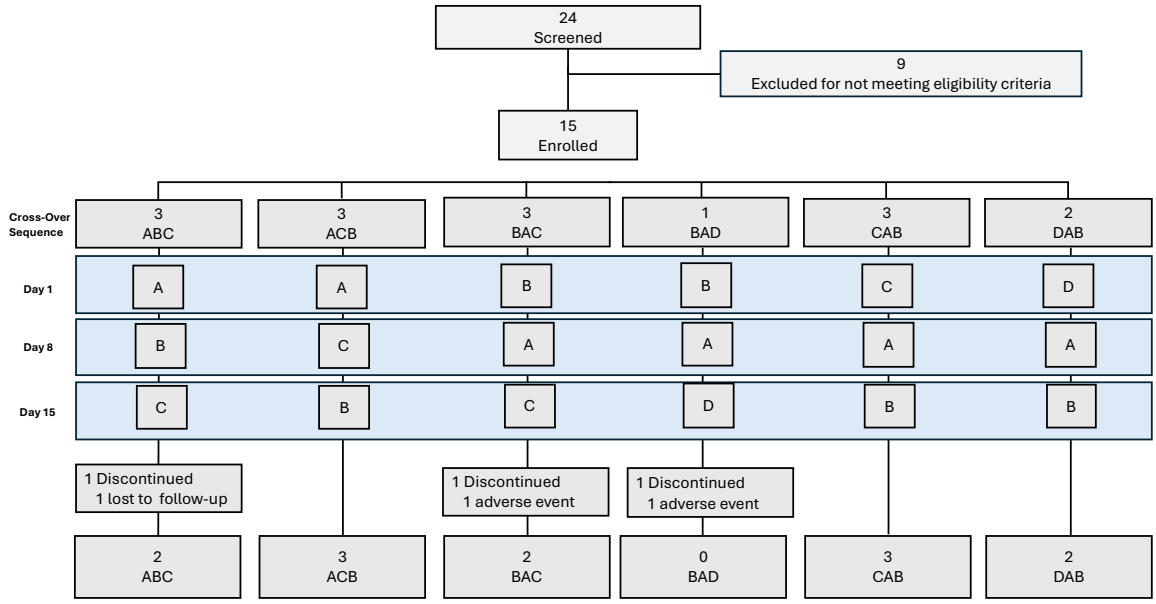
Randomised, placebo-controlled functional evaluation of INDV-2000 effects on cue reactivity in opioid dependence: An fMRI study

Research Type	Research Study
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1. Participant Flow



A = placebo; B = 100 mg INDV-2000 (low dose); C = 600 mg INDV-2000 (high dose); D = 400 mg INDV-2000 (high dose).

2. Baseline Characteristics

Table 1. Summary of Demographic Characteristics

Variable		Sequence						Overall (N=15)
		ABC (N=3)	ACB (N=3)	BAC (N=3)	BAD (N=1)	CAB (N=3)	DAB (N=2)	
Age (years)	Mean (SD)	46.7 (11.59)	48.0 (8.54)	50.7 (9.02)	–	46.3 (8.62)	52.0 (8.49)	48.2 (7.93)
	Range	36–59	40–57	42–60	44	37–54	46, 58	36–60
Sex n (%)	Male	3 (100.0)	2 (66.7)	1 (33.3)	1 (100.0)	2 (66.7)	–	9 (60.0)
	Female	–	1 (33.3)	2 (66.7)	–	1 (33.3)	2 (100.0)	6 (40.0)
Race n (%)	White	2 (66.7)	2 (66.7)	3 (100.0)	1 (100.0)	1 (33.3)	1 (50.0)	10 (66.7)
	Black or African American	1 (33.3)	1 (33.3)	–	–	–	1 (50.0)	3 (20.0)
	Asian	–	–	–	–	2 (66.7)	–	2 (13.3)
Ethnicity n (%)	Not Hispanic or Latino	3 (100.0)	3 (100.0)	3 (100.0)	1 (100.0)	3 (100.0)	2 (100.0)	15 (100.0)
Height (cm)	Mean (SD)	172.3 (8.62)	176.7 (10.12)	165.0 (1.73)	–	169.0 (1.73)	168.8 (11.67)	171.0 (7.55)
	Range	163–180	165–183	163–166	179	167–170	161–177	161–183
Weight (kg)	Mean (SD)	91.57 (7.278)	72.03 (17.628)	69.03 (9.236)	–	69.63 (6.914)	73.55 (18.738)	75.90 (13.288)
	Range	85.2–99.5	53.0–87.8	62.5–79.6	84.6	65.2–77.6	60.3–86.8	53.0–99.5
BMI (kg/m^2)	Mean (SD)	30.90 (2.905)	22.80 (3.351)	25.37 (3.190)	–	24.43 (2.919)	25.55 (3.041)	25.87 (3.757)
	Range	28.1–33.9	19.5–26.2	22.7–28.9	26.4	22.6–27.8	23.4–27.7	19.5–33.9
Alcohol* (units week)	n	–	1	1	1	2	–	5
	Mean (SD)	–	–	–	–	16.0 (1.41)	–	10.0 (6.20)
	Range	–	2	10	6	15–17	–	2–17
Childbearing potential‡ (%)	No	–	1 (33.3)	2 (66.7)	–	1 (33.3)	1 (50.0)	5 (33.3)
	Yes	–	–	–	–	–	1 (50.0)	1 (6.7)

BMI = body mass index; SD = standard deviation; N = total number of participants; n = number of applicable participants.
* Includes only those participants who drank alcohol; 1 UK unit of alcohol = 8 g ethanol.
‡ Includes only female participants.
Sequence is the planned sequence received: A = placebo, B = 100 mg INDV-2000, C = 600 mg INDV-2000, D = 400 mg INDV-2000

Table 2. Summary of Participant Opioid Use History

		Overall usage by participants						
		Any opioid	**Fentanyl**	**Heroin**	**Oxycodone**	**Methadone**	**Buprenorphine**	**Any other opioid**
Used in their lifetime (%)		15 (100.0)	3 (20.0)	15 (100.0)	2 (13.3)	15 (100.0)	12 (80.0)	1 (6.7)
Number of years used in lifetime*	Mean (SD)	21.71 (7.2)	1.23 (1.266)	19.79 (8.272)	1.00 (0.00)	14.27 (7.848)	1.43 (1.293)	–
	Range	4.4–33.0	0.1–2.6	1.4–32.0	1.0	0.6–31.0	1.0	2.0
Number of days used in the past 4 weeks	n	15	–	2	–	15	–	–
	Mean (SD)	28.5 (1.41)	–	4.0 (0.00)	–	28.0 (0.00)	–	–
	Range	28–32	–	4	–	28.0	–	–
Route of administration in the last 4 weeks								
Injection, smoking (%)		1 (6.7)	–	1 (6.7)	–	–	–	–
Oral (%)		15 (100.0)	–	–	–	15 (100.0)	–	–
Respiratory (inhalation) (%)		1 (6.7)	–	1 (6.7)	–	–	–	–

N = total number of participants; n = number of applicable participants using opioids in the last 4 weeks. * For ongoing substance use, the stop date was imputed as the participant's screening date. Note: Number of years used in lifetime for 'Any Opioid' was calculated as the time between the earliest start date and the latest end date, minus any reported periods of abstinence. Number of days used in the past 4 weeks for 'Any Opioid' was calculated by summing the number of days each opioid drug was used individually during the past 4 weeks.

Table 3. Summary of Participant Non-Opioid Use History

		Overall usage by participants						
		Any non-opioid	**Cocaine**	**Marijuana/ cannabinoids**	**Barbiturates**	**Benzodiazepines**	**Amphetamines/ methamphetamine**	**Phencyclidine**
Used in their lifetime (%)		15 (100.0)	15 (100.0)	13 (86.7)	–	9 (60.0)	2 (13.3)	–
Number of years used in lifetime*	Mean (SD)	29.62 (6.124)	18.01 (7.239)	27.32 (10.071)	–	14.01 (14.017)	3.00 (2.828)	–
	Range	19.4–40.0	7.0–30.0	1.3–40.0	–	0.2–33.0	1.0–5.0	–
Number of days used in the past 4 weeks	n	8	6	6	–	3	–	–
	Mean (SD)	11.3 (9.25)	2.3 (1.75)	7.7 (7.0)	–	10.0 (15.59)	–	–
	Range	4–29	1–5	2–20	–	1–28	–	–
Route of administration in the past 4 weeks								
Oral (%)		3 (20.0)	–	–	–	3 (20.0)	–	–
Respiratory (inhalation) (%)		7 (46.7)	3 (20.0)	6 (40.0)	–	–	–	–
Snorting (%)		3 (20.0)	3 (20.0)	–	–	–	–	–

N = total number of participants; n = number of applicable participants using non-opioids in the last 4 weeks. * For ongoing substance use, the stop date was imputed as the participant's screening date.

4. Outcome Measures

Primary Outcome

Table 4. Percentage signal change in each region of interest on the cue reactivity task

	Percentage signal change in each ROI on the cue reactivity task (mean [SD]).				
	Caudate nucleus	Amygdala	Insula	Anterior cingulate cortex	Posterior cingulate cortex
Placebo	0.15 (0.20)	0.01 (0.19)	0.09 (0.17)	0.03 (0.24)	0.24 (0.21)
Low dose	–0.12 (0.36)	0.10 (0.13)	0.01 (0.29)	–0.01 (0.20)	0.16 (0.51)
High dose	–0.04 (0.24)	0.08 (0.40)	0.04 (0.33)	–0.07 (0.29)	0.07 (0.36)
	Effect sizes (Cohen's d_z)				
Placebo vs low dose	0.70	0.50	0.32	0.16	0.16
Placebo vs high dose	0.58	0.14	0.12	0.22	0.42
Low dose vs high dose	0.18	0.05	0.08	0.20	0.13

ROI = region of interest; SD = standard deviation.

Table 5. Summary of clusters identified in whole-brain analysis with increased functional connectivity with INDV-2000 administration

Cluster index	**Contrast**	**Cluster size (voxels)**	**Cluster statistic**	**Mini coordinates**			**Regions**
				X	**Y**	**Z**	
1	Placebo > high dose	901	Z = 4.18, p = 0.04	6	26	–8	Anterior cingulate cortex, right orbitofrontal cortex, right medial frontal cortex
2	Placebo > low dose	1019	Z = 3.91, p = 0.02	34	50	18	Right frontal pole

Secondary Outcomes

Table 6. Summary of opioid craving and anxiety numeric rating scale data

	Placebo (N=12)	100 mg INDV-2000 (N=12)	400 mg INDV-2000 (N=2)	600 mg INDV-2000 (N=10)
Opioid Craving NRS	**Mean (SD) change from pre-dose**			
Pre-scan	–0.2 (0.58)	0.1 (0.29)	–2.0 (2.83)	–0.2 (0.63)
In-scan (pre-CR)	–0.2 (0.58)	0.0 (–)	–0.5 (4.95)	–0.2 (0.63)
In-scan (post-CR)	0.4 (0.90)	0.3 (0.62)	0.0 (2.83)	–0.2 (0.63)
Post-scan	0.0 (0.43)	0.5 (1.45)	–0.5 (3.54)	–0.2 (0.63)
Anxiety NRS	**Mean (SD) change from pre-dose**			
Pre-scan	–0.1 (0.51)	0.3 (0.75)	–1.0 (1.41)	0.0 (0.47)
In-scan (pre-CR)	0.5 (1.83)	0.6 (1.44)	4.5 (2.12)	–0.3 (1.16)
In-scan (post-CR)	0.6 (1.88)	0.5 (1.09)	2.5 (0.71)	–0.3 (0.67)
Post-scan	–0.4 (0.90)	–0.4 (0.79)	–0.5 (2.12)	–0.5 (0.85)

IMP = investigational medicinal product; CR = cue reactivity; SD = standard deviation. Response scored on a numeric rating scale (NRS) with 0 = "not at all" and 10 = "the most ever". Pre-dose was considered to be the last value obtained before IMP administration in each treatment period.

Table 7. Mean plasma concentrations of INDV-2000 after single oral doses of 100, 400 or 600 mg (PK analysis set)

Planned relative time (h)	Arithmetic mean (%CV) plasma concentrations of INDV-2000 (ng/mL)		
	100 mg (N=13)	400 mg (N=2)	600 mg (N=10)
Pre-dose	0^{13} (–)	0^{2} (–)	$0^{9,c}$ (–)
Pre-scan	$151.6^{2,a}$ (114.3)	204.5 (70.9)	408.9^{c} (116.3)
Post-scan	785.1 (49.9)	3,545.0 (84.0)	$2,785.9^{c}$ (43.1)
Discharge	569.9^{b} (43.5)	2,770.0 (59.2)	$1,962.7^{c}$ (52.8)

%CV = coefficient of variation; LLOQ = lower limit of quantification; N= number of participants in the pharmacokinetic (PK) analysis set at each dose level; n = number of measurements included in mean calculation (n = N unless otherwise stated). Numerical superscripts indicate the number of values below the limit of quantification, which were imputed to zero. LLOQ = 2 ng/mL.

a. n = 12; b. n = 10; c: n = 9

4. Adverse Events

Table 8. Overall summary of participants with treatment-emergent adverse events

	Placebo (N=13)	INDV-2000			All participants (N=15)
		100 mg (N=14)	400 mg (N=2)	600 mg (N=10)	
Number of participants with	**n (%) [number of TEAEs]**				
Any TEAE	4 (30.8) [4]	12 (85.7) [19]	2 (100.0) [5]	10 (100.0) [13]	15 (100.0) [41]
Any serious TEAE	–	–	–	–	–
Any TEAE leading to death	–	–	–	–	–
Any IMP-related TEAE	3 (23.1) [3]	11 (78.6) [15]	2 (100.0) [3]	10 (100.0) [13]	13 (86.7) [34]
Any methadone-related TEAE	–	–	–	–	–
Any TEAE leading to treatment withdrawal	–	–	–	–	–
Any TEAE leading to trial withdrawal	–	2 (14.3) [2]	–	–	2 (13.3) [2]
TEAE severity					
Mild	4 (30.8)	8 (57.1)	1 (50.0)	7 (70.0)	8 (53.3)
Moderate	–	3 (21.4)	1 (50.0)	2 (20.0)	5 (33.3)
Severe	–	1 (7.1)	–	1 (10.0)	2 (13.3)

N = total number of participants; n = number of participants with a TEAE; TEAE = treatment-emergent adverse event; IMP = investigational medicinal product (INDV-2000 or placebo).

Table 9. Treatment-emergent adverse events

System organ class Preferred term	Placebo (N=13)	INDV-2000			All participants (N=15)
		100 mg (N=14)	400 mg (N=2)	600 mg (N=10)	
	n (%) [number of TEAEs]				
Total	**4 (30.8)**	**12 (85.7)**	**2 (100.0)**	**10 (100.0)**	**15 (100.0)**
Nervous system disorders	**2 (15.4) [2]**	**11 (78.6) [12]**	**2 (100.0) [2]**	**10 (100.0) [12]**	**14 (93.3) [28]**
Somnolence	1 (7.7) [1]	11 (78.6) [11]	1 (50.0) [1]	10 (100.0) [10]	13 (86.7) [23]
Dizziness	–	–	–	2 (20.0) [2]	2 (13.3) [2]
Headache	–	1 (7.1) [1]	1 (50.0) [1]	–	2 (13.3) [2]
Choroid fissure cyst	1 (7.1) [1]	–	–	–	1 (6.7) [1]
Investigations	–	**2 (14.3) [2]**	**1 (50.0) [1]**	–	**3 (20.0) [3]**
Liver function test increased	–	2 (14.3) [2]	–	–	2 (13.3) [2]
Alanine aminotransferase increased	–	–	1 (50.0) [1]	–	1 (6.7) [1]
Psychiatric disorders	–	**2 (14.3) [2]**	**1 (50.0) [1]**	–	**3 (20.0) [3]**
Anxiety	–	1 (7.1) [1]	–	–	1 (6.7) [1]
Claustrophobia	–	1 (7.1) [1]	–	–	1 (6.7) [1]
Insomnia	–	–	**1 (50.0) [1]**	–	1 (6.7) [1]
Gastrointestinal disorders	**1 (7.7) [1]**	**1 (7.1) [2]**	**–**	**–**	**1 (6.7) [3]**
Nausea	1 (7.7) [1]	1 (7.1) [1]	–	–	1 (6.7) [2]
Vomiting	–	1 (7.1) [1]	–	–	1 (6.7) [1]
General disorders and administration site conditions	**1 (7.7) [1]**	–	–	–	**1 (6.7) [1]**
Energy increased	1 (7.7) [1]	–	–	–	1 (6.7) [1]
Infections and infestations	–	**–**	**1 (50.0) [1]**	**–**	**1 (6.7) [1]**
Lower respiratory tract infection	–	–	1 (50.0) [1]	–	1 (6.7) [1]

System organ class Preferred term	Placebo (N=13)	INDV-2000			All participants (N=15)
		100 mg (N=14)	400 mg (N=2)	600 mg (N=10)	
	n (%) [number of TEAEs]				
Skin and subcutaneous tissue disorders	–	–	–	**1 (10.0) [1]**	**1 (6.7) [1]**
Pruritus	–	–	–	1 (10.0) [1]	1 (6.7) [1]
Vascular disorders	–	**1 (7.1) [1]**	**–**	**–**	**1 (6.7) [1]**
Hypertension	–	1 (7.1) [1]	–	–	1 (6.7) [1]

N = total number of participants; n = number of participants with a TEAE; TEAE = treatment-emergent adverse event.
Participants with > 1 TEAE in any treatment period are counted only once per system organ class and preferred term for that period.

Table 10. Post-dose vital signs of clinical significance

Participant	Planned relative time	Time after last dose	Supine systolic BP (mm Hg)	Supine diastolic BP (mm Hg)	Supine pulse rate (beats/min)	Respiratory rate (breaths/min)	SpO_2 (%)	Tympanic temperature (°C)
Reference range:			90–140	40–90	40–100	10–16	≥ 94%	35.5–37.8 °C
PCC reference range:			85–160	50–110	50–110	12–24	< 90 to 100	35.5–38.0 °C
700-021	Follow-up	7 days	**164**	**107**	66	14	97	36.9
	Follow-up repeat	7 days	**149**	**97**	–	–	–	–

Values in **bold** were considered by the investigator to be of clinical significance. BP = blood pressure; NA = not applicable; PCC = potential clinical concern.