



Clinical trial results:

Simvastatin add-on to Escitalopram in patients with comorbid obesity and major depression: A multicenter, randomized, double-blind, placebo-controlled trial

Summary

EudraCT number	2018-002947-27
Trial protocol	DE
Global end of trial date	06 June 2024

Results information

Result version number	v1 (current)
This version publication date	23 August 2025
First version publication date	23 August 2025

Trial information

Trial identification

Sponsor protocol code	SIMCODE
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04301271
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité - Universitätsmedizin Berlin
Sponsor organisation address	Chariteplatz 1, Berlin, Germany, 10117
Public contact	Klinik für Psychiatrie und Psychotherapie Prof. Dr. Christian Otte, Charité – Universitätsmedizin Berlin, +49 30450 517531, simcode-studie@charite.de
Scientific contact	Klinik für Psychiatrie und Psychotherapie Prof. Dr. Christian Otte, Charité – Universitätsmedizin Berlin, +49 30450 517531, simcode-studie@charite.de

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	24 July 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 June 2024
Global end of trial reached?	Yes
Global end of trial date	06 June 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To examine whether add-on 40 mg/d Simvastatin to standard antidepressant medication (Escitalopram 20 mg/d) improves depression to a greater extent than adjunct placebo in patients with major depression and comorbid obesity

Protection of trial subjects:

The conduct of this study met all legal and regulatory current requirements (current ICH-GCP-guidelines) and in accordance with ethical principles of the Declaration of Helsinki.

Background therapy:

Major depressive disorder (MDD) and obesity are both linked to a higher risk of cardiovascular disease and stroke, further increasing their public health and economic impact. Importantly, MDD and obesity frequently co-occur and the presence of one condition increases the risk for developing the other. Statins (3-hydroxy-3-methylglutaryl Co-A reductase inhibitors) are among the most prescribed medications worldwide with well-established safety and efficacy. Recent guidelines recommend use of statins in primary prevention of cardiovascular disease, which has been linked to both MDD and obesity. However, no randomized controlled study so far has tested the antidepressive potential of statins in patients with MDD and comorbid obesity. Importantly, this is a difficult-to-treat population that often exhibits a chronic course of MDD and treatment resistance.

Evidence for comparator: -

Actual start date of recruitment	02 March 2020
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	Germany: 160
Worldwide total number of subjects	160
EEA total number of subjects	160

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)	160
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 9 study center in Germany between 05/09/2020 and 05/06/2024.
Recruitment start / start of study: (first patient first visit) Q1 2020 – postponed due to COVID-19 pandemic to Q3 2020

Pre-assignment

Screening details:

211 have been screened according the inclusion and exclusion criteria and 161 patients with comorbid obesity (body mass index ≥ 30) and major depression have been randomized.¹ Excluded after randomization because of consent withdrawn.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Simvastatin + Escitalopram

Arm description:

Simvastatin is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, Simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β -hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.
Simvastatin belongs to the statin class of medications, which are used to lower the risk of cardiovascular disease and manage abnormal lipid levels by inhibiting the endogenous production of cholesterol in the liver.

Arm type	Experimental
Investigational medicinal product name	Simvastatin
Investigational medicinal product code	C10AA01
Other name	CAS 79902-63-9, SimvaHexal, MAN 52531.04.00
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Fixed dose 40 mg/d without adjustment, orally once daily at bedtime over 12 weeks. It was be provided as add-on medication to standard antidepressant treatment [Escitalopram (fixed dose 10 mg/d week 1 - 2 and 20 mg/d week 3 - 12)].

Investigational medicinal product name	Escitalopram
Investigational medicinal product code	N06AB10
Other name	CAS 219861-08-2, CIPRALEX, MAN 55880.03.00 (08.April 2003)
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

placebo will be provided as add-on medication to standard antidepressant treatment with Escitalopram. Fixed dose of Escitalopram 10 mg/d in first two weeks, then increase to 20 mg/d oral film-coated tablets.

Arm title	Placebo + Escitalopram
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Arm description:

Escitalopram is a selective inhibitor of serotonin (5-HT) re-uptake with high affinity for the primary binding site. It also binds to an allosteric site on the serotonin transporter, with a 1000 fold lower affinity. Escitalopram has no or low affinity for a number of receptors including 5-HT_{1A}, 5-HT₂, DA D₁ and D₂ receptors, α ₁-, α ₂-, β -adrenoceptors, histamine H₁, muscarine cholinergic, benzodiazepine, and opioid receptors.

Arm type	Placebo
Investigational medicinal product name	Escitalopram
Investigational medicinal product code	N06AB10
Other name	CAS 219861-08-2
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Fixed dose of Escitalopram 10 mg/d in first two weeks, then increase to 20 mg/d oral film-coated tablets.

Tablet core: Microcrystalline cellulose, Colloidal anhydrous silica, Talc, Croscarmellose sodium, Magnesium stearate.

