Meta-Analysis of Two Randomized Controlled Trials Assessing the Efficacy of Mesdopetam (IRL790) in Levodopa-Induced Dyskinesia in Parkinson's Disease

HANSSON F., WERNER E., WATERS N., TEDROFF J., WATERS S.
Integrative Research Laboratories (IRLAB), Gothenburg, Sweden.

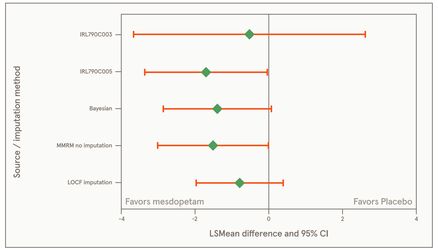
INTRODUCTION

- Mesdopetam (IRL790) is being developed for the treatment of disabling levodopa-induced dyskinesia (LID) in Parkinson's disease (PD).
- Mesdopetam belongs to a new class of central nervous system (CNS) active agents with dopamine D3 receptor antagonist properties
- Two phase II studies, IRL790C003, 4 weeks treatment period, and IRL790 C005, 12 weeks treatment period, have been performed in PD-LIDs. Here we present a meta-analysis of the key efficacy outcomes capturing LIDs and general motor function, combining data from both trials

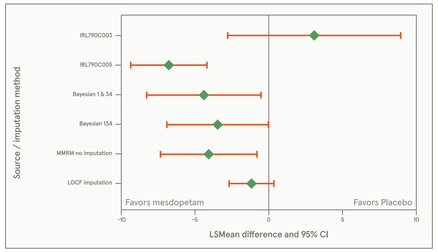
METHODS

- From both trials, the Full Analysis Set (FAS) was used, with patients randomized to 7.5mg Mesdopetam or Placebo.
- In study IRL790C003 patients on mesdopetam were allowed to up-titrate the dose to 10 mg b.id, while in study IRL790C005, down-titration to 5 mg bid was allowed.
- Patients with Amantadine co-medication were excluded (only allowed in IRL790C003)
- Results from each study (IRL790 7.5 bid vs. placebo) are presented individually (MMRM, with terms for baseline, treatment, visit, visit*treatment)
- For the meta-analysis, MMRM modelling was applied to the combined dataset without any imputation, estimating the contrast vs. placebo at 12 weeks
- As a more conservative approach, the last observation carried forward (LOCF) approach was applied (i.e. using the last valid data for subsequent visits)
- The Bayesian analysis uses a hierarchical model with a Beta-Binomial distribution for the likelihood. It accounts for dose effects, time effects, their interactions, study- and country-specific effects, and patient-specific random effects. Data from all dose groups were used. The model incorporates baseline measurements and uses an unbiased random-walk prior for dose and time to capture the expectation of similar effects from similar doses and visits. You can use the QR-code to access the source code defining the model.

UDYSRS TOTAL SUM OF 1A AND 1B AND THE SUM OF 1, 3 AND 4

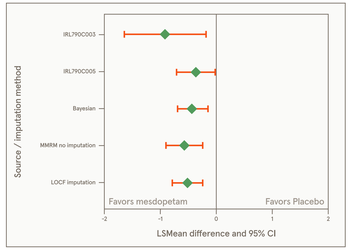


For UdysRS part 1, a significant improvement on mesdopetam vs. placebo was observed for the Ph2b study (IRL790C005). A similar tendency was seen in study IRL790C003 albeit with larger variability. Meta-analysis using MMRM or Bayesian modelling showed a significant effect estimated to 1.8-1.9 points vs. placebo.



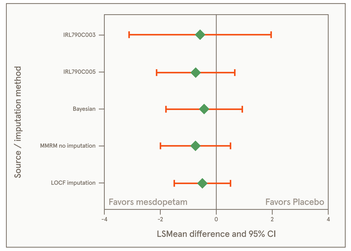
For UdysRS sum of parts 1, 3 & 4 (modified UdysRS), there was a significant improvement around 7 p compared to placebo in IRL790C005. In study IRL790C003, technical difficulties hampered the collection of UDysRS parts 3 and 4 rendering total UdysRS less reliable. Still, meta-analysis based on MMRM on the combined data came out with a significant improvement on UDysRS. Bayesian meta-analysis was performed both by using all UDysRS data (Bayesian 134) , and by using only part 1 from the C003 trial (Bayesian 1 & 34), yielding two somewhat different estimates, both consistent with the MMRM results, suggesting relevant clinical efficacy on UDysRS. Results applying LOCF were generally consistent with the other models.

UPDRS PART 2 AND SECTION 4.2



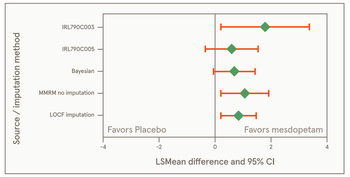
UPDRS Part 4 Question 2 (UPDRS 4.2) capturing functionally disabling dyskinesia, was included as a key secondary efficacy endpoint in both trials.

