.14	41062.28	0.21	0.0055
	CV%	73.0	73.0	75.1	75.1	76.8
	GM	NC	NC	NC	NC	NC
40	**N**	6	6	6	6	6
	Mean	45143.82	0.11	67401.35	0.17	0.0042
	CV%	40.2	40.2	45.5	45.5	52.3
	GM	41975.97	0.10	61539.69	0.15	0.0036
80	**N**	6	6	6	6	6
	Mean	60828.17	0.08	97364.88	0.12	0.0031
	CV%	12.1	12.1	30.6	30.6	26.4
	GM	60479.72	0.08	93575.26	0.12	0.0030
160	**N**	6	6	6	6	6
	Mean	101985.68	0.06	186960.48	0.12	0.0033
	CV%	30.3	30.3	37.5	37.5	29.3
	GM	97542.24	0.06	173639.57	0.11	0.0032
220	**N**	6	6	6	6	6
	Mean	120553.33	0.05	259123.83	0.12	0.0034
	CV%	22.8	22.8	22.4	22.4	26.7
	GM	117885.35	0.05	253330.63	0.12	0.0033
300	**N**	4	4	4	4	4
	Mean	248893.48	0.08	427288.15	0.14	0.0045
	CV%	31.4	31.4	33.5	33.5	24.2
	GM	239806.34	0.08	411659.06	0.14	0.0044
380	**N**	6	6	6	6	6
	Mean	200054.97	0.05	433234.02	0.11	0.0035
	CV%	37.7	37.7	21.2	21.2	31.5
	GM	189716.57	0.05	426219.22	0.11	0.0033

NC: Not calculable as at least one value was equal to zero

Table 6 of PK report (Appendix 16.4.1)
Source: Table 11.2.1 - 1 and Table 11.2.1 - 8

PHARMACODYNAMIC RESULTS

See ECG Safety Report provided in Appendix 16.4.2.

After single-dose administration of doses from 10 to 380 mg, no relevant dose-dependent increase in the placebo- and baseline-corrected (ΔΔ) QTcF interval was observed with mean maximum increases (90% CI) varying from 1.5 (–3.4, 6.5) to 5.5 (0.5, 10.4) msec in the DNDI-6148 dose groups.

Recent discussions regarding the evaluation of study drugs on QT/QTc indicate that most emphasis should be put on the outcome of the concentration-response analysis, acknowledging the fact that subject numbers are often small rendering the per time point analysis less robust [1] . The concentration-response modeling approach indicated a relationship between DNDI-6148 concentrations and ΔΔQTcF in that with increasing concentrations, ΔΔQTcF appeared to increase but the effects were small. In fact, at doses of up to and including 80 mg, a decrease in ΔΔQTcF was estimated. The upper limit of the 90% CI did not exceed 10 msec for any of the investigated single doses of DNDI-6148 and the maximum effect on ΔΔQTcF was estimated for a dose of 380 mg to be 1.65 (90% CI: -0.635, 3.94) msec.

After single-dose administration and when taking all dose groups together, values (90% CI) for ΔΔ heart rate (HR) ranged from –2.9 (–6.3, 0.5) bpm to 5.2 (1.8, 8.5) bpm, whereas they varied from –3.0

(–6.4, 0.3) bpm to 4.8 (1.4, 8.2) bpm in the placebo group. Together, these results do not indicate an effect of DNDI-6148 on HR.

The central tendency analysis did not indicate any effects of DNDI-6148 on the other ECG parameters PR interval and QRS duration.

The categorical and morphological analyses did not reveal any dose-dependent effect of DNDI-6148. In none of the subjects a QTcF value was recorded that exceeded 500 msec nor a change from baseline in QTcF that exceeded 60 msec.

Detailed results are provided in a separate report (Appendix 16.4.2).

EXPLORATORY RESULTS

Metabolic profiling and identification of DNDI-6148 in human plasma

See Metabolite profiling Report provided in Appendix 16.4.3.

Metabolic profiling of DNDI-6148 was conducted in human plasma samples of cohort 8 (receiving oral single dose of 380 mg DNDI-6148) from DNDi-6148-01 study (SGS LS study number: B1800077-3). Samples from active subjects were pooled by sampling time and analysed using UHPLC/MS method. The putative metabolites were detected and characterized using UHPLC/MS-MS. Three putative metabolites were observed:

- M1: oxidative deboronation of DNDI-6148
- M4: mono-oxygenation of DNDI-6148
- M5: mono-oxygenation and dehydrogenation of M1

All these metabolites were found in trace amounts.

CONCLUSION

This study was carried out in 64 healthy male volunteers. None of the subjects withdrew and none were withdrawn from the study.

Regarding safety:

No deaths, no serious and no severe AEs were reported during the study.

No clinically relevant findings were observed in clinical examination, biological parameters, vital signs or ECG parameters.

The highest dose planned as per protocol and administered was well-tolerated, and the maximal tolerated dose was not reached.

It was concluded that: single oral doses of DNDI-6148 (10 mg to 380 mg) or placebo were well tolerated in the included healthy male subjects.

Regarding Pharmacokinetics:

Three subjects had a major deviation (urine sample at D2 was added into the acid citric container 33 min after collection instead of 5 minutes as planned in the protocol) and were excluded from PK and PD populations.

The arithmetic mean profiles of DNDI-6148 plasma concentrations revealed similar patterns across all dose levels with concentrations increasing to reach their peak generally with median t_{max} between 4 and 6 h. Thereafter concentrations decreased. GM of $t_{1/2}$ of DNDI-6148 in plasma was around 13 h with 10 mg and 20 mg dose levels and between 17.1 h and 24.7 h with the other dose levels.

DNDI-6148 peak exposure (C_{max}) and overall exposure (AUC_{0-24}, AUC_{0-t}, $AUC_{0-\infty}$) increased with the increase in dose. Nevertheless, the dose proportionality analysis led to a power estimate around 0.85 for C_{max} and AUC_{0-24} and around 1 for $AUC_{0-\infty}$. The 90% CIs of the power model for C_{max} and AUC_{0-24} were fully excluded and below the predefined Smith reference interval (0.9387-1.0613) whereas for

$AUC_{0-\infty}$ the lower bound of the 90% CI was included in the reference interval and the upper bound was excluded. Hence the hypothesis of dose proportionality could not be accepted based on the criteria and the results suggested that exposure increased less than proportionally (i.e. increase in exposure when doubling the dose is less than twice). The lack of dose proportionality was however limited for all parameters as the bounds of the 90% CI were closed to the reference interval, especially $AUC_{0-\infty}$.

GM of MRT was between 19 h and 48 h.

GM of CL/F were similar for all dose levels (between 2 and 3 L/h) with low to high inter-individual variability. GM of Vz/F ranged from 53 L to 92 L with low to moderate inter-individual variability.

The percentage of the administered dose recovered in urine as DNDI-6148 and the renal clearance were similar between dose levels with fe_{0-72} GM values between 0.1% and 0.2% and CLr GM values between 0.003 L/h and 0.004 L/h between 40 and 380 mg dose levels.

Regarding Pharmacodynamics:

The results of the present study indicate that single-dose administration of dose levels of up to 380 mg DNDI-6148 did not cause a relevant increase in QTcF. No positive control group, *i.e.*, a group receiving a reference drug known to increase QTcF, was however included in this study which limits the interpretation of the results.
Details results and tables are provided in a separate report (Appendix 16.4.2).

Date of Report: 08/JUN/2023