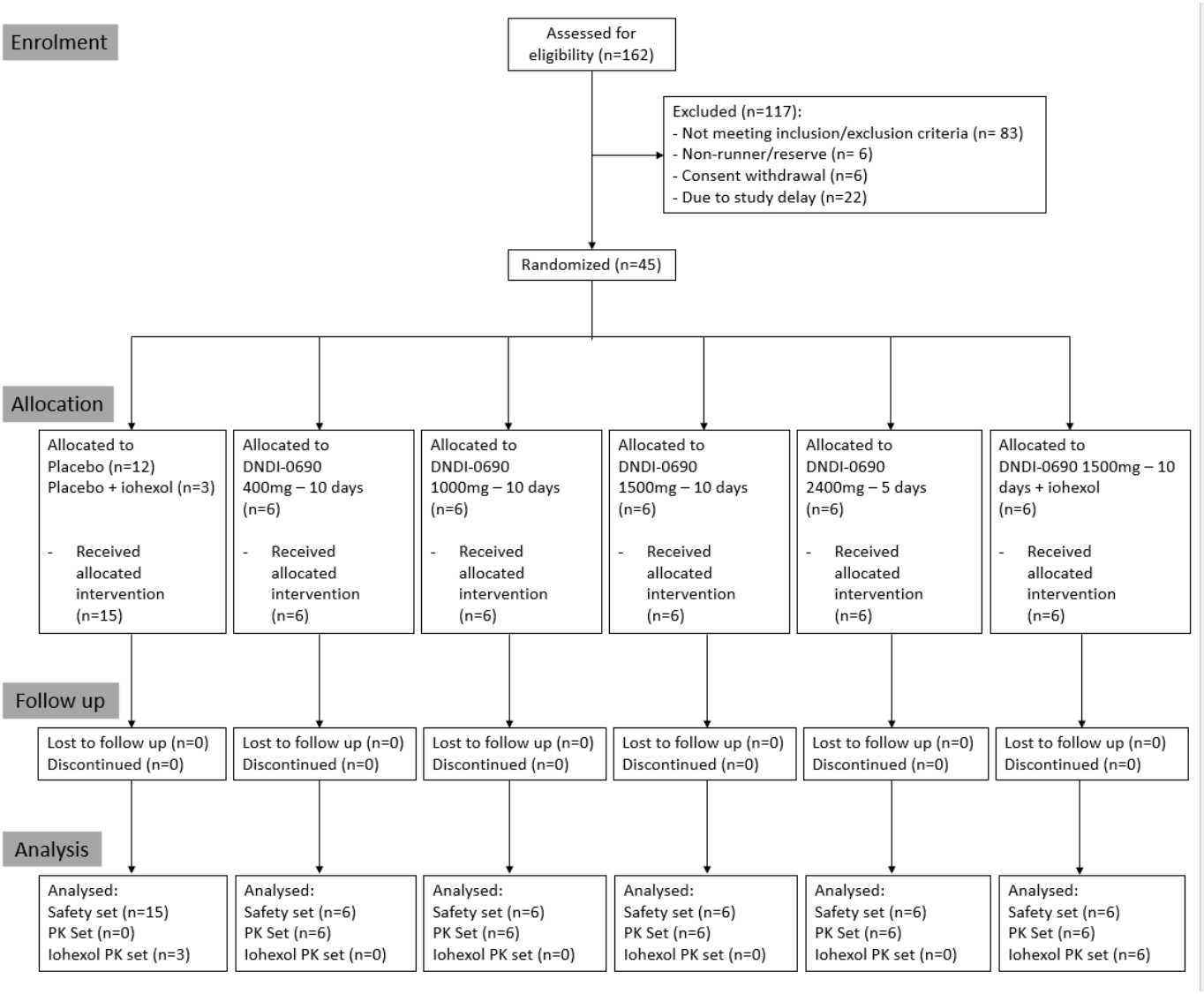
DNDi-0690-02

Participant Flow



Baseline Characteristics

Summary of Subject Demographics at Screening (Safety Set) - Percentages were calculated from the number of subjects in the safety set within a treatment group.

