Clinical trial results:
EFFICACY OF ORM-12741 ON AGITATION/AGGRESSION SYMPTOMS IN PATIENTS WITH ALZHEIMER'S DISEASE: A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP, MULTICENTRE STUDY OF 12 WEEKS

Summary

EudraCT number	2014-000217-30
Trial protocol	DE CZ FI PL BG RO HR
Global end of trial date	09 October 2017

Results information

Result version number	v1 (current)
This version publication date	18 October 2018
First version publication date	18 October 2018

Trial information

Trial identification

Sponsor protocol code	3098012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02471196
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Orion Pharma
Sponsor organisation address	Orionintie 1, Espoo, Finland, 02200
Public contact	clinicaltrials@orionpharma.com, Orion Corporation, Orion Pharma, +358 104261,
Scientific contact	clinicaltrials@orionpharma.com, Orion Corporation, Orion Pharma , +358 104261,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 October 2017
Global end of trial reached?	Yes
Global end of trial date	09 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate efficacy of ORM-12741 on agitation/aggression symptoms in patients with mild to moderate Alzheimer’s disease. The efficacy of ORM-12741 administered both as immediate release (IR) and modified release (MR) formulations will be evaluated and compared to placebo.

Protection of trial subjects:

The study data was monitored regularly by the Sponsor, and an independent data and safety monitoring board (DSMB) was established to protect the
ethical and safety interest of the study subjects and all others who could possibly be exposed to the study treatments. In addition, at the time of the scheduled interim analysis the DSMB evaluated the analyses for the efficacy.
Safety measurements including blood pressure, heart rate, 12-lead ECG and safety laboratory tests were performed before the study treatment, during each study visit and at the end of the study. Adverse events were collected throughout the study. Lorazepam (or oxazepam/alprazolam) were used as rescue therapy, if needed.
Patients were free to leave the study at any time but were also withdrawn in the event of a safety finding of clinical concern.

Background therapy:

Existing Alzheimer's disease therapy was allowed (cholinesterase inhibitors and memantine).

Evidence for comparator: -

Actual start date of recruitment	14 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 21
Country: Number of subjects enrolled	Romania: 12
Country: Number of subjects enrolled	Slovakia: 39
Country: Number of subjects enrolled	Croatia: 48
Country: Number of subjects enrolled	Bulgaria: 9
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	Finland: 4
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Serbia: 21
Country: Number of subjects enrolled	Russian Federation: 57
Country: Number of subjects enrolled	Ukraine: 86

Worldwide total number of subjects	308
EEA total number of subjects	144

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	62
From 65 to 84 years	231
85 years and over	15

Subject disposition

Recruitment

Recruitment details:

Patients with mild to moderate Alzheimer's disease were recruited.

Pre-assignment

Screening details:

Male or female subjects with a diagnosis of probable AD, written informed consent (IC) obtained from the subject and his/her caregiver. The subject had to have a history of progressive cognitive deterioration, brain imaging consistent with a diagnosis of AD, and a mini-mental state examination (MMSE) score between 10-24 (inclusive), at screening.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The study was double-blind. Blinding was done with double-dummy technique. None of the persons directly involved in the conduct of the study
had access to the treatment code. The DSMB had access to the treatment code. In addition, the bioanalytical laboratories and specified personnel responsible for the interim analysis had access to the treatment code.

Arms

Are arms mutually exclusive?	Yes
Arm title	ORM-12741 60 mg IR

Arm description:

ORM-12741 IR 60 mg twice a day

Arm type	Experimental
Investigational medicinal product name	ORM-12741 IR 60 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One ORM-12741 60 mg immediate-release capsule was given twice a day at about 12 h intervals for 12 weeks.

Arm title	ORM-12741 120 mg MR

Arm description:

ORM-12741 MR 120 mg twice a day

Arm type	Experimental
Investigational medicinal product name	ORM-12741 MR 120 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release capsule, hard
Routes of administration	Oral use

Dosage and administration details:

One ORM-12741 120 mg modified-release capsule was given twice a day at about 12 h intervals for 12 weeks.

Arm title	Placebo

Arm description:	
Placebo ORM-1271 capsules twice a day	
Arm type	Placebo
Investigational medicinal product name	Placebo ORM-12741 capsule
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2 Placebo ORM-12741 capsules were given twice a day at about 12 h intervals for 12 weeks.

Number of subjects in period 1	ORM-12741 60 mg IR	ORM-12741 120 mg MR	Placebo
Started	102	103	103
Completed	85	91	84
Not completed	17	12	19
Adverse event, serious fatal	1	2	1
Sponsor's decision	-	-	1
Adverse event, non-fatal	8	4	3
Other, caregiver's illness	1	-	-
Personal reason	6	5	12
Non-compliance	1	-	-
Lost to follow-up	-	1	1
Ache medic. stopped right before random.	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	308	308	
Age categorical Units: Subjects			
Adults (18-64 years)	62	62	
From 65-84 years	231	231	
85 years and over	15	15	
Gender categorical Units: Subjects			
Female	191	191	
Male	117	117	

End points

End points reporting groups	
Reporting group title	ORM-12741 60 mg IR
Reporting group description: ORM-12741 IR 60 mg twice a day	
Reporting group title	ORM-12741 120 mg MR
Reporting group description: ORM-12741 MR 120 mg twice a day	
Reporting group title	Placebo
Reporting group description: Placebo ORM-1271 capsules twice a day	

Primary: NPI-C agitation and aggression score (A+A)	
End point title	NPI-C agitation and aggression score (A+A)
End point description: Results of modifed ITT-population.	
End point type	Primary
End point timeframe: Difference from baseline after 12 weeks of treatment.	

End point values	ORM-12741 60 mg IR	ORM-12741 120 mg MR	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84[1]	94[2]	82[3]	
Units: Difference from baseline				
arithmetic mean (standard deviation)	-11.43 (± 10.21)	-13.72 (± 11.43)	-12.41 (± 9.89)	

Notes:

[1] - Modified ITT-population, table 14.1.2.3

[2] - Modified ITT-population, table 14.1.2.3

[3] - Modified ITT-population, table 14.1.2.3

Statistical analyses

Statistical analysis title	Change from baseline, A+A scores
Statistical analysis description: Treatment effect between placebo and ORM-12741 treatments, Repeated measurements ANCOVA	
Comparison groups	ORM-12741 60 mg IR v Placebo
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority[4]
Parameter estimate	Mean difference (final values)
Point estimate	1.58

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	3.5
Variability estimate	Standard error of the mean

Notes:

[4] - For multiple repeated continuous variables (normal distributed scores and sub-scores) comparisons between the treatment groups were
performed using a repeated measurements of analysis of covariance (RM-ANCOVA) model with 95% confidence intervals (CIs).

Statistical analysis title	Change from baseline, A+A scores

Statistical analysis description:

Treatment effect between placebo and ORM-12741 treatments, repeated measurements ANCOVA

Comparison groups	ORM-12741 120 mg MR v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.82
upper limit	1.94
Variability estimate	Standard error of the mean

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of the study treatment until the end-of study visit.	
Adverse event reporting additional description:	
In this study normal fluctuation in agitation symptoms was not to be reported as an AE.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	ORM-12741 60 mg IR
Reporting group description:	
ORM-12741 IR 60 mg twice a day, table 14.5.1.1	
Reporting group title	ORM-12741 120 mg MR
Reporting group description:	
ORM-12741 MR 120 mg twice a day	
Reporting group title	Placebo
Reporting group description:	
Placebo ORM-1271 capsules twice a day	

Serious adverse events	ORM-12741 60 mg IR	ORM-12741 120 mg MR	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 102 (3.92%)	5 / 103 (4.85%)	1 / 103 (0.97%)
number of deaths (all causes)	1	1	1
number of deaths resulting from adverse events	1	1	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 102 (0.00%)	1 / 103 (0.97%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 102 (0.00%)	1 / 103 (0.97%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	0 / 102 (0.00%)	1 / 103 (0.97%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cor pulmonale			
subjects affected / exposed	0 / 102 (0.00%)	1 / 103 (0.97%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 102 (0.98%)	1 / 103 (0.97%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic uremic syndrome			
subjects affected / exposed	1 / 102 (0.98%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 102 (0.00%)	0 / 103 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
Psychotic behaviour			
subjects affected / exposed	0 / 102 (0.00%)	1 / 103 (0.97%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	1 / 102 (0.98%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 102 (0.98%)	1 / 103 (0.97%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	ORM-12741 60 mg IR	ORM-12741 120 mg MR	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 102 (22.55%)	30 / 103 (29.13%)	28 / 103 (27.18%)
Investigations			
Haemoglobin decreased			
subjects affected / exposed	2 / 102 (1.96%)	0 / 103 (0.00%)	3 / 103 (2.91%)
occurrences (all)	2	0	3
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 102 (0.98%)	3 / 103 (2.91%)	0 / 103 (0.00%)
occurrences (all)	1	3	0
C-reactive protein increased			
subjects affected / exposed	1 / 102 (0.98%)	2 / 103 (1.94%)	1 / 103 (0.97%)
occurrences (all)	1	2	1
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 102 (2.94%)	5 / 103 (4.85%)	1 / 103 (0.97%)
occurrences (all)	5	5	2
Dizziness			
subjects affected / exposed	0 / 102 (0.00%)	6 / 103 (5.83%)	2 / 103 (1.94%)
occurrences (all)	0	8	3
Psychiatric disorders			
Agitation			
subjects affected / exposed	4 / 102 (3.92%)	1 / 103 (0.97%)	3 / 103 (2.91%)
occurrences (all)	4	1	3
Sleep disorder			
subjects affected / exposed	1 / 102 (0.98%)	0 / 103 (0.00%)	3 / 103 (2.91%)
occurrences (all)	1	0	3
Infections and infestations			

Pneumonia subjects affected / exposed occurrences (all)	1 / 102 (0.98%) 1	1 / 103 (0.97%) 1	2 / 103 (1.94%) 2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported