2. SYNOPSIS

Sponsor/company Orion Corporation Orion Pharma	**Individual study table referring to a specific part of the dossier**	(for National Competent Authority use only)
Finished product: Not applicable	**Volume:**	
Active ingredient: ORM-12741	**Page**	
Study code: 3098006		
Study title: Safety and efficacy of ORM-12741 on cognitive and behavioural symptoms in patients with Alzheimer's disease: A randomised, double-blind, placebo-controlled, parallel group, multicentre study of 12 weeks		
Investigators and study centres: Study coordinating investigator was Juha Rinne, Clinical Research Services Turku (CRST), Itäinen Pitkäkatu 4B, 20520 Turku, Finland. This study was conducted in 4 countries (18 centres): Finland (2), Poland (6), Romania (4) and Spain (6).		
Development phase: IIa	**Study period:** 27 Apr 2011-21 Sep 2012 (first subject first visit last subject last visit)	
Objectives: The primary objectives of the study were to evaluate the safety and tolerability of ORM-12741, and the efficacy of ORM-12741 on cognitive symptoms in patients with Alzheimer's disease (AD) receiving acetylcholinesterase (AChE) inhibitor therapy. The secondary objectives were to evaluate the efficacy of ORM-12741 on behavioural symptoms, the plasma trough concentrations of ORM-12741 in patients with AD receiving AChE inhibitor therapy, and the effects of ORM-12741 on plasma trough concentrations of the AChE inhibitors.		
Methodology: This was a phase IIa, randomised, double-blind, placebo-controlled, parallel-group, multicentre study. Patients with AD were randomised to 3 parallel groups to receive either of 30 to 60 mg (low dose) or 100 to 200 mg (high dose) of ORM-12741, or placebo for 12 weeks in addition to their stable AChE inhibitor therapy (donepezil, rivastigmine or galantamine). For each subject, there was a screening visit, a baseline visit (day 1), 5 visits during the treatment period (1, 2, 4, 8 and 12 weeks after the start of the study treatment) and an end-of-study visit. The duration of study was about 15 weeks for each subject.		
Sample size: The planned number of subjects was 99 and the actual number of subjects randomised was 100. The sample size was not based on a formal power calculation. However, it was expected to be sufficient for detecting trends in the cognitive and behavioural domains tested, enabling decision-making with regards to future studies.		
Diagnosis and main criteria for inclusion: Male or female patients with diagnosis of probable AD, written informed consent (IC) obtained from the patients and his/her caregiver. The patient had to have a history of progressive cognitive deterioration, brain imaging consistent with AD, at least a mild level of behavioural symptoms present with a neuropsychiatric inventory (NPI) score ≥ 15, mini-mental state examination (MMSE) score 12-21 at the screening visit and had to have been treated with donepezil, rivastigmine or galantamine for at least 3 months prior to screening, with a stable dose for at least 2 months prior to screening. Use of antipsychotics within 2 months prior to the screening was not allowed. Memantine and selective serotonin reuptake inhibitors (SSRIs) were allowed (added in protocol amendment, 10 Nov 2011). The patient had to be 55-90 years old and fulfil all of the inclusion criteria and none of the exclusion criteria.		

Investigational product, dose and mode of administration, batch numbers: ORM-12741 was provided as 30 mg or 100 mg capsules for oral administration. The low dose group received 30 mg twice a day (b.i.d.) and the high dose group received 100 mg b.i.d. for the first week after which the dose was increased to the maintenance dose of 60 or 200 mg b.i.d., respectively. The batch numbers for ORM-12741 30 mg capsules were 11A20/1 and 11A20/2, and for ORM-12741 100 mg capsules were NA102L1 and NB005L1.
Duration of treatment: 12 weeks
Reference product, dose and mode of administration, batch numbers: Placebo capsules for ORM-12741 for oral administration. The batch number for placebo capsules was MM002L1. The batch number for placebo capsules used to test the ability to swallow oral medications, as a criterion for eligibility, was MI001L1.
Bioanalytics: ORM-12741, ORM-13720, ORM-13859, ORM-13861 and AChE inhibitor (donepezil, galantamine, rivastigmine) concentrations in plasma were determined by validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods.
Variables and methods of assessments: Efficacy variables: The following cognitive tests were assessed: • Cognitive Drug Research (CDR) System to evaluate the following variables: Quality of Episodic Secondary Memory, Quality of Working Memory, Speed of Memory, Power of Attention, Continuity of Attention, Quality of Memory (post-hoc) as well as CDR subscores • Controlled Oral Word Association Test (COWAT) and the Category Fluency Test (CFT) The following behavioural and psychological symptom tests were assessed: • NPI to evaluate the following variables: NPI total scores (10 behavioural areas), NPI Psychotic cluster score (3 behavioural areas), NPI total score by severity and frequency, NPI subscores, NPI caretaker distress score (10 behavioural areas), and NPI caretaker distress subscores • Cornell Scale for Depression in Dementia (CSDD). In addition, the Cognitive Failures Questionnaire (CFQ) and the overall change in subject's clinical condition by Clinical Global Impression of Change (CGI-C) were assessed. Pharmacokinetic (PK) variables: ORM-12741, ORM-13720, ORM-13859, ORM-13861, donepezil, galantamine and rivastigmine concentrations in plasma were tabulated. Due to the sparse blood sampling, no PK variables were calculated
Pharmacogenetic (PG) variables: A protocol-specified blood sample for DNA extraction was collected from all subjects, but the optional blood sample only from subjects who signed a separate PG IC. The objective of the protocol-specified sample was to determine the carrier status for the genes (markers) that have been associated with behavioural and psychological symptoms in AD and which may affect the target receptor, and therefore may predict the subject's response to the study treatment. The objective of the optional sample is to study possible genetic factors that influence the absorption, distribution, metabolism, excretion, efficacy and safety of ORM-12741, its metabolites or AChE inhibitors. PG results will be reported in a separate report. Safety variables: Safety was assessed by adverse events (AEs), vital signs, 12-lead electrocardiogram (ECG), physical examination and laboratory safety assessments. Suicidality was assessed by Columbia-Suicide Severity Rating Scale (C-SSRS).

Statistical methods: The evaluation for primary and secondary objectives of this study was based on descriptive statistics and these results were supported by using statistical analyses. Given the exploratory objectives of the trial, p-values from statistical analyses serve as descriptors of trends, and there are no adjustments for multiplicity.

Evaluation of efficacy:

All efficacy variables (CDR test battery composite scores and subscores, COWAT, CFT total score, NPI total score, NPI psychotic cluster score, NPI individual symptom scores, CSDD, total score, CFQ total score and CGI-C score) were summarised using descriptive statistics and appropriate figures. For multiple repeated continuous efficacy variables (normal distributed scores and subscores), comparisons between the treatment groups were performed using a repeated measurements of analysis of covariance (RM ANCOVA) model with 95% confidence intervals (CI). For multiple repeated categorical efficacy variables (CGI-C), comparisons between the treatment groups were performed using a generalised linear model with 95% CIs.

The main emphasis was the CDR test battery composite scores Power of Attention, Quality of Working Memory, Quality of Episodic Secondary Memory, Speed of Memory Retrieval, and the NPI total and psychotic cluster score.

Evaluation of PK:

The ORM-12741, ORM-13720, ORM-13859, ORM-13861 in each treatment groups were summarised using descriptive statistics. The AChE inhibitor (donepezil, rivastigmine, galantamine) concentrations in plasma were summarised using descriptive statistics and analysed using an analysis of covariance (ANCOVA) model.

Evaluation of safety:

The AEs were displayed in a frequency table. The number and proportion of subjects having each AE, severity of AEs and causality to the drug were given. Serious AEs and other significant AEs were evaluated case by case.

The actual values and corresponding changes from baseline for supine and standing heart rate (HR), blood pressure (BP), and 12-lead ECG variables were summarised using descriptive statistics.

Suicidality was summarised using descriptive statistics.

Laboratory safety variables were summarised using descriptive statistics and analysed using ANCOVA model.

Summary-Conclusions

Disposition:

A total of 132 subjects were screened and 100 subjects were randomised into the study: 33 into the ORM-12741 30-60 mg (low dose) group, 33 into the ORM-12741 100-200 mg (high dose) group and 34 into the placebo group.

Of the randomised subjects, 91 subjects (91%) completed the study and 9 subjects (9%) discontinued the study. The reasons for premature discontinuation was AE in 3 subjects, lost to follow-up in 1 subject, reason 'other' in 2 subjects and personal reason in 3 subjects.

The modified intent-to-treat (M-ITT) population comprised 100 subjects, per-protocol (PP) population 85 subjects and safety population 100 subjects.

Demography and other baseline characteristics:

More females (59%) than males (41%) were randomised into the study and most (99%) subjects were Caucasian. Mean age was 72 years (range 55-90 years), and mean body index was 25.3 kg/m^2 (range 16.4-33.9 kg/m^2). The mean MMSE score at screening was 18.5 (range 12-21) and mean total NPI varied between 19.4 and 23.7 scores (range 15-57 scores). There were no notable differences in any demography or other baseline characteristics between the treatment groups.

Efficacy results:

Evaluation of cognition

CDR System

Of the pre-defined primary CDR System variables, ORM-12741 was statistically significantly superior to placebo in the Quality of Episodic Memory composite score. During the 12-week treatment period, the mean

Quality of Episodic Memory scores increased by 0.71 scores in the low dose group, decreased by -0.81 scores in the high dose group and decreased by -38.76 scores in the placebo group. Both ORM-12741 doses produced statistically significant (p = 0.030) overall benefit compared with placebo over the 12 weeks of treatment. In pairwise comparisons, estimate for difference between low dose and placebo was 16.46 (95% CI 0.28 to 32.63, p = 0.046) and between high dose and placebo 20.62 (95% CI 4.57 to 36.67, p = 0.012). The low dose was significantly superior to placebo at weeks 4 and 12, while the high dose was superior to placebo at weeks 8 and 12. At 12 weeks, the effect size was 1.09 for low dose vs. placebo (p = 0.001) and 1.02 for high dose vs. placebo (p = 0.002). The results of the PP analysis corroborate the M-ITT analysis.

ORM-12741 was also superior (p = 0.013) to placebo in the Quality of Memory composite score, a post-hoc variable, which combined the accuracy scores from all 6 of the working and episodic memory tasks. Of the CDR system tests used, this showed the clearest improvement with ORM-12741. Again, placebo showed a steady decline during the 12-week treatment period

There was no statistically significant (p = 0.193) overall treatment effect for ORM-12741 vs. placebo in the pre-defined Quality of Working Memory composite score. However, the low dose showed an overall trend (p = 0.079) for improving working memory over the 12 weeks, and the low dose was superior (p = 0.006) to placebo at week 12. In the PP population, both doses were superior (low dose, p = 0.009 and high dose, p = 0.020) to placebo at 12 weeks.

Speed of Memory, which combines the speed scores from the 2 working memory and 2 episodic recognition tasks, did not show any consistent differences during the study between ORM-12741 and placebo.

No statistically significant differences were detected between ORM-12741 and placebo in the CDR System tests of Power of Attention and Continuity of Attention, both of which measure attention and information processing.

COWAT and CFT

No significant treatment effects were seen in executive function measures COWAT and CFT between the treatment groups over the 12 weeks of treatment.

Behavioural and psychological symptoms

NPI and CSDD

There was a statistically significant improvement in NPI Caregiver Distress scores in both doses of ORM-12741 compared with placebo at week 12 with no clear difference between the active treatment groups. The mean estimate for the difference between low dose and placebo was -2.13 (95% CI -3.92 to -0.35, p = 0.020) and between high dose and placebo -1.94 (95% CI -3.70 to -0.18, p = 0.031).

