A 12-week proof-of-concept efficacy and safety study of ORM-12741 in patients with moderate Alzheimer's disease

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The Methodological Question Being Addressed

The initial evaluation of the cognitive and behavioral benefits of new chemical entities (NCE) in patients with Alzheimer's disease (AD) in an optimal and efficient manner remains challenging. The current study was designed to evaluate an NCE in a reasonably sized safety and efficacy proof-of-concept setting that optimized selection of study endpoints and patient population.

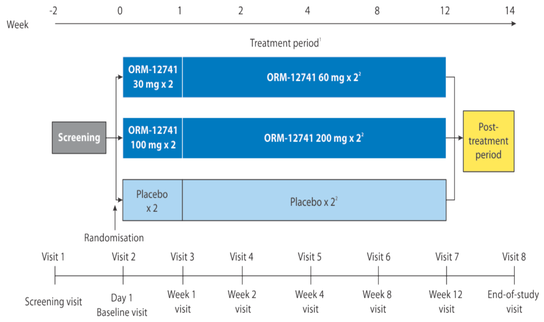
Introduction

ORM-12741 is a highly potent and selective alpha-2C adrenoceptor (AR) antagonist that has demonstrated efficacy in rodent models suggesting beneficial effects on both cognition and behavioral symptoms in AD, as well as good tolerability across seven Phase I studies. This is the first study of a selective alpha-2C AR antagonist in AD patients.

The primary objectives of the study were to evaluate safety, tolerability and efficacy of ORM-12741 as add-on therapy in patients with AD.

Methodology

This was a phase 2a, randomized, double-blind, placebo-controlled, parallel group, multicenter study in moderate AD patients (MMSE score 12-21) with behavioral symptoms (Neuropsychiatric Inventory [NPI] score of ≥15). Patients were allocated to two flexible dose levels of either 30 to 60 mg or 100 to 200 mg of ORM-12741 or matching placebo twice a day for 12 weeks as add-on to their stable cholinesterase inhibitor therapy (Fig. 1). Stable treatment with memantine and antidepressants was also allowed.



[1] ORM-12741 or placebo was taken in addition to AChE inhibitor therapy
[2] if the higher dose was not tolerated, the patient could return to the lower dose latest on week 2 visit

Figure 1. Design of the trial.

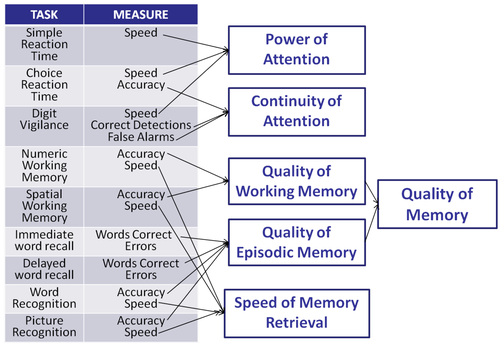


Figure 2. CDR composite scores

Efficacy was assessed primarily with computerized tests from the CDR System (Fig. 2), from which the following standard composite scores were derived: Quality of Memory (QM), Quality of Episodic Memory (QEM), Quality of Working Memory (QWM), Speed of Memory, Power of Attention and Continuity of Attention. QM comprises the accuracy scores from 2 working memory tasks (spatial and numeric) and 4 episodic memory tasks (immediate and delayed word recall, word recognition and picture recognition). The QWM and QEM composites contain the accuracy scores from the respective working and episodic memory tasks.

NPI total and Caregiver Distress scores were assessed to quantify the effects on behavioral and psychological symptoms.

Results

Disposition of subjects is presented in Table 1 and demographics are shown in Table 2.

Table 1. Disposition of randomized study subjects

Variable	Placebo N=34	ORM-12741 30-60 mg N=33	ORM-12741 100-200 mg N=33	Total N=100
	Number (%) of subjects			
Intent-to-treat population (ITT)	34 (100)	33 (100)	33 (100)	100 (100)
Per-protocol population (PP)	29 (85.3)	27 (81.8)	29 (87.9)	85 (85.0)
Completed study	33 (97.1)	28 (84.8)	30 (90.9)	91 (91.0)
Discontinued study	1 (2.9)	5 (15.2)	3 (9.1)	9 (9.0)

Table 2. Demographics

Variable		Placebo N=34	ORM-12741 30-60 mg N=33	ORM-12741 100-200 mg N=33	Total N=100
Sex, n (%)	Female	17 (50.0)	19 (57.6)	23 (69.7)	59 (59.0)
	Male	17 (50.0)	14 (42.4)	10 (30.3)	41 (41.0)
Age, years	Mean	72.3	71.8	71.8	72.0
	Range	56-90	55-87	56-87	55-90
MMSE scores	Mean	18.1	18.6	19.0	18.5
	Range	12-21	13-21	13-21	12-21

The number of patients using AD medications was comparable in the groups: donepezil 20-23 subjects/group, galantamine 1-2/group, rivastigmine 9-10/group, and memantine 3-5/group.

Clear and statistically significant positive treatment effects were noted for ORM-12741 on Quality of Memory (Fig. 3) and Quality of Episodic Memory (Fig. 4) compared to placebo over the 12-week treatment period with no clear difference in efficacy between the two active dose groups. In addition, a positive trend was noted in Quality of Working Memory, primarily for the low dose group (Fig. 5). No significant differences were identified on the other CDR composite scores.

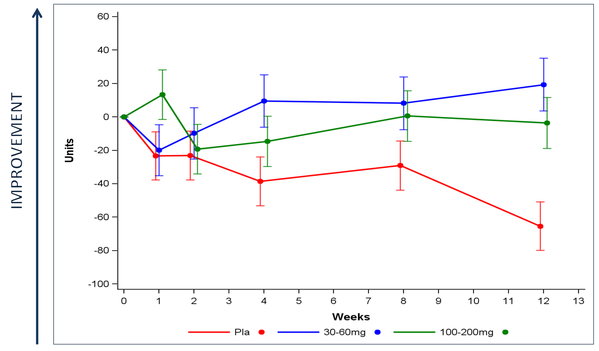


Figure 3. Quality of Memory (ITT population). Values are LSMeans (SEM) for changes from baseline. Main treatment effect p=0.013. Pairwise comparisons from baseline up to week 12: Placebo vs. ORM-12741 30-60 mg: p=0.006, Placebo vs. ORM-12741 100-200 mg: p=0.019.
Effect size at week 12:
Placebo vs. ORM-12741 30-60 mg: 1.5
Placebo vs. ORM-12741 100-200 mg: 1.1

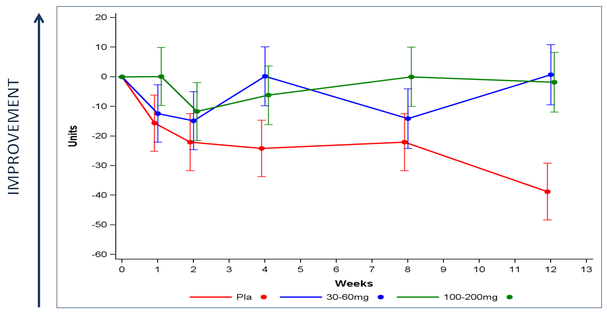


Figure 4. Quality of Episodic Memory (ITT population). Values are LSMeans (SEM) for changes from baseline. Main treatment effect p=0.03. Pairwise comparisons from baseline up to week 12: Placebo vs. ORM-12741 30-60 mg: p = 0.046, Placebo vs. ORM-12741 100-200 mg: p = 0.012.
Effect size at week 12:
Placebo vs. ORM-12741 30-60 mg: 1.09
Placebo vs. ORM-12741 100-200 mg: 1.02

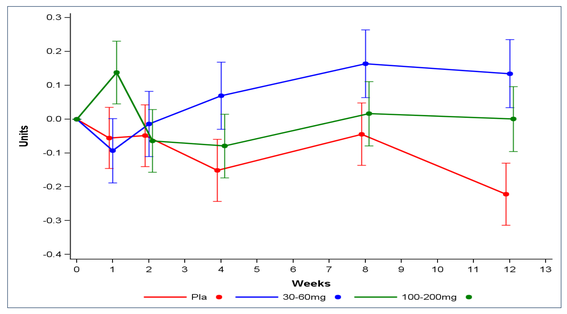


Figure 5. Quality of Working Memory (ITT population). Values are LSMeans (SEM) for changes from baseline. Main treatment effect p=0.19. Pairwise comparisons from baseline up to week 12: Placebo vs. ORM-12741 30-60 mg: p = 0.079, Placebo vs. ORM-12741 100-200 mg: p = 0.22.
Effect size at week 12:
Placebo vs. ORM-12741 30-60 mg: 0.88
Placebo vs. ORM-12741 100-200 mg: 0.55

Statistically significant positive treatment effects were noted for ORM-12741 also on NPI Caregiver Distress score (Fig. 6). In addition, a positive trend was noted for NPI total score, primarily for the low dose group (Fig. 7).

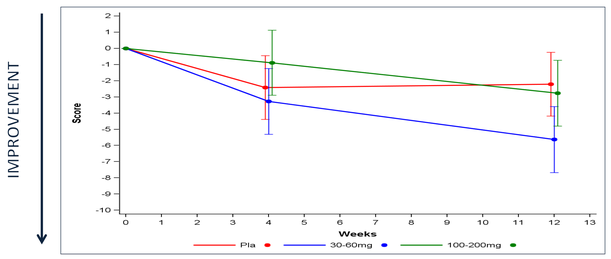


Figure 6. NPI total score (ITT population). Values are LSMeans (SEM) for changes from baseline. Main treatment effect p=0.12. Pairwise comparisons from baseline up to week 12: Placebo vs. ORM-12741 30-60 mg: p=0.11, Placebo vs. ORM-12741 100-200 mg: p=0.72

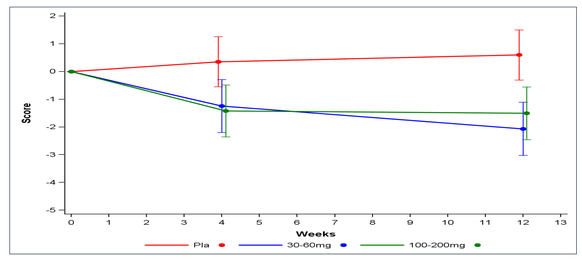


Figure 7. NPI Caregiver Distress score (ITT population). Values are LSMeans (SEM) for changes from baseline. Main treatment effect p=0.034. Pairwise comparisons from baseline up to week 12: Placebo vs. ORM-12741 30-60 mg: p = 0.020, Placebo vs. ORM-12741 100-200 mg: p=0.031

There were no clear differences in adverse event profiles between the treatment groups (Tables 3 and 4). No significant differences were noted in mean heart rate, blood pressure, ECG or safety laboratory variables in the active groups when compared to the placebo group.

Table 3. Summary of adverse events

Variable	Placebo N=34	ORM-12741 30-60 mg N=33	ORM-12741 100-200 mg N=33
	Number (%) of subjects		
Subjects with AEs	21 (61.8)	18 (54.5)	21 (63.3)
Subjects with related AEs	6 (17.6)	8 (24.2)	10 (30.3)
Subjects with serious AEs	0	0	1 (3.0)[1]
Discontinued due to AE	0	1 (3.0)	2 (6.1)
Dose reduced due to AE	3 (8.8)	2 (6.1)	3 (9.1)

[1] Cholestasis (asymptomatic high AST, ALT, GGT and ALP)

Table 4. Most commonly reported adverse events (present in ≥ 5 subjects)

Variable	Placebo N=34	ORM-12741 30-60 mg N=33	ORM-12741 100-200 mg N=33
	Number (%) of subjects		
Headache	4 (11.8)	2 (6.1)	1 (3.0)
Urinary tract infection	3 (8.8)	1 (3.0)	5 (15.2)
Nausea	3 (8.8)	2 (6.1)	1 (3.0)
Vomiting	1 (2.9)	1 (3.0)	4 (12.1)
Diarrhoea	2 (5.9)	2 (6.1)	1 (3.0)
Irritability	3 (8.8)	-	2 (6.1)

Conclusions

Significant positive effects of ORM-12741 on composite measures of memory in moderate AD patients as add-on therapy over 12 weeks were observed. In addition, ORM-12741 was generally well tolerated in the study. These findings are encouraging and warrant further exploration in longer term trials.

Disclosures: The study was sponsored by Orion Pharma. Jutta Hänninen and Juha Rouru are employees of Orion Pharma. Keith Wesnes is employee of Bracket which supplied the CDR System for the study. Mike Murphy and Henry Riordan are employees of Worldwide Clinical Trials, the CRO that supported trial conduct.