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IRL757C001 – A FIRST-IN-HUMAN TRIAL ON IRL757, A CORTICAL ENHANCER IN CLINICAL DEVELOPMENT FOR THE TREATMENT OF APATHY IN AD/PD

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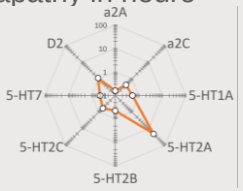
Introduction

IRL757 is a small molecule compound in development for treatment of apathy in AD/PD. The key pharmacodynamic effect is to increase synaptic availability of DA, NE and ACh in cortical areas including the prefrontal cortex (pfc). This is accompanied by increased synaptic activity in pfc and limbic areas, reflecting increased connectivity in this circuitry, involved in apathy in neuro-degenerative disorders.

IRL757 is active in rodent models of cognition and effort-for-reward. It displays no locomotor stimulant or inhibitory effects.



In vitro receptor binding

Study design (sponsor code IRL757C001)

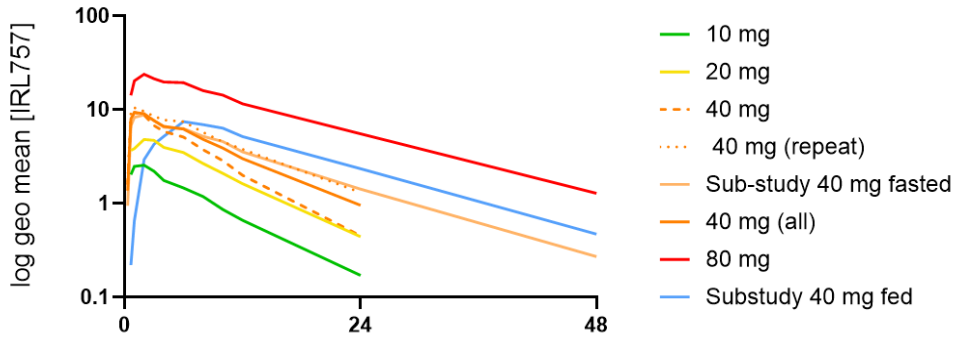
IRL757C001 (NCT06493045) is a double-blind, placebo-controlled, single (SAD; doses of 10-80 mg) and multiple ascending dose (MAD; doses of 10-30 mg b.i.d.) study in male & female healthy volunteers with a parallel group design. A food interaction sub-study with cross-over design using 40 mg was included in the SAD. Study assessments include PK sampling and safety monitoring: vital signs, AEs, safety laboratory assessment and ECG. MAD data are not yet unblinded.

This study was performed by CTC Clinical Trial Consultants AB, Sweden and funded by The Michael J. Fox Foundation for Parkinson's Research, grant ID: MJFF-024267

PK Results

SAD Cohort	Dose (mg)	n	t_{max} (h)	C_{max} (µM)	AUC_{inf} (µM×h)	CL/F (L/h)	$t_{1/2}$ (h)	C_{max}/ Dose	AUC_{inf}/ Dose
SAD1	10	6	1.5 (0.7-2)	2.84 (34)	24.7 (58.6)	2.2 (59)	6.7 (40)	0.28	2.47
SAD2	20	6	1.5 (0.7-3)	5.88 (13)	56.2 (40.1)	1.9 (40)	6.8 (37)	0.29	2.81
SAD3	40	6	1.0 (0.7-1)	9.54 (11)	78.1 (37.1)	2.8 (37)	5.9 (34)	0.24	1.95
SAD5	40	6	0.8 (0.7-6)	11.3 (22)	134 (48.2)	1.6 (48)	9.0 (48)	0.28	3.35
SAD4	80	6	2.0 (1-6)	24.2 (18)	403 (41.2)	1.1 (41)	11.4 (22)	0.30	5.04
All 40[a]	40	18	1.0 (0.7-6)	10.1 (16)	107 (42.5)	2.0 (42)	8.0 (40)	0.25	2.68

SAD PK parameters. Data presented as geometric mean (CV%), except for t_{max} for which median(range) is presented. [a]Summary of the three 40 mg cohorts; SAD3, SAD5 and the fasting part of the food interaction sub-study (plasma concentrations from fed part is shown in the graph below only)



SAD Plasma concentration vs. time profiles. Shown are log geometric mean concentrations (µM) *vs.* time (h).

MAD Cohort *Day*	Dose (mg b.i.d)	t_{max} (h)	C_{max} (µM)	$AUC_{0\text{-}12h}$ (µM·h/)	AUC_{inf} (µM·h)	$t_{1/2}$ (h)	C_{max}/ Dose	AUC/ Dose[1]	AR C_{max}	AR AUC_{tau}
MAD1 *Day1*	10	1.0 (0.7-8)	2.23 (19)	15.9 (18.8)	22.6 (31.3)	6.2 (28)	0.23	2.26	ND	ND
MAD1 *Day10*	10	1.0 (0.7-3)	5.06 (33)	44.7 (41.2)	ND	12.1 (25)	0.51	4.47	2.27	2.82
MAD2 *Day1*	20	0.7 (0.3-1.1)	6.00 (16)	37.1 (20.2)	51.4 (29.3)	6.2 (24)	0.30	2.57	ND	ND
MAD2 *Day10*	20	1.0 (0.7-2)	12.2 (28)	105 (36.6)	ND	11.7(30)	0.61	5.25	2.04	2.83
MAD3 *Day1*	30	0.7 (0.7-2)	12.8 (16)	77.1 (22)	107(38)	5.9 (33)	0.43	3.57	ND	ND
MAD3 *Day10*	30	1.0 (0.7-6)	23.3 (36)	184(52)	ND	10.5 (38)	0.78	6.13	1.82	2.38

MAD PK parameters. Data presented as geometric mean (CV%), except for t_{max} for which median (range) is presented. [1]AUCinf/Dose for Day1, and AUC0-12h/Dose for Day10. n=9/cohort. ND= Not determined

Demographics & Safety

Dose (mg)	n	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m²)	Sex M/F count(%)
10	6	35 (12.5)	176 (7)	77 (20)	24.9 (5.4)	4/2 (67/33)
20	6	34 (6.0)	176 (10)	68 (9)	21.7 (0.7)	3/3 (50/50)
40[a]	18	34 (10.2)	174 (6)	76 (12)	25.0 (3.3)	10/8 (56/44)
80	6	40 (13.4)	171 (14)	75 (16)	25.6 (2.8)	2/4 (33/67)

SAD Demographic data presented as mean (SD), and males/females, count (percentage). [a]Aggregate of the three 40 mg cohorts; SAD3, SAD5 and the fasting part of the food interaction sub-study.

Dose cohorts were demographically balanced. AEs were mild. The most common AEs were nervous system disorders (dizziness, headache) reported for 10% and 50% of IRL757 and placebo treated subjects, respectively. Fatigue was reported for 10% of IRL757 and 10% of placebo treated subjects. IRL757 had no impact on vital signs, ECG, or lab parameters. Blinded review of MAD safety data indicates a similar tolerability/safety profile upon repeated dosing.

Conclusions

The SAD part of the trial is completed. IRL757 displayed rapid absorption and log-linear decline with a half-life of 6 - 11 hours. C_{max} increased dose-proportionally while AUC increased supra-proportionally.

IRL757 displayed no impact on safety parameters, and low frequency of AEs. The food-interaction sub-study showed delayed t_{max} with food intake, with slightly lower C_{max} but no effect on AUC.

Blinded data from the MAD part showed exposures covering the expected therapeutic range, and ~12 h half-life at steady state, supporting b.i.d dosing. Collectively, the safety, tolerability and pharmacokinetic profile supports further development of IRL757.