A trend towards improved NPI total scores was seen in favour of low dose vs. placebo. This seemed to be driven by effects of the individual NPI items, and by the frequency scores rather than the severity scores of the NPI. Small numerical benefits in favour of ORM-12741 vs. placebo were seen in the NPI Psychotic Cluster score and the CSDD. However, these differences did not reach statistical significance.

Global and self-rated assessments

No significant treatment effects were seen in CFQ or CGI-C between the treatment groups.

Pharmacokinetics

Neither ORM-12741 nor any of its metabolites accumulated during 12 weeks of treatment. The steady state of the concentrations was reached at the week 2 visit. The metabolite/parent ratios of the measured plasma concentrations were lower in the high dose group than in the low dose group.

ORM-12741 treatment did not significantly affect the plasma concentrations of AChE inhibitors donepezil, rivastigmine or galantamine.

Safety results:

A total of 158 AEs were reported by 60 subjects (60%) after the start of study treatment. The total number subjects with at least 1 AE did not differ between the treatment groups but more subjects reported related AEs in the high dose group than in the other 2 groups (Table 1). However, no differences in the profile of related AEs were observed between the treatment groups. The most common AEs by preferred term are shown in Table 2.

Table 1. Summary of adverse events

Preferred term	ORM-12741 30-60 mg N = 33	ORM-12741 100-200 mg N = 33	Placebo N = 34
	Number (%) of subjects		
Subjects with AEs	18 (54.5)	21 (63.6)	21 (61.8)
Subjects with related AEs	8 (24.2)	10 (30.3)	6 (17.6)
Subjects with SAEs	0	1 (3.0)	0
Discontinued due to AE	1 (3.0)	2 (6.1)	0
Dose reduced due to AE	2 (6.1)	3 (9.1)	3 (8.8)

Table 2. The most common adverse events (reported by ≥ 5 subjects)

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

During the study, 1 subject experienced cholestasis with asymptomatic high AST, ALT, GGT and ALP values. This event was reported as an SAE and led to premature discontinuation of the subject from the study.

In addition to the subject that was reported to have asymptomatic but remarkably high liver function test values and was reported to have an SAE (cholestasis), 3 subjects with temporally treatment related AST or ALT increases ≥ 2 x ULN were seen. Of these, 2 were in the high dose group and 1 in the placebo group. No statistically significant effects between the treatment groups were seen in the mean liver function test values.

No clinically meaningful changes were seen in standing and supine BP or supine HR. The mean changes from baseline in standing HR were numerically slightly greater in the high dose group than in the placebo group; however, these differences were small and not statistically significant. The number of subjects with an increase from baseline in HR > 10 bpm and > 20 bpm was slightly higher in the high dose group than in the placebo group. The number of subjects with high (> 100 bpm) HR values or increased HR values from baseline (> 30 bpm) was small, with no notable differences between the treatment groups. No notable changes were noted in BP in the orthostatic test. Small but statistically significant increases in HR in the orthostatic test were seen with ORM-12741 compared with placebo.

No clinically meaningful changes were seen in ECG variables. There were no differences in QTc interval. However, there was some trend for decreases in PR and QRS duration in the ORM-12741 groups compared with placebo in the beginning of the study. No concerns were raised from C-SSRS data.

Conclusion:

Both ORM-12741 doses were potentially more effective than placebo in preventing development of memory deficits in subjects with AD who were receiving AChE inhibitor therapy in this 12-week proof of concept study. There were no clear differences in efficacy between the ORM-12741 doses. ORM-12741 showed a trend towards a better outcome in subject's behavioural symptoms, as assessed using NPI total score, and significantly better outcome, as assessed using NPI Caretaker Distress score.

The safety profile was acceptable for all treatments. More related AEs were reported, including 1 SAE of cholestasis, and there was a small non-significant trend for increased HR in standing position in the high dose group. No clinically meaningful changes were seen in BP and ECG variables.

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