Film coating: Hypromellose 6cP (E464), Titanium dioxide (E171), Macrogol 3000

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Based on the randomization codes, the pharmacy centrally provided for each center sequentially numbered, tamper-proof containers, which are equal in weight and similar in appearance containing IMP or placebo.

Tablet core: Microcrystalline cellulose, Colloidal anhydrous silica, Talc, Croscarmellose sodium, Magnesium stearate.

Film coating: Hypromellose 6cP (E464), Titanium dioxide (E171), Macrogol 3000

Number of subjects in period 1	Simvastatin + Escitalopram	Placebo + Escitalopram
Started	81	79
Completed	81	79

Baseline characteristics

Reporting groups

Reporting group title	Simvastatin + Escitalopram
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Reporting group description:

Simvastatin is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, Simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β -hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin belongs to the statin class of medications, which are used to lower the risk of cardiovascular disease and manage abnormal lipid levels by inhibiting the endogenous production of cholesterol in the liver.

Reporting group title	Placebo + Escitalopram
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Reporting group description:

Escitalopram is a selective inhibitor of serotonin (5-HT) re-uptake with high affinity for the primary binding site. It also binds to an allosteric site on the serotonin transporter, with a 1000 fold lower affinity. Escitalopram has no or low affinity for a number of receptors including 5-HT_{1A}, 5-HT₂, DA D₁ and D₂ receptors, α ₁-, α ₂-, β -adrenoceptors, histamine H₁, muscarine cholinergic, benzodiazepine, and opioid receptors.

Reporting group values	Simvastatin + Escitalopram	Placebo + Escitalopram	Total
Number of subjects	81	79	160
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)	81	79	160
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	39	39	
full range (min-max)	20 to 64	19 to 63	-
Gender categorical			
Units: Subjects			
Female	63	63	126
Male	18	16	34
Chronic depression			
Chronic depression was defined as duration of current depressive episode for 104 weeks or longer.			
Units: Subjects			
no	64	56	120
yes	12	15	27
no records	5	8	13
Hypertension			
Units: Subjects			

no	24	19	43
yes	57	60	117
LDL >100mg/dL			
Units: Subjects			
no	17	18	35
yes	62	60	122
no records	2	1	3
Body Mass Index			
Body mass index is calculated as weight in kilograms divided by height in meters squared.			
Units: score			
median	38.7	37.6	
inter-quartile range (Q1-Q3)	33.5 to 43.1	34.7 to 41.4	-
MADRS			
MADRS = Montgomery-Åsberg DepressionvRating Scale			
Units: score			
arithmetic mean	25.8	25.2	
standard deviation	± 4.8	± 5.2	-
Duration of current episode			
Units: week			
median	27	40	
inter-quartile range (Q1-Q3)	16 to 53	20 to 82	-

End points

End points reporting groups

Reporting group title	Simvastatin + Escitalopram
Reporting group description: Simvastatin is a lipid-lowering agent that is derived synthetically from a fermentation product of <i>Aspergillus terreus</i> . After oral ingestion, Simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β -hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol. Simvastatin belongs to the statin class of medications, which are used to lower the risk of cardiovascular disease and manage abnormal lipid levels by inhibiting the endogenous production of cholesterol in the liver.	
Reporting group title	Placebo + Escitalopram
Reporting group description: Escitalopram is a selective inhibitor of serotonin (5-HT) re-uptake with high affinity for the primary binding site. It also binds to an allosteric site on the serotonin transporter, with a 1000 fold lower affinity. Escitalopram has no or low affinity for a number of receptors including 5-HT _{1A} , 5-HT ₂ , DA D ₁ and D ₂ receptors, α ₁ -, α ₂ -, β -adrenoceptors, histamine H ₁ , muscarine cholinergic, benzodiazepine, and opioid receptors.	

Primary: Change score in MADRS

End point title	Change score in MADRS
End point description: MADRS (Montgomery-Asberg-Depression Rating Scale) The MADRS is a rating scale to measure depression severity. Each MADRS item is rated on a 0 to 6 scale. Total score range from 0-60, where higher MADRS scores indicate higher levels of depressive symptoms.	
End point type	Primary
End point timeframe: 12 weeks	

End point values	Simvastatin + Escitalopram	Placebo + Escitalopram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	79		
Units: score				
arithmetic mean (standard deviation)	12 ($\pm$ 8)	12 ($\pm$ 9)		

Statistical analyses

Statistical analysis title	Sensitivity analyses MADRS
Comparison groups	Simvastatin + Escitalopram v Placebo + Escitalopram

Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.71
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.08
upper limit	3.02
Variability estimate	Standard deviation

Secondary: change LDL

End point title	change LDL
End point description:	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Simvastatin + Escitalopram	Placebo + Escitalopram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	79		
Units: mg/dl				
arithmetic mean (standard deviation)	87 (± 35)	120 (± 31)		

Statistical analyses

Statistical analysis title	exploratory analysis
Comparison groups	Simvastatin + Escitalopram v Placebo + Escitalopram
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.14

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.39
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

overall study

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Placebo + Escitalopram
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Reporting group description: -

Reporting group title	Simvastatin + Escitalopram
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Reporting group description: -

Serious adverse events	Placebo + Escitalopram	Simvastatin + Escitalopram	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 79 (1.27%)	1 / 81 (1.23%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Surgical and medical procedures - Other, specify	Additional description: Curretage		
subjects affected / exposed	1 / 79 (1.27%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy, puerperium and perinatal conditions - Other, specify			
subjects affected / exposed	1 / 79 (1.27%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy loss			
subjects affected / exposed	1 / 79 (1.27%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			

subjects affected / exposed	0 / 79 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Placebo + Escitalopram	Simvastatin + Escitalopram	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 79 (54.43%)	62 / 81 (76.54%)	
General disorders and administration site conditions			
polydipsia			
subjects affected / exposed	2 / 79 (2.53%)	1 / 81 (1.23%)	
occurrences (all)	2	1	
Flu like symptoms			
subjects affected / exposed	9 / 79 (11.39%)	7 / 81 (8.64%)	
occurrences (all)	9	8	
Fatigue/ Malaise			
subjects affected / exposed	10 / 79 (12.66%)	10 / 81 (12.35%)	
occurrences (all)	10	11	
Reproductive system and breast disorders			
sexual dysfunction			
subjects affected / exposed	2 / 79 (2.53%)	7 / 81 (8.64%)	
occurrences (all)	2	7	
Irregular menstruation			
subjects affected / exposed	1 / 79 (1.27%)	2 / 81 (2.47%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 79 (2.53%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Libido decreased			
subjects affected / exposed	2 / 79 (2.53%)	2 / 81 (2.47%)	
occurrences (all)	2	3	
Insomnia			

subjects affected / exposed occurrences (all)	6 / 79 (7.59%) 6	4 / 81 (4.94%) 4	
Restlessness subjects affected / exposed occurrences (all)	7 / 79 (8.86%) 8	6 / 81 (7.41%) 7	
Investigations CPK increased subjects affected / exposed occurrences (all)	7 / 79 (8.86%) 7	5 / 81 (6.17%) 5	
ALT /GPT increased subjects affected / exposed occurrences (all)	3 / 79 (3.80%) 3	2 / 81 (2.47%) 2	
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	0 / 79 (0.00%) 0	3 / 81 (3.70%) 3	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	20 / 79 (25.32%) 20	23 / 81 (28.40%) 23	
Migraine subjects affected / exposed occurrences (all)	0 / 79 (0.00%) 0	2 / 81 (2.47%) 2	
Restless legs syndrome subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2	0 / 81 (0.00%) 0	
Tremor subjects affected / exposed occurrences (all)	3 / 79 (3.80%) 3	2 / 81 (2.47%) 2	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	6 / 79 (7.59%) 6	10 / 81 (12.35%) 10	
Eye disorders Blurred vision subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2	1 / 81 (1.23%) 1	

Gastrointestinal disorders			
diarrhea			
subjects affected / exposed	9 / 79 (11.39%)	7 / 81 (8.64%)	
occurrences (all)	10	8	
Vomiting			
subjects affected / exposed	3 / 79 (3.80%)	5 / 81 (6.17%)	
occurrences (all)	3	5	
Gastrointestinal pain			
subjects affected / exposed	2 / 79 (2.53%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Dry mouth			
subjects affected / exposed	1 / 79 (1.27%)	3 / 81 (3.70%)	
occurrences (all)	1	3	
Nausea			
subjects affected / exposed	12 / 79 (15.19%)	17 / 81 (20.99%)	
occurrences (all)	12	17	
Constipation			
subjects affected / exposed	5 / 79 (6.33%)	1 / 81 (1.23%)	
occurrences (all)	5	1	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	7 / 79 (8.86%)	3 / 81 (3.70%)	
occurrences (all)	8	3	
Urticaria			
subjects affected / exposed	3 / 79 (3.80%)	1 / 81 (1.23%)	
occurrences (all)	3	1	
Musculoskeletal and connective tissue disorders			
muscle ache/neck pain			
subjects affected / exposed	4 / 79 (5.06%)	2 / 81 (2.47%)	
occurrences (all)	4	2	
back pain/ lumbago			
subjects affected / exposed	2 / 79 (2.53%)	3 / 81 (3.70%)	
occurrences (all)	2	3	
Infections and infestations			
COVID-19			

subjects affected / exposed	3 / 79 (3.80%)	1 / 81 (1.23%)	
occurrences (all)	3	1	
Upper respiratory tract infection	Additional description: Tonsillitis/Sinusitis		
subjects affected / exposed	2 / 79 (2.53%)	1 / 81 (1.23%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2021	update protocol Version 1.3. dated 26/05/2021 and PICF dated 11/05/2021; Change in inclusion criteria, change in cancellation criteria
06 December 2021	update Protokol Version 1.4 ,dated 24/09/2021 and PICF , dated 24/09/2021; Changes according to SmPC - SimvaHEXAL Information from May 2020

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported