



## Clinical trial results: Randomized Controlled Trial of Simvastatin in Amnestic MCI Patients Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2008-002226-11 |
| Trial protocol           | DE             |
| Global end of trial date | 31 August 2020 |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 18 June 2022 |
| First version publication date | 18 June 2022 |

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | SIMaMCI |
|-----------------------|---------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Charité - Universitätsmedizin Berlin  |
| Sponsor organisation address | Charitéplatz 1, Berlin, Germany, D-10117  |
| Public contact               | Klinik für Psychiatrie, AG Peters, Campus Benjamin Franklin, Charité - Universitätsmedizin Berlin Hochschulambulanz für Psychiatrie und Psychotherapie, 0049 030 450 517 685, |
| Scientific contact           | Klinik für Psychiatrie, AG Peters, Campus Benjamin Franklin, Charité - Universitätsmedizin Berlin Hochschulambulanz für Psychiatrie und Psychotherapie, 0049 030 450 517 685, |

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                       | 31 August 2020 |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 31 August 2020 |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 31 August 2020 |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

Simvastatin significantly reduces the conversion rate to Alzheimer's dementia in probands with MCI as compared to MCI receiving placebo

Protection of trial subjects:

During the first three months of the study monthly assessment of laboratory parameters, vital signs and a physical exam, thereafter every 6 months. In between phone contacts were performed with the patient. Standardized adverse event reports. Serious adverse event reports were immediately transferred to the PI electronically by the remote data entry system.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 01 November 2008 |
| 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 | Germany: 270 |
| Worldwide total number of subjects   | 270          |
| EEA total number of subjects         | 270          |

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)                      | 55  |
| From 65 to 84 years                       | 208 |
| 85 years and over                         | 7   |

## Subject disposition

### Recruitment

Recruitment details:

Date of study / recruitment start: 01.11.2008

Date of termination of recruitment: 31.08.2018

Territories for recruitment in Germany included the following centers: Berlin, Bonn, Erlangen, Frankfurt, Freiburg, Göttingen, Halle, Heidelberg, Mannheim, Marburg, München, Rostock and Ulm.

### Pre-assignment

Screening details:

Subjects were recruited at the memory clinics of the participating centres. Screening criteria: neuropsychological screening examination (CDR with a score of at least 0.5), CERAD, WMS-LM); memory impairment at least six months; age 55-90; cholesterol equal to or above 90 to 160 mg/dl; certain co-medication was not allowed.

### Period 1

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

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

Placebo

|  |               |
|--|---------------|
| Arm type                               | Placebo       |
| Investigational medicinal product name | Placebo       |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

Placebo contains: 1 hard capsul, the colour was swedish-orange, 8 mm in diameter and a weight of 190 mg. They contained lactose monohydrate, magnesium stearate, cellulose powder and microcrystalline cellulose. From visit 2-4 the patients would receive 3 boxes with 34 capsules. From visit 5 to 12 they would receive a box with 96 capsules all three months. The patients took one capsule each day in the evening.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Simvastatin 20 mg |
|------------------|-------------------|

Arm description:

Threatment medication of 20 mg Simvastatin

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Simvastatin   |
| Investigational medicinal product code | 79902-63-9    |
| Other name                             | SimvaHexal    |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

A capsule of Simvastatin 20 mg contains: 1 hard capsul, the colour was swedish-orange, 8 mm in diameter and a weight of 190 mg. They contained: 20 mg simvastatin, pregelatinized cornstarch, butylhydroxyanisole, 61,25 mg lactose monohydrate, microcrystalline cellulose, citric acid monohydrate, magnesium stearate. A filmcoating with: hydroxypropylmethyl cellulose, talc, titanium dioxide, iron-(III)

-oxide (E 172), iron-(III)-hydroxide-oxide (E 172). Furthermore the capsules contained DAC NRF a capsule filler to uphold the blinding of the patients and to suppress the typical rattling inside the capsule.

From visit 2-4 the patients would receive 3 boxes with 34 capsules. From visit 5 to 12 they would receive a box with 96 capsules all three months. The patients took one capsule each day in the evening.

|  |                   |
|--|-------------------|
| <b>Arm title</b>                           | Simvastatin 60 mg |
| Arm description:                           |                   |
| Threatment medication of 60 mg Simvastatin |                   |
| Arm type                                   | Active comparator |
| Investigational medicinal product name     | Simvastatin       |
| Investigational medicinal product code     | 79902-63-9        |
| Other name                                 | SimvaHexal        |
| Pharmaceutical forms                       | Capsule, hard     |
| Routes of administration                   | Ocular use        |

Dosage and administration details:

A capsule of Simvastatin 60 mg contains: 1 hard capsual, the colour was swedish-orange, 8 mm in diameter and a weight of 190 mg. They contained: 60 mg simvastatin, ascorbic acid, pregelatinized cornstarch, butylhydroxyanisole, 421,4 mg lactose monohydrate, microcrystalline cellulose, citric acid monohydrate, magnesium stearate. A filmcoating with: hydroxypropylmethyl cellulose, talc, titanium dioxide, indigocarmin, aluminum salt (E 132). Furthermore the capsules contained DAC NRF a capsule filler to uphold the blinding of the patients and to suppress the typical rattling inside the capsule.