Parameter	Statistic	Placebo* (N=15)	Part A			Part B	Part C	DNDI-0690 Overall (N=30)	Overall (N=45)
			Cohort 1: 400mg DNDI-0690 (N=6)	Cohort 2: 1000mg DNDI-0690 (N=6	Cohort 3: 1500mg DNDI-0690 (N=6)	2400mg DNDI-0690 (N=6)	1500mg DNDI-0690 + Iohexol (N=6)		
Age (yrs)	n	15	6	6	6	6	6	30	45
	Mean	32.2	29.3	30.7	31.8	36.7	38.0	33.3	32.9
	SD	5.54	5.01	12.37	7.68	11.11	10.00	9.56	8.39
Height (m)	n	15	6	6	6	6	6	30	45
	Mean	1.793	1.752	1.793	1.778	1.790	1.757	1.774	1.780
	SD	0.0754	0.0668	0.0650	0.0801	0.0200	0.0450	0.0576	0.0639
Weight (kg)	n	15	6	6	6	6	6	30	45
	Mean	82.71	79.30	81.23	79.97	90.08	82.30	82.58	82.62
	SD	10.551	8.577	12.979	6.692	7.567	9.614	9.536	9.765
BMI (body mass index) **(kg/m^2)**	n	15	6	6	6	6	6	30	45
	Mean	25.693	25.805	25.153	25.467	28.100	26.612	26.227	26.049
	SD	2.7360	1.8757	2.7564	3.5818	2.1190	2.2349	2.6297	2.6466
Gender:									
Male	n (%)	15 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	30 (100.0)	45 (100.0)
Female	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity:									
Not Hispanic/Latino	n (%)	15 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	30 (100.0)	45 (100.0)
Hispanic/Latino	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Race:									
Black/African American	n (%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
American Indian/Alaska Native	n (%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Asian	n (%)	1(6.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(2.2)
Native Hawaiian/Other Pacific Islander	n (%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
White	n (%)	14(93.3)	6(100.0)	6(100.0)	5(83.3)	6(100.0)	6(100.0)	29(96.7)	43(95.6)
Mixed	n (%)	0(0.0)	0(0.0)	0(0.0)	1(16.7)	0(0.0)	0(0.0)	1(3.3)	1(2.2)
Other	n (%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Outcome measures

Part A&B&C: A total of 25 TEAEs were reported by 14 (31.1%) subjects during the study (**Error! Reference source not found.**).

Table S1: Overall Summary of TEAEs by Severity and Relationship (Safety Set)

		Part A			Part B	Part C		
	Placebo* (N=15)	Cohort 1: 400mg DNDI-0690 (N=6)	Cohort 2: 1000mg DNDI-0690 (N=6)	Cohort 3: 1500mg DNDI-0690 (N=6)	2400mg DNDI-0690 (N=6)	1500mg DNDI-0690 + Iohexol (N=6)	DNDI-0690 Overall (N=30)	Overall (N=45)
Number of TEAEs	8	1	4	8	1	3	17	25
Number (%) of subjects reporting at least one:								
TEAE	3 (20.0)	1 (16.7)	3 (50.0)	3 (50.0)	1 (16.7)	3 (50.0)	11 (36.7)	14 (31.1)
Serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE Leading to Withdrawal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE Leading to Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number (%) of subjects with TEAE by severity:								
Mild	3 (20.0)	1 (16.7)	2 (33.3)	1 (16.7)	1 (16.7)	2 (33.3)	7 (23.3)	10 (22.2)
Moderate	0 (0.0)	0 (0.0)	1 (16.7)	2 (33.3)	0 (0.0)	0 (0.0)	3 (10.0)	3 (6.7)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (3.3)	1 (2.2)
Life-Threatening	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number (%) of subjects with TEAE by relationship to study drug:								
Definitely Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Probably Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Possibly Related	2 (13.3)	0 (0.0)	2 (33.3)	2 (33.3)	0 (0.0)	1 (16.7)	5 (16.7)	7 (15.6)
Possibly Not Related	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	2 (6.7)	2 (4.4)
Not Related	1 (6.7)	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)	2 (33.3)	4 (13.3)	5 (11.1)

Definitely related, probably related and possibly related classify as related events. Possibly not related and not related classify as not related events.

Part C:

Table S2: Summary of Statistical Analysis of mGFR Calculated from Plasma Iohexol Concentrations - Part C (Iohexol PK Set)

Dose Level	Parameter	Peak	Geometric LS-Means (95% CI)		Geometric LS-Mean Ratio (%) (90% C.I.)
			Day -1	Day 10	Day 10 / Day -1
Placebo + Iohexol (N=3)	Plasma mGFR (mL/min)	A	102 (83.0, 125)	97.6 (79.5, 120)	95.76 (85.29 - 107.52)
		B	97.9 (77.0, 124)	95.2 (74.9, 121)	97.22 (86.24 - 109.59)
1500 mg DNDI-0690 + Iohexol (N=6)	Plasma mGFR (mL/min)	A	118 (111, 124)	116 (110, 123)	98.86 (94.64 - 103.27)
		B	114 (108, 120)	113 (107, 118)	99.10 (95.17 - 103.20)

Peaks A and B correspond to Iohexol isomers detected by HPLC.

Table S3 Summary of Derived DNDI-0690 Plasma and Urine PK Parameters (PK Set)

			Part A			Part B	Part C
			Cohort 1: 400mg DNDI-0690 (N=6)	Cohort 2: 1000mg DNDI-0690 (N=6)	Cohort 3: 1500mg DNDI-0690 (N=6)	2400mg DNDI-0690 (N=6)	1500mg DNDI-0690 + Iohexol (N=6)
Day 1	C_{max} (ug/mL)	N	6	6	6	6	
		Geo. Mean	1.00	1.73	1.70	2.87	N/A
		CV%	26.9	39.6	38.4	16.2	
	T_{max} (h)	N	6	6	6	6	
		Median (min-max)	3.50 (2.00-4.00)	3.50 (2.02-3.53)	2.75 (2.00-9.00)	3.75 (3.00-6.00)	N/A
		CV%	22.6	18.9	72.4	26.2	
	AUC_{0-24} (h*ug/mL)	N	6	6	5[1]	6	
		Geo. Mean	10.8	20.7	16.8	41.9	N/A
		CV%	45.7	52.4	60.1	20.2	
	Ae_{0-24} (mg)	N	6	6	6	6	
		Geo. Mean	0.0437	0.0519	0.0520	0.0897	N/A
		CV%	30.9	41.9	46.0	24.5	
Day 10 (Part A + C) Day 5 (Part B)	$C_{max, ss}$ (ug/mL)	N	6	6	6	6	6
		Geo. Mean	1.49	2.53	2.59	3.68	2.93
		CV%	28.4	38.2	21.5	23.5	35.5
	T_{max} (h)	N	6	6	6	6	6
		Median (min-max)	3.50 (3.50-4.00)	3.50 (2.00-4.00)	3.00 (3.00-4.00)	3.25 (2.00-4.00)	3.00 (2.00-4.00)
		CV%	7.0	29.4	12.9	21.6	21.1
	$t_{1/2}$ (h)	N	6	6	6	6	6
		Geo. Mean	8.13	11.3	10.1	15.5	11.4
		CV%	21.2	28.5	33.4	23.1	14.6
	AUC_{0-24} (h*ug/mL)	N	6	6	6	6	6
		Geo. Mean	17.4	33.8	34.7	55.5	41.0
		CV%	39.7	52.3	34.4	29.2	43.6
	AUC_{0-inf} (h*ug/mL)	N	6	6	6	6	6
		Geo. Mean	20.6	45.8	44.8	87.2	55.3
		CV%	45.3	64.7	46.3	39.3	45.9
Day 10 (Part A + C) Day 5 (Part B)	Ae_{0-24} (mg)	N	6	6	6	6	
		Geo. Mean	0.0263	0.0979	0.112	0.125	N/A
		CV%	78.8	38.0	45.0	31.7	

ss = steady state ; Ae_{0-24}= amount of dose excreted in urine from 0 to 24 h

Adverse events

System Organ Class Preferred Term	Severity	Number (%) of Subjects Placebo* (N=15)		Part A Cohort 1: 400mg DNDI-0690 (N=6)		Part A Cohort 2: 1000mg DNDI-0690 (N=6)		Part A Cohort 3: 1500mg DNDI-0690 (N=6)		Part B: 2400mg DNDI-0690 (N=6)		Part C: 1500mg DNDI-0690 + Iohexol (N=6)		DNDI-0690 Overall (N=30)		Overall (N=45)	
GASTROINTESTINAL DISORDERS	MILD	1	(6.7)	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.3)	2	(4.4)
	MODERATE	0	(0.0)	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	1	(3.3)	1	(2.2)
ABDOMINAL DISCOMFORT	MODERATE	0	(0.0)	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	1	(3.3)	1	(2.2)
ABDOMINAL PAIN UPPER	MILD	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.2)
CONSTIPATION	MILD	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.3)	1	(2.2)
DIARRHOEA	MILD	0	(0.0)	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	1	(3.3)	1	(2.2)
NAUSEA	MILD	0	(0.0)	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	1	(3.3)	1	(2.2)
VOMITING	MILD	1	(6.7)	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	1	(3.3)	2	(4.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	MILD	1	(6.7)	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	1	(3.3)	2	(4.4)
CHILLS	MILD	0	(0.0)	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	1	(3.3)	1	(2.2)
PYREXIA	MILD	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.2)
INFECTIONS AND INFESTATIONS	MILD	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(33.3)	2	(6.7)	2	(4.4)
ORAL HERPES	MILD	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(16.7)	1	(3.3)	1	(2.2)
UPPER RESPIRATORY TRACT INFECTION	MILD	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(16.7)	1	(3.3)	1	(2.2)
INVESTIGATIONS	MILD	0	(0.0)	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	1	(3.3)	1	(2.2)
	MODERATE	0	(0.0)	0	(0.0)	1	(16.7)	2	(33.3)	0	(0.0)	0	(0.0)	3	(10.0)	3	(6.7)
	SEVERE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(16.7)	1	(3.3)	1	(2.2)
ALANINE AMINOTRANSFERASE INCREASED	MILD	0	(0.0)	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	1	(3.3)	1	(2.2)
TRANSAMINASES INCREASED	MODERATE	0	(0.0)	0	(0.0)	1	(16.7)	2	(33.3)	0	(0.0)	0	(0.0)	3	(10.0)	3	(6.7)
	SEVERE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(16.7)	1	(3.3)	1	(2.2)

System Organ Class Preferred Term	Severity	Number (%) of Subjects Placebo* (N=15)		Part A Cohort 1: 400mg DNDI-0690 (N=6)		Part A Cohort 2: 1000mg DNDI-0690 (N=6)		Part A Cohort 3: 1500mg DNDI-0690 (N=6)		Part B: 2400mg DNDI-0690 (N=6)		Part C: 1500mg DNDI-0690 + Iohexol (N=6)		DNDI-0690 Overall (N=30)		Overall (N=45)	
METABOLISM AND NUTRITION DISORDERS	MILD	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.2)
DECREASED APPETITE	MILD	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	MILD	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.3)	1	(2.2)
BACK PAIN	MILD	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.3)	1	(2.2)
NERVOUS SYSTEM DISORDERS	MILD	2	(13.3)	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.3)	3	(6.7)
DIZZINESS	MILD	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.2)
HEADACHE	MILD	2	(13.3)	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.3)	3	(6.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	MILD	1	(6.7)	0	(0.0)	1	(16.7)	0	(0.0)	1	(16.7)	0	(0.0)	2	(6.7)	3	(6.7)
COUGH	MILD	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)	1	(3.3)	1	(2.2)
DRY THROAT	MILD	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.3)	1	(2.2)
EPISTAXIS	MILD	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.2)