A significant improvement on mesdopetam vs. placebo was observed for the Ph2a study (IRL790C003). A similar tendency was seen in study IRL790C005 albeit with smaller amplitude. Meta-analysis indicated significant improvement, ca 0.4-0.5 points, vs. placebo, consistent across statistical methods.



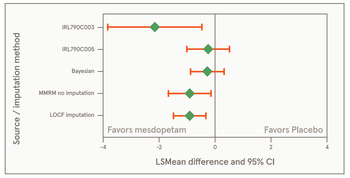
UPDRS part 2 was also a key secondary endpoint, included as a safety measure. Both studies, as well as the meta-analysis, consistently indicated a lack of effect of mesdopetam on this scale, ie no negative impact of mesdopetam on overall motor function was detected.

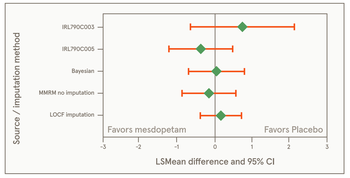
GOOD ON TIME, BAD ON TIME AND OFF TIME



Good ON time was significantly improved vs. placebo in the phase 2a trial (IRL790C003), but showed only a small numerical improvement vs. placebo in study IRL790C005. Meta-analysis suggested a significant improvement, around 1.3 h vs placebo using MMRM), and 0.5 h, not significant, using Bayesian modelling.

A corresponding pattern in favor of mesdopetam compared to placebo was seen in terms of reduction of Bad ON.





For OFF-time the studies yielded divergent results and the meta-analyses suggested no significant effect, in agreement with the lack of negative effect of mesdoptam on motor function assessed by UPDRS part 2.

DEMOGRAPHICS

Baseline demographics were generally similar across studies and treatment groups, with the exception of a larger proportion of female subjects in the placebo arm in study IRL790C005.

		IRL790C003		IRL790C005		Metaanalysis	
		Mesdopetam n=27	Placebo n=17	Mesdopetam n=29	Placebo n=34	Mesdopetam n=56	Placebo
Age (years)	Mean (SD)	67.5 (7.4)	67.2 (7.3)	64.4 (10.3)	66 (6)	65.9 (9)	66.4 (6.4)
Body Mass Index (kg/m2)	Mean (SD)	27.1 (8)	25.4 (4.2)	26.3 (4.6)	25.8 (6.4)	26.7 (6.5)	25.7 (5.7)
MMSE total score	Mean (SD)	28.6 (1.3)	28.9 (0.9)	28.6 (1.4)	28.4 (1.6)	28.6 (1.3)	28.6 (1.4)
year since diagnosis	Mean (SD)	11.9 (6.5)	9 (4.1)	10.9 (6.5)	10.9 (4)	11.4 (6.4)	10.3 (4.1)
Sex	Female	12 (44.4%)	6 (35.3%)	10 (34.5%)	22 (64.7%)	22 (20.6%)	28 (26.2%)
	Male	15 (55.6%)	11 (64.7%)	19 (65.5%)	12 (35.3%)	34 (31.8%)	23 (21.5%)
Hoehn and Yahr Stage	0	1 (3.7%)				1 (0.9%)	
	1	1 (3.7%)	1 (5.9%)	1 (3.4%)	1 (2.9%)	2 (1.9%)	2 (1.9%)
	2	21 (77.8%)	10 (58.8%)	16 (55.2%)	16 (47.1%)	37 (34.6%)	26 (24.3%)
	3	4 (14.8%)	6 (35.3%)	11 (37.9%)	15 (44.1%)	15 (14%)	21 (19.6%)
	4			1 (3.4%)	2 (5.9%)	1 (0.9%)	2 (1.9%)

CONCLUSIONS

Overall, the results of the meta-analysis were consistent independent of method of imputation. Also, the meta-analyses gave more precise estimates of the treatment effects, compared to the estimates obtained by analysing each study separately.

The meta-analyses indicate significant and clinically relevant effects on mesdopetam vs. placebo on several outcomes capturing disabling dyskinesia: UdysRS, parts 1a and 1b, historical score, and parts 3+4, the objective score, as well as MDS-UPDRS 4.2, capturing functional disability associated with dyskinesias

Meta-analyses also suggested improved Good ON-time and a corresponding decrease in Bad ON-time. However, diary data were less consistent across studies in the analyses. The introduction of the inclusion criterion in the Phase 2b trial, ≥2 h Bad ON-time, may have contributed to a reduced signal on Good/Bad ON in the latter trial.

There were no negative effect of mesdopetam of overall motor function, assessed by MDS-UPDRS part 2, or on daily OFF-time.

In fact, in the phase 2b trial OFF time was dose dependently reduced[1]. This could be related to the lower dose range applied in the latter trial, applying 7.5 mg bid as the maximum dose.

In conclusion, meta-analyses confirms clinically meaningful, antidyskinetic effects of mesdopetam 7.5 mg bid measured by different outcome scales, with no concomitant impairment of motor function or increase in OFF-time.

Contact information
Fredrik Hansson
fredrik.hansson@irlab.se

References
[1]A. Antonini et al. 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 [abstract]. Mov Disord. 2023; 38 (suppl 1).