Clinical trial results:
Simvastatin addition to improve symptoms, cognition and metabolic syndrome in patients with recent-onset schizophrenia.

Summary

EudraCT number	2013-000834-36
Trial protocol	NL
Global end of trial date	19 December 2019

Results information

Result version number	v1 (current)
This version publication date	03 August 2022
First version publication date	03 August 2022
Summary attachment (see zip file)	copy of medical journal article (sbab010.pdf)

Trial information

Trial identification

Sponsor protocol code	43806

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	ClinicalTrials.gov: NCT01999309

Notes:

Sponsors

Sponsor organisation name	University Medical Center Utrecht
Sponsor organisation address	Heidelberglaan 100, Utrecht, Netherlands,
Public contact	S.S. Gangadin, University Medical Center Utrecht, +88 887556366, S.S.Gangadin@umcutrecht.nl
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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	10 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2019
Global end of trial reached?	Yes
Global end of trial date	19 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to investigate the proposed beneficial effect of simvastatin as compared to placebo when given in addition to antipsychotic medication on symptom severity as measured with the Positive and Negative Syndrome Scale (PANSS).

Protection of trial subjects:

Patiants were thorougly screened, patients with hypercholesterolemia were excluded
Assessments were kept to a minimum
Blood levels were checked every visit by an independent physician to ensure safety
Most common side effects of simvastatin were assessed systematically at every visit

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 119
Worldwide total number of subjects	119
EEA total number of subjects	119

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)	119
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from Dutch inpatient and outpatient settings

Pre-assignment

Screening details:

2.3. Inclusion criteria
1. A DSM-IV-R diagnosis of: 295.x (schizophrenia, schizophreniform disorder, or schizoaffective disorder) or 298.9 (psychosis NOS)
2. Onset of first psychosis no longer than 3 years ago
3. Age between 18 and 50 years
4. Written informed consent is obtained.
5. Female patients of childbearing potential nee

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Simvastatin

Arm description:

Simvastatin 40mg daily

Arm type	Experimental
Investigational medicinal product name	Simvastatin 40mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

40mg, one tablet daily

Arm title	placebo

Arm description:

placebo pill identical in shape, color and smell

Arm type	Placebo
Investigational medicinal product name	Placebo Simvastatin 40mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

40mg, one tablet daily

Number of subjects in period 1	Simvastatin	placebo
Started	61	58
Completed	47	43
Not completed	14	15
Adverse event, non-fatal	6	4
Practical reasons	1	1
Refusal to continue	7	8
Lost to follow-up	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Simvastatin
Reporting group description:	
Simvastatin 40mg daily	
Reporting group title	placebo
Reporting group description:	
placebo pill identical in shape, color and smell	

Reporting group values	Simvastatin	placebo	Total
Number of subjects	61	58	119
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	61	58	119
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	26.4	28.0	
standard deviation	± 5.8	± 7.9	-
Gender categorical			
Units: Subjects			
Female	14	13	27
Male	47	45	92
Metabolic syndrome			
Assessed as defined by the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLB; [17]), by measuring weight, height, blood pressure, waist circumference, and body mass index (BMI).			
Units: Subjects			
yes	14	16	30
no	47	42	89
PANSS total			
assessed with Positive and Negative syndrome scale			
Units: scores			
arithmetic mean	58.9	56.8	
standard deviation	± 13.0	± 15.0	-
BACS total			
cognition assessed with Brief Assessment of Cognition in Schizophrenia			
Units: standardised units			
arithmetic mean	-0.7	-0.8	
standard deviation	± 0.8	± 0.7	-

End points

End points reporting groups	
Reporting group title	Simvastatin
Reporting group description: Simvastatin 40mg daily	
Reporting group title	placebo
Reporting group description: placebo pill identical in shape, color and smell	

Primary: PANSS total score	
End point title	PANSS total score
End point description: Schizophrenia symptom severity was evaluated with the Positive and Negative Syndrome Scale (=PANSS total score). reported values are changes from baseline	
End point type	Primary
End point timeframe: 12 months post-baseline	

End point values	Simvastatin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	43		
Units: scores				
arithmetic mean (standard error)	54.7 (± 1.5)	52.9 (± 1.7)		

Statistical analyses

Statistical analysis title	Primary endpoint PANSS
Statistical analysis description: Linear mixed models for repeated measurements. To model the effect of simvastatin, we included time point, treatment, sex and study site as fixed factors, age and baseline scores as covariates and subject as random intercept factor. To evaluate whether group differences varied over time, we also assessed the time*treatment interaction effect. When significant, group differences were compared at the individual time points.	
Comparison groups	placebo v Simvastatin
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)

Primary: BACS total score

End point title	BACS total score

End point description:

Neurocognitive functioning will be assessed with the Brief Assessment of Cognition in Schizophrenia (BACS; [22]), including the following tests:
1.Verbal memory: List Learning
2.Working memory: Digit Sequencing Task
3.Motor speed: Token Motor Task
4.Verbal fluency: Category Instances
5.Verbal fluency: Controlled Oral Word Association Test
6.Attention and speed of information processing: Symbol Coding
7.Executive functions: Tower of London

End point type	Primary

End point timeframe:

12 months post-baseline

End point values	Simvastatin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	43		
Units: standardized units				
arithmetic mean (standard error)	-0.6 (± 0.4)	-0.6 (± 0.5)		

Statistical analyses

Statistical analysis title	Primary endpoint BACS

Statistical analysis description:

Analysis of covariance
(ANCOVA) was applied for group differences in cognitive
performance at 6 and 12 months of treatment,
including baseline score as a covariate. BACS total composite
score was calculated by converting raw test scores
of the subtasks into z-scores and averaging these standardized
scores.

Comparison groups	Simvastatin v placebo
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.55
Method	ANCOVA
Parameter estimate	Mean difference (final values)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 28-11-2013 - 19-12-2019 (treatment period only)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20
Reporting groups	
Reporting group title	Simvastatin
Reporting group description: Simvastatin 40mg daily	
Reporting group title	placebo
Reporting group description: placebo pill identical in shape, color and smell	

Serious adverse events	Simvastatin	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 61 (6.56%)	12 / 58 (20.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Psychiatric disorders			
Hospital admission for psychotic relapse			
subjects affected / exposed	2 / 61 (3.28%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hospital admission for other psychiatric conditions	Additional description: admissions for: anxiety, depression, substance abuse, suicidal behaviour, agression		
subjects affected / exposed	4 / 61 (6.56%)	11 / 58 (18.97%)	
occurrences causally related to treatment / all	0 / 4	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Simvastatin	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 61 (93.44%)	50 / 58 (86.21%)	
Vascular disorders			
Dizziness			
subjects affected / exposed	2 / 61 (3.28%)	7 / 58 (12.07%)	
occurrences (all)	3	7	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 61 (13.11%)	6 / 58 (10.34%)	
occurrences (all)	8	6	
Sleep deficit	Additional description: Sleep disturbance		
subjects affected / exposed	5 / 61 (8.20%)	7 / 58 (12.07%)	
occurrences (all)	5	7	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	11 / 61 (18.03%)	10 / 58 (17.24%)	
occurrences (all)	25	15	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 61 (3.28%)	4 / 58 (6.90%)	
occurrences (all)	2	5	
Dyspepsia			
subjects affected / exposed	5 / 61 (8.20%)	3 / 58 (5.17%)	
occurrences (all)	6	3	
Nausea			
subjects affected / exposed	4 / 61 (6.56%)	9 / 58 (15.52%)	
occurrences (all)	6	12	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 61 (3.28%)	5 / 58 (8.62%)	
occurrences (all)	2	5	
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	4 / 61 (6.56%)	7 / 58 (12.07%)	
occurrences (all)	4	7	
Musculoskeletal and connective tissue disorders			

Musculoskeletal pain			
subjects affected / exposed	10 / 61 (16.39%)	3 / 58 (5.17%)	
occurrences (all)	13	4	
Myalgia			
subjects affected / exposed	13 / 61 (21.31%)	13 / 58 (22.41%)	
occurrences (all)	13	13	
Infections and infestations			
Influenza			
subjects affected / exposed	12 / 61 (19.67%)	12 / 58 (20.69%)	
occurrences (all)	14	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 June 2014	Amendment 1, June 2014 - Specification of exclusion due to elevated levels of creatine-kinase (i.e. elevated levels had to co-occur with previously experienced muscle toxicity or familial risk of muscular disorders). - Changes in patient information and informed consent o Addition of an instructional movie clip explaining the involvement of the immune system in psychosis o Storage of blood samples in the UMC Utrecht Biobank - Addition of outcome measures o Magnetic Resonance Imaging scans o Childhood Trauma Questionnaire o Blood samples o Movement disorders (SHRS and BARS) - Additions of study procedures o Urinary pregnancy test at screening
01 October 2014	Amendment 2, October 2014 - Addition of the University Medical Center Groningen as a study site
01 November 2014	Amendment 3, November 2014 - Change in study medication o Qualitative composition of the pills was not different from previous batch. The following batches will have a longer shelf life and a slightly different appearance. Placebo appearance was adjusted accordingly.
01 April 2015	Amendment 4, April 2015 - Changes in recruitment process o Via Utrecht Pharmacy Practice Network for Education Research o Via several mental health care organisations (i.e. GGZ-NHN, GGZ Ingeest, Altrecht GGZ, and Arkin/AMC).
01 April 2017	Amendment 5, April 2017 - Change in total number of subjects (new target: 150). o Change was made as a result of interim analyses and adjusted power calculations - Changes in patient information and informed consent o Voluntary option for sharing data with other research groups within the UMC Utrecht o Voluntary option for sharing data and material with other research groups outside the UMC Utrecht, specifically abroad. - Changes in recruitment process o Via several mental health care organisations (i.e. Reinier van Arkel, GGZ Centraal).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported