



## 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:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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                |
| <b>Arm title</b>             | 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.

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | 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.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b>    | 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:<br>ORM-12741 IR 60 mg twice a day        |                     |
| Reporting group title   | ORM-12741 120 mg MR |
| Reporting group description:<br>ORM-12741 MR 120 mg twice a day       |                     |
| Reporting group title   | Placebo             |
| Reporting group description:<br>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:<br>Results of modified ITT-population.                 |  |
| End point type  | Primary                                    |
| End point timeframe:<br>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 <sup>[1]</sup>  | 94 <sup>[2]</sup>   | 82 <sup>[3]</sup> |  |
| 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:<br>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 <sup>[4]</sup>       |
| 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).

|                                   |                                  |
|-----------------------------------|----------------------------------|
| <b>Statistical analysis title</b> | 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 %

| <b>Non-serious adverse events</b>                     | 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 | 1 / 102 (0.98%) | 1 / 103 (0.97%) | 2 / 103 (1.94%) |
| occurrences (all)           | 1               | 1               | 2               |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported