RESULTS FROM IRL790C005 – A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE IIB STUDY EVALUATING THE EFFICACY OF MESDOPETAM ON DAILY ON-TIME WITHOUT TROUBLESOME DYSKINESIA IN PATIENTS WITH PARKINSON'S DISEASE

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OBJECTIVE AND BACKGROUND

The objective of the Phase IIb study was to investigate efficacy and safety of three doses of mesdopetam as adjunct treatment in patients with PD experiencing troublesome levodopa-induced dyskinesia. Mesdopetam, a dopamine D3-receptor antagonist with anti-dyskinetic and anti-psychotic properties in preclinical models, displayed antidyskinetic effects and an acceptable safety profile in a previously conducted 4-week Phase Ib and in a 4-week IIa study in PD.

DESIGN/METHODS

This was a double-blind, placebo-controlled, study conducted in the US/Europe/Israel. Patients on stable regimen of anti-parkinson medication, experiencing troublesome dyskinesia, were randomized to placebo or mesdopetam (2.5, 5 or 7.5 mg) b.i.d. for 12 weeks. According to the study protocol subjects were allowed to adjust their dose one time during the course of the study. The primary endpoint was daily ON-time without troublesome dyskinesia ("good ON") measured by Hauser diaries. Secondary endpoints included UDysRS (parts 1+3+4), UDysRS objective score (3+4), time in different motor-states ("good ON", "bad ON", OFF), MDS-UPDRS, CGI, MMSE, along with pharmacokinetics, safety and tolerability. Data generated were analyzed for the Full Analysis Set (FAS) based on randomized dose, and in the protocol compliant subjects with adjustment to actual dose received. To adjust for variability in sleep time, Hauser diary data were also scaled to 16 hours of awake time.

RESULTS

192 subjects were screened and 156 subjects with PD and severe levodopa-induced dyskinesia were randomized to treatment. 125 subjects completed the 12 weeks treatment period and 24 subjects made a dose adjustment during the course of the study. The subject disposition is given in Figure 1 and subject demographics in Table 2.

Figure 1. Subject disposition

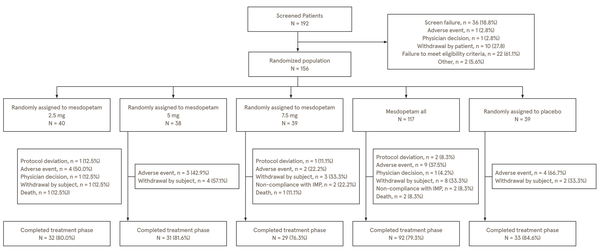


Table 2. Subject demographics

	Mesdopetam 2.5 mg b.i.d.	Mesdopetam 5 mg b.i.d.	Mesdopetam 7.5 mg b.i.d.	Placebo b.i.d.
	N=40	N=38	N=38	N=39
Age (SD)	65.0 (9.3)	64.9 (9.6)	65.0 (10.2)	64.5 (8.5)
Male (%)	26 (65.0)	21 (55.3)	21 (55.3)	14 (35.9)
Female (%)	14 (35.0)	17 (44.7)	17 (44.7)	25 (64.1)
BMI (kg/m²)	27.14	26.14	26.03	25.58
PD diagnosis (yrs) (SD)	8.9 (4.9)	9.3 (5.9)	11.3 (6.2)	10.3 (4.1)
Daily levodopa dose (mg)	768	761	1013	769
"Good ON"-time (h) (SD)	7.1 (2.5)	6.5 (2.4)	6.4 (2.9)	6.4 (2.9)

Safety and tolerability

Mesdopetam was well tolerated with an adverse event and safety profile on par with placebo. Serious adverse events (SAEs) occurred in 4 (3.4%) of mesdopetam-treated subjects and 3 (7.7%) of placebo-treated subjects. Table 3 shows treatment emergent adverse events (TEAEs) with >5% incidence.

Pharmacokinetics

Plasma exposures of mesdopetam were dose linear and consistent with previous trials.

Table 3. Treatment Emergent Adverse Events with >5% incidence.

	2.5 mg	5 mg	7.5 mg	All mesdopetam	Placebo
	N=40	N=38	N=38	N=116	N=39
Parkinsonism	1 (2.5%)	3 (7.9%)	1 (2.6%)	5 (4.3%)	4 (10.3%)
Dyskinesia	4 (10%)	1 (2.6%)	1 (2.6%)	6 (5.2%)	3 (7.7%)
Fall	2 (5%)	2 (5.3%)	2 (5.3%)	6 (5.2%)	2 (5.1%)
Mobility decreased	2 (5%)	4 (10.5%)	2 (5.3%)	8 (6.9%)	0

Efficacy

Table 1 shows the main efficacy results for the FAS and for the protocol compliant subjects. The treatment effect on Hauser diary "good ON" (ON-time without troublesome dyskinesia) did not reach statistical significance for the FAS, whereas in the protocol compliant subjects significant and clinically meaningful efficacy was observed on "good ON", scaled to 16h awake time, at the 7.5mg b.i.d. dose. Figure 3a shows the change from baseline in "good ON" for the FAS and Figure 3b shows change in "good ON" for the protocol compliant subjects Numerical data are also given in Table 1.

Further, mesdopetam demonstrated anti-dyskinetic effects across all doses as measured by UDysRS (sum of parts 1,3 and 4) – a comprehensive measure of ON-phase dyskinesia taking both objective physician ratings and patient ratings into account (Figure 2a and 2b).

Mesdopetam treatment also dose-dependently reduced OFF-time (Table 1 and Figure 4a and 4b). The change from baseline in OFF-time showed a dose-dependent improvement with mesdopetam treatment with a numerical improvement vs. placebo ranging from 0.7 hours (FAS, Figure 4a) to 1.27 hours (protocol compliant subjects, Figure 4b).

The key secondary endpoint MDS-UPDRS part 2 was unchanged by mesdopetam treatment demonstrating that mesdopetam did not affect normal motor function.

In the analyses based on subjects fully compliant with the study protocol and the actual dose received, the results were more pronounced and showed a consistent dose-response relationship across key efficacy endpoints, "good ON", UDysRS, OFF-time.

Figure 2a. UDysRS Score (parts 1 + 3 and 4) and Objective Score (parts 3+4) change from baseline @ 12 wks, FAS (LS means/SE)

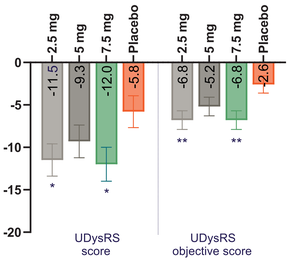


Figure 2b. UDysRS Score (parts 1 + 3 and 4) and Objective Score (parts 3+4) change from baseline @ 12 wks, protocol compliant subjects (LS means/SE)

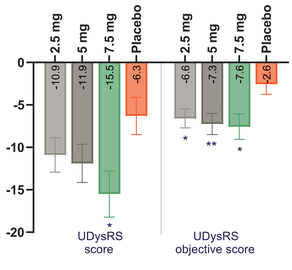


Figure 3a. "Good ON"$_{16h}$ change from baseline @ 12 wks, FAS (LS means/SE)

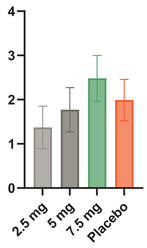


Figure 3b. "Good ON"$_{16h}$ change from baseline @ 12 wks, protocol compliant subjects

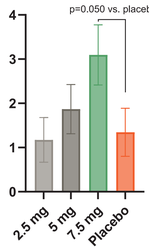


Table 1. Efficacy results;
Full Analysis Set (FAS) and Protocol Compliant Subjects

	Full Analysis Set			Protocol Compliant Subjects[1]		
Dose	2.5 mg	5 mg	7.5 mg	2.5 mg	5 mg	7.5 mg
N=	35	35	33	30	24	17
Primary endpoint						
"Good ON" (h)	-0.77	-0.25	0.25	-0.06	0.17	1.51 (p=.090)
"Good ON"$_{16h}$ (h)[2]	-0.62	-0.23	0.49	-0.17	0.52	1.75 (p=.050)
Key secondary endpoints						
MDS-UPDRS 4.2	-0.2	-0.1	-0.3	-0.1	0	-0.5 (p=.089)
UDysRS 1b+4	-2.6	-2.1	-3.5 (p=0.062)	-1.7	-2.7	-5.5* (p=0.019)
OFF (hours)	0.039	-0.26	-0.70	-0.32	-0.57	-1.27 (p=.051)
MDS-UPDRS 2	-0.8	-0.7	-0.0	-0.6	-0.4	-0.8
Other secondary endpoints						
UDysRS 1+3+4	-5.7* (p=0.035)	-3.5	-6.2* (p=0.026)	-4.6	-5.6 (p=0.078)	-9.2* (p=0.011)
"Bad ON" (hours)	0.28	0.34	-0.14	0.22	-0.46	-0.93

Shown are LS mean differences vs. placebo (MMRM). [1] Dose received. [2] Scaled to 16h awake, post-hoc analysis.

Figure 4a. OFF-time change from baseline @ 12 wks, FAS (LS means/SE)

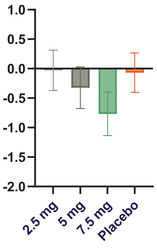
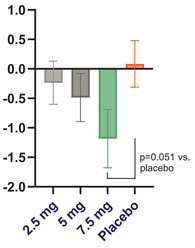


Figure 4b. OFF-time change from baseline @ 12 wks, protocol compliant subjects



CONCLUSIONS

This Phase IIb study exploring dose response on efficacy and safety of mesdopetam, in subjects with levodopa-induced dyskinesia, indicated that mesdopetam appears to have the rare ability to both reduce dyskinesia and improve parkinsonism without compromising normal motor function, coupled with a safety and tolerability profile not different from placebo.

The estimates of efficacy and the additional safety data obtained in this study enabled the identification of the optimal dose, 7.5 mg b.i.d. – allowing for the design of a pivotal study program.

Ref: Waters 2020. doi: 10.1124/jpet.119.264226; Sjöberg 2021. doi: 10.1002/prp2.792; Svenningsson 2018. doi: 10.1038/s41531-018-0071-3

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