From visit 2-4 the patients would receive 3 boxes with 34 capsules. From visit 5 to 12 they would receive a box with 96 capsules all three months. The patients took one capsule each day in the evening.

| <b>Number of subjects in period 1</b> | Placebo | Simvastatin 20 mg | Simvastatin 60 mg |
|---------------------------------------|---------|-------------------|-------------------|
| Started                               | 99      | 32                | 139               |
| Completed                             | 99      | 32                | 139               |

## Baseline characteristics

## End points

### End points reporting groups

|   |                   |
|---|-------------------|
| Reporting group title   | Placebo           |
| Reporting group description:<br>Placebo                                     |                   |
| Reporting group title   | Simvastatin 20 mg |
| Reporting group description:<br>Therapeutic medication of 20 mg Simvastatin |                   |
| Reporting group title   | Simvastatin 60 mg |
| Reporting group description:<br>Therapeutic medication of 60 mg Simvastatin |                   |

### Primary: Change in CDR-SOB

|  |                   |
|--|-------------------|
| End point title  | Change in CDR-SOB |
| End point description:<br>We looked at changes in the CDR Sum of Boxes during the duration of 24 months and also at 36 months. We used Kaplan Meier Curves to compare the CDR Sum of Boxes for different study subgroups which are shown in Figure 6.2. Also attached is the data for these figures in form of excel documents. There is no significant difference for any of the groups. The highest difference is received comparing placebo with Simvastatin 20 mg. |                   |
| End point type   | Primary           |
| End point timeframe:<br>24 months but we also looked in changes during the whole duration of 3 years too.  |                   |

| End point values            | Placebo         | Simvastatin 20 mg | Simvastatin 60 mg |  |
|-----------------------------|-----------------|-------------------|-------------------|--|
| Subject group type          | Reporting group | Reporting group   | Reporting group   |  |
| Number of subjects analysed | 99              | 32                | 139               |  |
| Units: Artificial Number    |                 |                   |                   |  |
| number (not applicable)     | 99              | 32                | 139               |  |

|                                   |   |
|-----------------------------------|---|
| <b>Attachments (see zip file)</b> | Change in CDR-SOB/Primary Endpoint.pdf<br>Primary Endpoint Change in CDR SOB - Results.xlsx |
|-----------------------------------|---|

### Statistical analyses

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Longitudinal change in cognition                |
| Comparison groups                 | Placebo v Simvastatin 20 mg v Simvastatin 60 mg |

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 270                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           |                         |
| P-value                                 | < 0.1                   |
| Method                                  | Wilcoxon (Mann-Whitney) |
| Parameter estimate                      | Delta                   |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| Variability estimate                    | Standard deviation      |

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**Secondary: Length of conversion-free Intervall, starting at the time of randomization, with conversion being defined as an increase of the CDR-Score beyond 0.5**

|                 |  |
|-----------------|--|
| End point title | Length of conversion-free Intervall, starting at the time of randomization, with conversion being defined as an increase of the CDR-Score beyond 0.5 |
|-----------------|--|

End point description:

Analysis: Length of conversion-free interval, starting at the time of randomization, with conversion being defined as an increase of the CDR score beyond 0.5. Kaplan Meier Curves using CDR score comparing different study subgroups are shown in Figure 6.1. Also attached is the data for these figures in form of excel documents. There is no significant difference for any of the groups. The highest difference is received comparing placebo with Simvastatin 20 mg.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

3 years

| End point values            | Placebo         | Simvastatin 20 mg | Simvastatin 60 mg |  |
|-----------------------------|-----------------|-------------------|-------------------|--|
| Subject group type          | Reporting group | Reporting group   | Reporting group   |  |
| Number of subjects analysed | 99              | 32                | 139               |  |
| Units: Artificial Units     |                 |                   |                   |  |
| number (not applicable)     | 99              | 32                | 139               |  |

|                                   |  |
|-----------------------------------|--|
| <b>Attachments (see zip file)</b> | Length of conversion-free Intervall/2 secondary Endpoint.pdf<br>2. Secondary Endpoint Length of conversion-free Intervall.xlsx |
|-----------------------------------|--|

**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Change in ADCS-ADL score**

|                 |                          |
|-----------------|--------------------------|
| End point title | Change in ADCS-ADL score |
|-----------------|--------------------------|

End point description:

Analysis: Functional status, as assessed by the ADCS-ADL scale for MCI. This scale evaluates the level of functioning in daily living. The ADCS-ADL scale for MCI has been adapted to accommodate activities that are most relevant at prodromal and early dementia stages. Kaplan Meier Curves using ADCS-ADL

score comparing different study subgroups. The corresponding plot is shown in the added Figure. Also attached is the data for these figures in form of excel documents.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 3 years              |           |

| End point values            | Placebo         | Simvastatin 20 mg | Simvastatin 60 mg |  |
|-----------------------------|-----------------|-------------------|-------------------|--|
| Subject group type          | Reporting group | Reporting group   | Reporting group   |  |
| Number of subjects analysed | 99              | 32                | 139               |  |
| Units: Artificial Units     |                 |                   |                   |  |
| number (not applicable)     | 99              | 32                | 139               |  |

|                                   |  |
|-----------------------------------|--|
| <b>Attachments (see zip file)</b> | Change in ADCS-ADL score/3 secondary Endpoint - Change in<br>3. Secondary Endpoint Change in ADCS-ADL.xlsx |
|-----------------------------------|--|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in volumetric brain measures (structural MRI)

|   |  |
|---|--|
| End point title   | Change in volumetric brain measures (structural MRI) |
| End point description:  |  |
| Also, volumetric MRI measures of hippocampi will be obtained to assess neuronal loss. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| 3 years   |  |

| End point values            | Placebo         | Simvastatin 20 mg | Simvastatin 60 mg |  |
|-----------------------------|-----------------|-------------------|-------------------|--|
| Subject group type          | Reporting group | Reporting group   | Reporting group   |  |
| Number of subjects analysed | 99              | 32                | 139               |  |
| Units: Artificial Units     |                 |                   |                   |  |
| number (not applicable)     | 99              | 32                | 139               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in CSF and blood measures of beta-amyloid peptides, total and phosphorylated TAU Proteins and measures of cerebral cholesterol metabolites

|  |   |
|--|---|
| End point title  | Change in CSF and blood measures of beta-amyloid peptides, total and phosphorylated TAU Proteins and measures of cerebral cholesterol metabolites |
| End point description:<br>As surrogate markers CSF concentrations of cholesterol metabolites, $\beta$ -amyloid peptides and TAU proteins will be determined. |   |
| End point type   | Secondary   |
| End point timeframe:<br>3 years  |   |

| End point values            | Placebo         | Simvastatin 20 mg | Simvastatin 60 mg |  |
|-----------------------------|-----------------|-------------------|-------------------|--|
| Subject group type          | Reporting group | Reporting group   | Reporting group   |  |
| Number of subjects analysed | 99              | 32                | 139               |  |
| Units: Artificial Units     |                 |                   |                   |  |
| number (not applicable)     | 99              | 32                | 139               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Impact on cost efficacy Ratio (ICER)

|   |                                      |
|---|--------------------------------------|
| End point title   | Impact on cost efficacy Ratio (ICER) |
| End point description:<br>The study will be complemented by detailed cost efficacy analyses: Incremental cost efficacy ratios (ICERs) and net monetary benefits will be calculated and analysed on the basis of cost estimates and major study outcomes by using bootstrapping and other health economic methods. |                                      |
| End point type  | Secondary                            |
| End point timeframe:<br>For the whole duration of the study   |                                      |

| End point values            | Placebo         | Simvastatin 20 mg | Simvastatin 60 mg |  |
|-----------------------------|-----------------|-------------------|-------------------|--|
| Subject group type          | Reporting group | Reporting group   | Reporting group   |  |
| Number of subjects analysed | 99              | 32                | 139               |  |
| Units: Artificial Units     |                 |                   |                   |  |
| number (not applicable)     | 99              | 32                | 139               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacogenetic prediction parameters

|   |                                       |
|---|---------------------------------------|
| End point title   | Pharmacogenetic prediction parameters |
| End point description:<br>Pharmacogenetic studies will be used as prediction of outcome, focussing especially on those genes impacting on cholesterol metabolism. |                                       |
| End point type  | Secondary                             |
| End point timeframe:<br>3 years   |                                       |

| End point values            | Placebo         | Simvastatin 20 mg | Simvastatin 60 mg |  |
|-----------------------------|-----------------|-------------------|-------------------|--|
| Subject group type          | Reporting group | Reporting group   | Reporting group   |  |
| Number of subjects analysed | 99              | 32                | 139               |  |
| Units: Artificial Units     |                 |                   |                   |  |
| number (not applicable)     | 99              | 32                | 139               |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in ADAS-Cog and FCSRT score

|  |                                    |
|--|------------------------------------|
| End point title  | Change in ADAS-Cog and FCSRT score |
| End point description:<br>Cognitive status, as assessed by the ADAS-cog test series and the Free and Cued Selective Reminding test (FCSRT). The FCSRT was divided into FCSRT 'Freie Wiedergabe' and 'Summe Wiedergabe'. For 'FCSRT Freie Wiedergabe': here we used the three fcsrt scores: fcsrt4, fcsrt7 and fcsrt10 and calculated the sum. For 'FCSRT Summe Wiedergabe': here we used the three fcsrt scores: fcsrt6, fcsrt9 and fcsrt12 and calculated the sum.<br><br>Instead of considering each visit separately, we generate a longitudinal visualization of the delta-values of the different cognitive scores. The corresponding plots are shown in the added Figures. Also attached is the data for these figures in form of excel documents. |                                    |
| End point type   | Secondary                          |
| End point timeframe:<br>3 years  |                                    |

| End point values            | Placebo         | Simvastatin 20 mg | Simvastatin 60 mg |  |
|-----------------------------|-----------------|-------------------|-------------------|--|
| Subject group type          | Reporting group | Reporting group   | Reporting group   |  |
| Number of subjects analysed | 99              | 32                | 139               |  |
| Units: Artificial Units     |                 |                   |                   |  |
| number (not applicable)     | 99              | 32                | 139               |  |

|                                   |  |
|-----------------------------------|--|
| <b>Attachments (see zip file)</b> | Change in ADAS-Cog and FCSRT score/First secondary |
|-----------------------------------|--|

- |   |
|---|
| <ol style="list-style-type: none"><li>1. Secondary Endpoint Change in ADAS-Cog.xlsx</li><li>1. Secondary Endpoint Change in FCSRT - Freie Wiedergabe.</li><li>1. Secondary Endpoint Change in FCSRT - Summe Wiedergabe.</li></ol> |
|---|

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

overall period

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |     |
|-----------------|-----|
| Dictionary name | own |
|-----------------|-----|

|                    |   |
|--------------------|---|
| Dictionary version | 1 |
|--------------------|---|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Simvastatin 20 mg |
|-----------------------|-------------------|

Reporting group description: -

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Simvastatin 60 mg |
|-----------------------|-------------------|

Reporting group description: -

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events  | Simvastatin 20 mg | Simvastatin 60 mg | Placebo          |
|---|-------------------|-------------------|------------------|
| Total subjects affected by serious adverse events                   |                   |                   |                  |
| subjects affected / exposed   | 4 / 32 (12.50%)   | 42 / 139 (30.22%) | 40 / 99 (40.40%) |
| number of deaths (all causes)                                       | 0                 | 1                 | 1                |
| number of deaths resulting from adverse events                      | 0                 | 1                 | 1                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |                  |
| deterioration in health due to cancer, diverse                      |                   |                   |                  |
| subjects affected / exposed   | 0 / 32 (0.00%)    | 7 / 139 (5.04%)   | 2 / 99 (2.02%)   |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 9             | 0 / 2            |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             | 1 / 1            |
| Injury, poisoning and procedural complications                      |                   |                   |                  |
| Fracture after fall event   |                   |                   |                  |
| subjects affected / exposed   | 1 / 32 (3.13%)    | 7 / 139 (5.04%)   | 4 / 99 (4.04%)   |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 7             | 0 / 4            |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             | 0 / 0            |
| General disorders and administration site conditions                |                   |                   |                  |
| Surgery, diverse reasons  |                   |                   |                  |
| subjects affected / exposed   | 0 / 32 (0.00%)    | 14 / 139 (10.07%) | 10 / 99 (10.10%) |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 14            | 0 / 13           |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             | 0 / 0            |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| Psychiatric disorders                           |                |                 |                |
| Depression                                      |                |                 |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 139 (0.00%) | 2 / 99 (2.02%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 4          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Infections and infestations                     |                |                 |                |
| Urinary tract disorder                          |                |                 |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 139 (0.00%) | 0 / 99 (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          |
| Respiratory (lung embolism/ Bronchitis)         |                |                 |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 139 (0.00%) | 3 / 99 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                     | Simvastatin 20 mg | Simvastatin 60 mg | Placebo          |
|---|-------------------|-------------------|------------------|
| Total subjects affected by non-serious adverse events |                   |                   |                  |
| subjects affected / exposed                           | 9 / 32 (28.13%)   | 67 / 139 (48.20%) | 46 / 99 (46.46%) |
| Injury, poisoning and procedural complications        |                   |                   |                  |
| Fracture, diverse                                     |                   |                   |                  |
| subjects affected / exposed                           | 2 / 32 (6.25%)    | 7 / 139 (5.04%)   | 9 / 99 (9.09%)   |
| occurrences (all)                                     | 2                 | 8                 | 11               |
| Nervous system disorders                              |                   |                   |                  |
| Headache  |                   |                   |                  |
| subjects affected / exposed                           | 3 / 32 (9.38%)    | 8 / 139 (5.76%)   | 6 / 99 (6.06%)   |
| occurrences (all)                                     | 5                 | 21                | 9                |
| Musculoskeletal and connective tissue disorders       |                   |                   |                  |
| Muscle and skeletal discomfort                        |                   |                   |                  |
| subjects affected / exposed                           | 4 / 32 (12.50%)   | 32 / 139 (23.02%) | 17 / 99 (17.17%) |
| occurrences (all)                                     | 8                 | 42                | 24               |
| Back pain   |                   |                   |                  |
| subjects affected / exposed                           | 1 / 32 (3.13%)    | 10 / 139 (7.19%)  | 9 / 99 (9.09%)   |
| occurrences (all)                                     | 1                 | 14                | 15               |

|                             |                |                   |                  |
|-----------------------------|----------------|-------------------|------------------|
| Infections and infestations |                |                   |                  |
| flu-like infect             |                |                   |                  |
| subjects affected / exposed | 2 / 32 (6.25%) | 22 / 139 (15.83%) | 20 / 99 (20.20%) |
| occurrences (all)           | 2              | 34                | 22               |
| Bronchitis                  |                |                   |                  |
| subjects affected / exposed | 0 / 32 (0.00%) | 11 / 139 (7.91%)  | 5 / 99 (5.05%)   |
| occurrences (all)           | 0              | 12                | 6                |
| urinary tract               |                |                   |                  |
| subjects affected / exposed | 2 / 32 (6.25%) | 4 / 139 (2.88%)   | 2 / 99 (2.02%)   |
| occurrences (all)           | 2              | 4                 | 2                |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment  |
|---------------|--|
| 28 March 2014 | <p>Since the SIMaMCI study started in 2008, the prescription of cholesterol lowering drugs, especially statins has increased substantially in Germany (plus 184% between 2001 and 2011). It was estimated that at that time about two-third up to three quarter of MCI patients visiting memory clinics already receive lipid lowering agents (LLA) or have taken LLA at least for a short period of time (for example until nutritional changes were successfully implemented).</p> <p>In conclusion from reviewing the literature and from discussions with the members of the DSMB and steering committee it was justified to assume that a pretreatment with statins, equivalent to 20 mg simvastatin, not longer than two years in total before entering the clinical trial can be regarded as comparable to non-treatment with respect to the primary and secondary outcome variables in the SIMaMCI trial.</p> <p>A second topic of the implemented changes in the trial design of the SIMaMCI study reflects a general trend in clinical trials in AD and its preclinical forms: While so far the time to conversion was used as primary endpoint (categorical variable) it was at that time widely recommended to use the CDR-SOB (sum of boxes) instead. Compared to the global CDR score, the CDR-SOB is a more sensitive measure, which allows the analysis of the primary endpoint already after a treatment period of 24 months. To further enhance the significance of the study a flexible treatment duration was initiated: minimal treatment time per patient was 24 months with a follow-up time of additional two years to be able to collect data also for the secondary endpoint the CDR global score.</p> |
| 24 May 2019   | <p>The cohort of the SIMaMCI-study is well phenotyped/characterized by the screening- and baseline-assessments. This is even true for participants, that dropped out. This addendum for Long-Term Follow-Up aims to follow up all participants, that consent in the assessment, in the long-term. Participants were assessed by a single interview via phone. By that, the initial etiological characterization (amnestic MCI with high risk of an early stage of Alzheimer's disease) was validated, as in this case significant deterioration were expected in the long-term. This validation of the initial characterization of the participants had the goal to strengthen the scientific value of the SIMaMCI-study.</p> <p>This amendment had no impact on the study-treatment nor the duration of the study-treatment. The interview will be performed after the end of treatment. All interviews will be performed before the date of the last patient out.</p>  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The result for the endpoints four to seven are missing since we have not finished analysing the data for these points. We will provide them once our analysis is finished regarding these end points.

Notes: