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 - Unversitätsmedizin Berlin Hochschulambulanz für Psychiatrie und Psychotherapie, 0049 030 450 517 685,
Scientific contact	Klinik für Psychiatrie, AG Peters, Campus Benjamin Franklin, Charité - Unversitätsmedizin 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
Arm title	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 capsual, 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.

Arm title	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 capsual, 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 surpress 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.

Arm title	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 surpress 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.

Number of subjects in period 1	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: Placebo	
Reporting group title	Simvastatin 20 mg
Reporting group description: Threatment medication of 20 mg Simvastatin	
Reporting group title	Simvastatin 60 mg
Reporting group description: Threatment medication of 60 mg Simvastatin	

Primary: Change in CDR-SOB

End point title	Change in CDR-SOB
End point description: 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 signicant difference for any of the groups. The highest difference is received comparing placebo with Simvastatin 20 mg.	
End point type	Primary
End point timeframe: 24 months but we also looked in changes during the hole 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: Artifical Number				
number (not applicable)	99	32	139	

Attachments (see zip file)	Change in CDR-SOB/Primary Endpoint.pdf Primary Endpoint Change in CDR SOB - Results.xlsx

Statistical analyses

Statistical analysis title	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

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 signicant 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: Artifical Units				
number (not applicable)	99	32	139	

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

Statistical analyses

No statistical analyses for this end point

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: Artifical Units				
number (not applicable)	99	32	139	

Attachments (see zip file)	Change in ADCS-ADL score/3 secondary Endpoint - Change in 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: Artifical 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 phosphorylized TAU Proteins and measures of cerebral cholesterol metabolites

End point title	Change in CSF and blood measures of beta-amyloid peptides, total and phosphorylized TAU Proteins and measures of cerebral cholesterol metabolites

End point description:

As surrogate markers CSF concentrations of cholesterol metabolites, β-amyloid peptides and TAU proteins will be determined.

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: Artifical 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:

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:

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: Artifical 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:

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:

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: Artifical 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:

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.

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:

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: Artifical Units				
number (not applicable)	99	32	139	

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

1. Secondary Endpoint Change in ADAS-Cog.xlsx
1. Secondary Endpoint Change in FCSRT - Freie Wiedergabe.
1. Secondary Endpoint Change in FCSRT - Summe Wiedergabe.

Statistical analyses

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 %

Non-serious adverse events	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	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). 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. 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.
24 May 2019	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. 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.

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: