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Simvastatin add-on to escitalopram in patients with comorbid obesity and major depression (SIMCODE): study protocol of a multicentre, randomised, double-blind, placebo-controlled trial

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ABSTRACT

Introduction Major depressive disorder (MDD) and obesity are both common disorders associated with significant burden of disease worldwide. Importantly, MDD and obesity often co-occur, with each disorder increasing the risk for developing the other by about 50%–60%. Statins are among the most prescribed medications with well-established safety and efficacy. Statins are recommended in primary prevention of cardiovascular disease, which has been linked to both MDD and obesity. Moreover, statins are promising candidates to treat MDD because a meta-analysis of pilot randomised controlled trials has found antidepressive effects of statins as adjunct therapy to antidepressants. However, no 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 is more likely to be treatment resistant. Thus, in this confirmatory randomised controlled trial, we will determine whether add-on simvastatin to standard antidepressant medication with escitalopram is more efficacious than add-on placebo over 12 weeks in 160 patients with MDD and comorbid obesity.

Methods and analysis This is a protocol for a randomised, placebo-controlled, double-blind multicentre trial with parallel-group design (phase II). One hundred and sixty patients with MDD and comorbid obesity will be randomised 1:1 to simvastatin or placebo as add-on to standard antidepressant medication with escitalopram. The primary outcome is change in the Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline to week 12. Secondary outcomes include MADRS response (defined as 50% MADRS score reduction from baseline), MADRS remission (defined as MADRS score <10), mean change in patients' self-reported Beck Depression Inventory (BDI-II) and mean change in high-density lipoprotein, low-density lipoprotein and total cholesterol from baseline to week 12.

Strengths and limitations of this study

- This is a confirmative randomised controlled trial to examine the antidepressive potential of simvastatin as add-on therapy in patients with major depressive disorder (MDD) and comorbid obesity.
- Importantly, depressed patients with obesity are a difficult-to-treat population that often exhibits a chronic course of MDD and treatment resistance.
- This trial is not designed to examine long-term effects of add-on statin therapy (beyond 12 weeks of follow-up).
- This trial is not powered to explore effects in subgroups (eg, patients with type 2 diabetes mellitus).

Ethics and dissemination This protocol has been approved by the ethics committee of the federal state of Berlin (Ethik-Kommission des Landes Berlin, reference: 19/0226—EK 11) and by the relevant federal authority (Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), reference: 4043387). Study findings will be published in peer-reviewed journals and will be presented at (inter)national conferences.

Trial registration numbers NCT04301271, DRKS00021119, EudraCT 2018-002947-27.

INTRODUCTION

Scientific background and study rationale

The WHO's global burden of disease (GBD) study demonstrated that of all diseases worldwide, major depressive disorder (MDD) is among the top five with regard to years lived with disability[1] and by far the leading cause of disability resulting from all psychiatric disorders.[2] The 12 months

prevalence of MDD in adults according to the World Mental Health Survey is approximately 6%, which is comparable to estimates from other (inter-)national surveys.[3] Mortality rates in MDD are twice as high as in the general population and translate to a reduced life expectancy of approximately 14.0 years in men and 10.1 years in women based on a cohort study of all Danish residents aged 15 or older.[4]

According to the GBD study, the overall prevalence of obesity in adults was 12.0% in 2015 and ranged from 1.6% in Vietnam to 34.9% in Egypt.[5] According to the latest global estimates of the WHO, 11% of adult men and 15% of adult women were obese in 2016 and the prevalence ranged from 29% among the Region of the Americas to 2% in some of the West African countries.[6] In the German adult population (age range: 18–79 years), the prevalence of obesity is 23.3% in men and 23.9% in women, respectively.[7] In adult patients with obesity, mortality rates are elevated (HR 1.64, CI 1.61 to 1.67) and they increase in relation to body mass index (BMI) as recently confirmed in a meta-analysis of 239 studies from four continents.[8] In the GBD study, obesity was estimated to cause 3.4 million deaths in the general population, and accounted for 3.9% of years of life lost, and 3.8% of disability-adjusted life years worldwide.[9]

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 by approx. 50%–60%.[10]

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are among the most prescribed medications worldwide with well-established safety and efficacy. Recent guidelines recommend the use of statins in primary prevention of cardiovascular disease,[11] which has been linked to both MDD and obesity. Moreover, statins are promising candidates to treat MDD. Evidence for antidepressive effects of statins has accumulated from four independent lines of research: animal studies,[12] meta-analysis of prospective cohort studies,[13] meta-analysis of pilot controlled trials[14] and a nationwide cohort study.[15] However, no randomised 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 is more likely to show treatment resistance to standard pharmacological therapy.[16 17] Depressed patients who are overweight or obese responded significantly slower to antidepressant treatment compared with normal-weight patients.[18] In a recent scoping review, excess body weight predicted non-response to treatment with antidepressants.[19] Given the enormous public health impact of MDD and obesity and given the evidence of antidepressive effects of statins, a controlled trial of adjunct statin treatment in comorbid patients appears warranted.

STUDY AIMS AND HYPOTHESIS

Primary

To examine whether add-on 40 mg/d simvastatin to standard antidepressant medication (escitalopram 20 mg/d) (SIM+ES) improves depression to a greater extent than adjunct placebo (PL+ES) in patients with MDD and comorbid obesity over a period of 12 weeks. We hypothesise that SIM+ES will improve depression to a greater extent than PL+ES in patients with comorbid obesity and major depression.

Secondary

To examine whether SIM+ES improves response rates, remission rates, self-reported depression, patients' impression of change, clinicians' impression of severity and change, quality of life, social functioning, lipid values and immune function and cellular metabolism to a greater extent than PL+ES in patients with major depression and comorbid obesity. We hypothesise that SIM+ES will improve (a) response rates and remission rates, (b) patients' impression of change, clinicians' impression of severity and improvement, quality of life, social functioning, self-report depression, (c) lipid values and (d) immune function and cellular metabolism to a greater extent over 12 weeks than PL+ES in patients with comorbid obesity and major depression.

METHODS

This protocol has been prepared in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement.[20] Please see online supplemental table 1 for the SPIRIT checklist.

Study design and sample

The study will include 160 patients divided into two treatment groups and recruited from several centres (public academic hospitals/departments) located in Germany. Group 1 will receive placebo add-on to escitalopram (PL+ES) and group 2 will receive simvastatin add-on to escitalopram (SIM+ES). For an overview of the study design, please see figure 1.

Patients will be recruited from depression and obesity outpatient clinics and inpatient wards from each study site. In addition, we will use existing and established networks of all sites within the psychiatric community to include depressed out-patients from general practitioners and psychiatrists. Thus, we will ensure high generalisability of our study population. There will be no specific sex distribution as no sex specific differences concerning efficacy and safety of simvastatin are expected. The first study sites have been initiated in March 2020 and the study is expected to end in January 2023.

Eligibility criteria and assessment

The main inclusion criteria for the SIMCODE trial are as follows: (i) written informed consent; (ii) major depressive episode according to DSM 5 (Diagnostic and Statistical Manual of Mental Disorders fifth Edition); (iii)

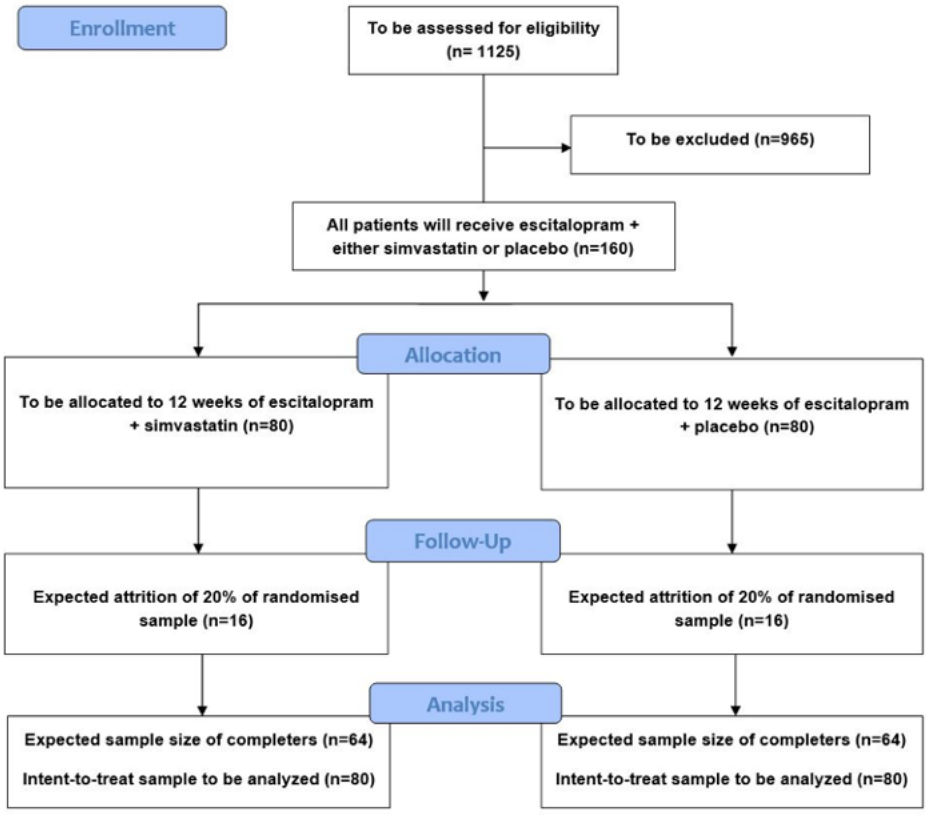

Figure 1 Study flow chart according to CONSORT. We assume that we need to screen n=1125 patients aged 18–65 with major depression according to Diagnostic and Statistical Manual of Mental Disorders five and obesity (body mass index ≥30) for eligibility at eight recruiting centres to randomise n=160 participants. The sample size and assumed dropout rate (20%) is conservatively based on three earlier pilot RCTs of add-on statin to SSRI treatment in depressed patients. CONSORT, Consolidated Standards of Reporting Trials; SSRI, selective serotonin reuptake inhibitors; RCT, randomised controlled trials.[23 31 32]

Montgomery-Åsberg Depression Rating Scale (MADRS) score ≥18; (iv) BMI ≥30; (v) age between 18 and 65 years (≥18 und≤65); (vi) in case of non-psychotropic medication: stable pharmacological medication for at least 14 days prior to study entry; (vii) no antidepressant intake during the last 7 days prior to study entry (discontinuation of effective medication to enable study participation is prohibited); (viii) no prior treatment with escitalopram in index episode; (ix) less than three trials with antidepressants in index episode; (x) no treatment with ketamine, electroconvulsive therapy (ECT) or other stimulatory treatments in index episode; (xi) none of the following disorders: schizophrenia, schizoaffective disorder and bipolar disorder. In addition, patients with any severe, unstable general medical condition or contraindications for simvastatin or escitalopram will not be included in the study.

Main exclusion criteria are as follows: (i) current use of statins; (ii) current use of antidepressants; (iii) acute suicidal tendencies (MADRS Item 10>4); (iv) pregnancy, breastfeeding or women with childbearing potential without acceptable form of contraception (defined as Pearl index <1); (v) current use of psychotropic medication (eg, antipsychotics, anticonvulsants, lithium or St. John's Wort) except for benzodiazepines, non-benzodiazepines and opiates (vi) clinically significant abnormalities in 12-lead ECG (eg, corrected Q–T interval prolongation ≥500 ms or increase ≥60 ms from baseline visit). In addition, there are several more exclusion criteria including medication that is contraindicated with simvastatin or escitalopram. Please see online supplemental table 2 for complete inclusion and exclusion criteria.

A screening visit will be carried out to establish eligibility and to obtain informed consent. After informed consent, we will assess the severity of depressive episode using MADRS, duration of the index episode, number of episodes, previous treatment as requested by the guideline of the European Medicines Agency on clinical trials in depression.[21] During the screening visit, several other procedures will be performed including a physical examination, Mini International Neuropsychiatric Interview (MINI; German Translation V.7.0.2),[22] measurement of body weight and height for determination of BMI, ECG and safety laboratory including pregnancy test for women.

To ensure that the study is conducted according to the study protocol, to current laws and to general guidelines, a training of all investigators/subinvestigators have been conducted prior to initiation. The trial will be initiated by the principal investigator (PI) team (CO, WRC) and a trial monitor at each site before patient enrolment at that site begins.

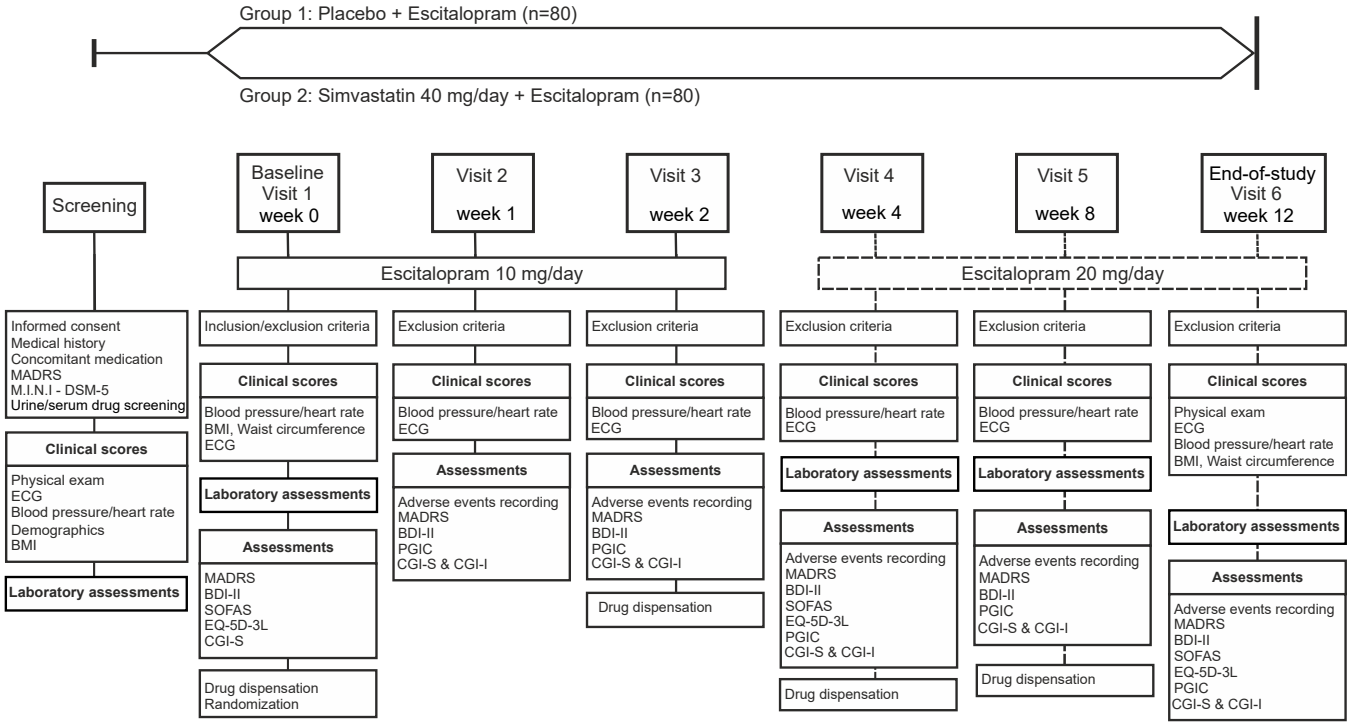

Figure 2 Scheme of intervention in SIMCODE study. Overview of design and procedures of the SIMCODE study. BDI-II, Beck-Depressions-Inventar II; BMI, body mass index; CGI-I, Clinicians' Global Impression of Improvement; CGI-S, Clinicians' Global Impression of Severity of illness; EQ-5D-3L, Generic Quality of Life Questionnaire; MADRS, Montgomery-Åsberg Depression Scale; MINI, Mini International Neuropsychiatric Interview; PGIC, Patient Global Impression of Change; SOFAS, Social and Occupational Functioning Assessment Scale.

Intervention

Each patient in this study will be treated with escitalopram, a well-established standard-antidepressant, which is readily available because it is commonly used as generic drug in Germany. Add-on placebo serves as the control condition for adjunct simvastatin (40 mg/d). Simvastatin and placebo will be provided by the pharmacy of the Charité—Universitätsmedizin Berlin and will be administered in a double-blind fashion. Escitalopram will be provided by the pharmacy of the Charité, stored and dispensed at each study site in a non-blinded fashion. Patients will receive simvastatin or placebo orally in a fixed dosage of 40 mg once a day at bedtime. Patients will receive 10 mg escitalopram orally in a fixed dosage of 10 mg once a day in the morning for the first 2 weeks, then increased to 20 mg once a day in the morning until the end of study. Drug dispensation will take place at baseline (visit 1), at visit 3 (only escitalopram), visit 4 and visit 5. See figure 2 for scheme of intervention.

Rationale for statin choice and dosage

Among the available stains, we decided to use simvastatin (SimvaHEXAL) in a dosage of 40 mg/d based on the following considerations: simvastatin was used in this dose in one of three randomised controlled trials (RCTs) showing evidence versus placebo as adjunct treatment to selective serotonin reuptake inhibitors (SSRIs);[23] it was superior to atorvastatin in depressed patients with heart disease;[24] it passes the blood–brain barrier[25] and it is available as generic drug (costs for 40 mg/d simvastatin: around 100 EUR per year). We decided against using a dose of 80 mg/d simvastatin due to the increased risk of muscle injury and the corresponding warning from the US Food and Drug Administration[26] (see *3.8 Safety*).

Rationale for antidepressant choice and dosage

All depressed patients enrolled in the trial will be continuously treated with a gold standard antidepressant (escitalopram) as described by the German National Disease Management Guideline ('Nationale Versorgungsleitlinie') for the treatment of MDD. For escitalopram, a dose–response relationship has been suggested. Especially for patients with severe depression, the high standard dose of 20 mg/d was shown to be superior compared with 10 mg/d.[27] A fixed-dose of 10 mg/d escitalopram for the entire study duration of 12 weeks would therefore not allow the optimal treatment for some patients. Thus, we consider this option ethically not justifiable. A dose increase from 10 to 20 mg/d based on individual patient response would however interfere with comparability of the SIM+ES group and PL+ES group, because a strong decrease in depressive symptoms in the SIM+ES group compared with PL+ES group could potentially be masked by a higher percentage of escitalopram dose escalation in the PL+ES group. Therefore, we will increase escitalopram to 20 mg/d after giving a low standard dose of 10 mg/d in the first 2 weeks. In case of adverse reactions

related to escitalopram, we will follow the instructions for dose adjustment described in *3.8 Safety*.

Patients are instructed to return unused medication and compliance will be determined by count of the remaining pills and patients will be considered compliant if they report taking more than 90% of their drug (as in previous studies with simvastatin in central nervous system diseases).[28 29]

Permitted comedications

Medication that is contraindicated with simvastatin, and escitalopram or concomitant treatment with antidepressants other than escitalopram will not be permitted (see inclusion/exclusion criteria in online supplemental table S2). In case of current treatment with antidepressants at study entry, a wash-out of prior antidepressants for at least seven drug-free days prior to inclusion may be permitted (see inclusion criteria in online supplemental table S2). However, discontinuation of effective medication to enable study participation is prohibited. Other psychotropic drugs (including antipsychotics, anticonvulsants, lithium or St. John's Wort) are not permitted during the study period with the following exceptions: (1) in case of sleep difficulties, benzodiazepine or nonbenzodiazepine hypnotics (eg, zolpidem, zopiclone) will be allowed on an 'as needed basis'; (2) in case of acute anxiety or agitation, a benzodiazepine (preferably lorazepam) may be prescribed not exceeding 3 mg/d (other benzodiazepines at the equivalent dosage), (3) opiates for pain relief (see exclusion criteria in online supplemental table S2). Any clinical exacerbation requiring a higher benzodiazepine regimen or prescription of antipsychotics ('rescue medication') will be considered as a serious adverse event (SAE) (see *3.8 Safety and* online supplemental material). In case of non-psychotropic medication, stable pharmacological medication for at least 14 days prior to study entry will be permitted. Patients with any changes in medication dose or frequency of therapy during the 14 days prior to study entry will not participate in the study (see inclusion criteria in online supplemental table S2). Concomitant use of statins will not be permitted (see exclusion criteria in online supplemental table S2).

Sample size calculation

So far, there are three small pilot RCTs in depressed patients (sample sizes ranging from n=48 to n=68) that have all found statistically significant beneficial effects of add-on statins versus placebo with large, clinically relevant effect sizes. A meta-analysis[14] of these trials has found a standardised mean difference between add-on statins and add-on placebo of −0.73 (95 % CI −1.04 to −0.42, p<0.001). However, it is well known that initial studies tend to overestimate the true effect size.[30] Therefore, we conservatively assume a standardised treatment difference (also known as Cohen's d) of 0.5, which is smaller than those reported by the three pilot RCTs.[23 31 32] Given a SD of 6–8 points on the MADRS, as commonly observed in RCTs in this population,[33–35] a standardised effect size of 0.5 translates into a mean difference of 3–4 points, which is considered clinically relevant because it is about twice as large as the minimal clinically important difference (MCID) of 1.6–1.9 points that has been reported for the MADRS.[36] Thus, a sample size of 64 patients per group results in a power of 80% for a comparison of the mean changes in MADRS score from baseline to week 12 between the two groups using a two-sample t-test at the usual two-sided level of 5%. As the analyses will be adjusted for baseline scores, the actual power is likely to be higher; this will be confirmed in a blinded sample size review once 50% of the patients have reached week 12.[37] Accounting for about 20% dropout, we aim to recruit 80 patients per group (ie, 160 patients in total). Based on sex-specific prevalence rates and recruitment in our earlier studies,[38 39] we expect that about two-thirds of the sample will be women. This will allow sex-specific analyses.

As the analyses will be adjusted for baseline scores, the actual power is likely to be higher than 80%. To confirm this in an interim analysis, a blinded sample size review will be carried out, once 50% of the patients have reached week 12. Based on blinded estimates of the mean square error and the dropout rate, the required sample size will be recalculated and the sample size will be adjusted up to a maximum total sample size of 240 patients, if necessary.[37]

Outcomes

As primary outcome variable, we will use the change in MADRS[40] score from baseline to week 12. As secondary outcome variables, we will use MADRS response (defined as 50% MADRS score reduction from baseline), MADRS remission (defined as MADRS score <10) and MADRS MCID. Also, we will assess as secondary outcome variables change scores in patients' self-reported Beck Depression Inventory (BDI-II) as well as the MCID according to BDI.[41] We will additionally determine the clinician's impression of the severity of illness (Clinical Global Impression scale—Severity of illness),[42] the clinician's impression whether and to what extent symptoms have improved (Clinical Global Impression scale—Improvement),[42] the patient's impression whether and to what extent symptoms have improved (Patients' Global Impression of Change Scale), social functioning (Social and Occupational Functioning Assessment Scale, SOFAS), quality of life (EuroQol-5 Dimensions-3 Levels Questionnaire), with a calculated MCID[43] and change scores in high-density lipoprotein, low-density lipoprotein and total cholesterol. At selected sites, additional blood samples for assessment of immune function and cellular metabolism will be obtained and analysed in an exploratory fashion. For the characteristics and definitions of primary and secondary endpoints, see table 1. The efficacy and other outcome assessments at screening, baseline and different follow-up visits are shown in table 2.

Randomisation and blinding

Subjects will be randomised 1:1 to simvastatin or placebo (SIM+ES vs PL+ES) based on a randomisation list provided

Table 1 Characteristics and definitions of primary and secondary endpoints

Outcome	Instrument	Rating	Domain	Exactly defined outcome	Variable
Primary	MADRS*†	Clinician-rated	Severity of depression	Mean change from baseline	Continuous
Secondary/efficacy (exploratory)	MADRS*†	Clinician-rated	Severity of depression	► Percentage response (>50% reduction from baseline) ► Percentage remission (MADRS score <10 post-treatment) ► Percentage minimal clinically important difference (MCID; change from baseline score >1.9)	Dichotomous
Secondary/efficacy (exploratory)	BDI-II†‡	Self-rated	Severity of depression	► Mean change from baseline ► Percentage MCID (>17.5% change from baseline)	Continuous dichotomous
Secondary exploratory	CGI-S†§	Clinician-rated	Severity of illness	Median change from baseline	Ordinal
Secondary exploratory	CGI-I†¶	Clinician-rated	Improvement/worsening of illness	Response defined as 'much improved' or 'very much improved' post-treatment	Dichotomous
Secondary exploratory	PGIC†**	Self-rated	Subjective improvement	Response defined as 'much improved' or 'very much improved' post-treatment	Dichotomous
Secondary exploratory	SOFAS†††	Clinician-rated	Social functioning	Mean change from baseline	Continuous
Secondary exploratory	EQ-5D-3L†‡‡	Self-rated	Quality of life	Mean change from baseline percentage MCID (change from baseline score >0.74)	Continuous dichotomous
Secondary exploratory	HDL, LDL, total cholesterol	Laboratory values	Metabolism	Mean change from baseline	Continuous
Secondary exploratory	Immune function and cellular metabolism	Laboratory values	Immune function	Mean change from baseline	Continuous

*The MADRS is a rating scale to measure depression severity. Each MADRS item is rated on a 0–6 scale. Total score ranges from 0 to 60, where higher MADRS scores indicate higher levels of depressive symptoms.
†This instrument has been validated in German.
‡The Beck Depression Inventory-II is a 21-item validated instrument for the self-report of depressive symptoms, with individual item scores summed to yield a total possible BDI score that ranges from 0 to 63. BDI scores from 0 to 13 suggest absent to minimal depressive symptoms, from 14 to 19 mild symptoms, from 20 to 28 moderate symptoms and from 29 to 63 severe symptoms.
§The CGI-S evaluates the severity of psychopathology on a scale of 0–7. Considering total clinical experience, a participant is assessed on severity of mental illness at the time of rating according to: 0=not assessed; 1=normal (not at all ill); 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients.
¶The CGI-I is a clinician-rated instrument to measure clinicians' change in overall status on a scale ranging from 1 (very much improved) to 7 (very much worse).
**The PGIC is a participant-rated instrument to measure participant's change in overall status on a scale ranging from 1 (very much improved) to 7 (very much worse).
††The SOFAS is a rating scale used to determine social functioning on a scale ranging from 0 to 100. A higher score represents better social and occupational functioning.
‡‡The EQ-5D-3L is a generic instrument of quality of life related to health. It contains five dimensions of health (mobility, personal care, daily activities, pain/discomfort and anxiety/depression) and each of them has three levels of seriousness (without problems, some problems or moderate problems and serious problems). The second part of the EQ-5D is a Visual Analogue Scale ranging from 0 (worse health status imaginable) to 100 (best imaginable health status). In it, the individual must mark the point in the vertical line that best reflects the assessment of their global health status today.
BDI-II, Beck-Depressions-Inventar II; BMI, body mass index; CGI-I, Clinicians' Global Impression of Improvement; CGI-S, Clinicians' Global Impression of Severity of illness; EQ-5D-3L, Generic Quality of Life Questionnaire; MADRS, Montgomery-Åsberg Depression Scale; MINI, Mini International Neuropsychiatric Interview; PGIC, Patient Global Impression of Change; SOFAS, Social and Occupational Functioning Assessment Scale.

Table 2 Visit and documentation schedule

Assessments	Screening	Baseline (visit 1) week 0	Visit 2 week 1	Visit 3 week 2	Visit 4 week 4	Visit 5 week 8	End-of-study (visit 6) week 12
Screening and consent							
Informed consent	X						
Inclusion criteria		X					
Exclusion criteria		X	X	X	X	X	X
Medical history	X						
Treatment status		X					
MINI—DSM-5	X						
Urine/serum drug screening	X						
Concomitant medication	X						
Safety							
Physical exam	X						X
ECG	X	X	X	X	X	X	X
Blood pressure and heart rate	X	X	X	X	X	X	X
Safety laboratory (incl. pregnancy test—women only)	X	X			X	X	X
Adverse events recording			X	X	X	X	X
Effectiveness							
MADRS	X	X	X	X	X	X	X
BDI-II		X	X	X	X	X	X
Social functioning and quality of life							
SOFAS		X			X		X
EQ-5D-3L		X			X		X
Other							
Demographics	X						
BMI	X	X					X
Waist circumference		X					X
PGIC			X	X	X	X	X
CGI-S		X	X	X	X	X	X
CGI-I			X	X	X	X	X
Laboratory (lipid assessment)		X					X
Laboratory (immune function and cellular metabolism)		X			X	X	X
Drug dispensation		X		X	X	X	

BDI-II, Beck-Depressions-Inventar II; BMI, Body-Mass-Index; CGI-I, Clinicians' Global Impression of Improvement; CGI-S, Clinicians' Global Impression of Severity of illness; EQ-5D-3L, Generic Quality of Life Questionnaire; MADRS, Montgomery-Åsberg Depression Scale; MINI, Mini International Neuropsychiatric Interview; PGIC, Patient Global Impression of Change; SOFAS, Social and Occupational Functioning Assessment Scale.

by the trial statistician. The randomisation will be based on a permuted block procedure stratified by study site.

Based on the randomisation codes, the pharmacy will centrally provide for each centre sequentially numbered, tamper-proof container, which are equal in weight and similar in appearance containing simvastatin or placebo. The pharmacy keeps the randomisation list unavailable to investigators/subinvestigators and the sponsor/sponsor representative until the end of study. Investigators/subinvestigators and patients will be blinded to the treatment. Simvastatin is an effective serum lipid-lowering drug that can decrease lipid levels. Particularly, LDL cholesterol is expected to be lower in the SIM+ES group. In order to ensure continued blinding, lipid values will be assessed only at V1 and the last trial visit (V6) to minimise the risk for unblinding of investigators/subinvestigators by revealing the lipid profile. At the same time, not assessing the lipid status of patients during the entire study participation would not represent current

practice where lipid status is an important part of cardiovascular risk assessment. No unblinding of the investigators/subinvestigators due to specific side effects of simvastatin treatment is to be expected.

In case of an emergency, the blinding will be broken immediately, and the patient will receive immediate medical care. The local investigator will be responsible for deciding if knowledge of the group assignment is required for the medical care of the patient and initiate the unblinding procedure. Emergency envelopes for the unblinding are enclosed in the packages sent to the investigator site and are stored by the local investigator. When emergency envelopes are opened prematurely, date, time, reason for opening and name of the person opening have to be documented. After unblinding, the treatment of the individual participant will be stopped immediately; however, the participant will not be excluded from the analysis (see online supplemental material for more information on premature termination of the individual participant). An identical copy of the emergency envelopes for the unblinding will be sent and stored securely at the coordinating site (Charité—Universitätsmedizin Berlin). This way the coordinating staff is additionally available for immediate unblinding.

Safety

Simvastatin and escitalopram are approved for several indications since decades and have an established safety profile. All depressed patients enrolled in the trial will be continuously treated with a gold standard antidepressant (escitalopram) as described by the German National Disease Management Guideline ('Nationale Versorgungsleitlinie') for the treatment of MDD. In case of adverse reactions related to escitalopram, we will allow dose adjustments such as temporary dose reduction from 10 to 5 mg/d or from 20 to 10 mg/d for the duration of the adverse reaction. See table 2 for an overview of safety assessments at screening, baseline and different follow-up visits. We list the risks and detailed safety considerations for both medications, as well as definitions for adverse event (AE), serious AE and Suspected Unexpected Serious Adverse Reactions (SUSAR) in the online supplemental material.

All (S)AEs and SU*SA*Rs will be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalisation or any other medically required intervention. Standard procedures for reporting of (S)AEs and SUSARs will be used.

For specifications for premature termination of the individual participant and the clinical study, see online supplemental material.

Data management

Patient related data will be recorded in study files (source data) under the participant's real name. The information required by the protocol will be entered onto the electronic case report forms (eCRF—secuTrial) under a pseudonym. Every patient will receive a patient number/pseudonym which will be unique for this individual patient. Data required for the analysis will be acquired and transferred electronically to a central database at the Coordinating Center for Clinical Studies of Charité by means of the electronic data capture system secuTrial). The trial data will be stored digitally on a remote server with daily backups. After end of study, all data will be exported for checks of consistency and plausibility. After performing the checks, the data matrix will be transferred in pseudonymised form for the statistical evaluation. The statistical analysis and the biometrical report will be provided by the biostatistician in cooperation with the PI.

Data analysis plan

The primary analysis population will be the intention-to-treat (ITT) population. The ITT population will include all randomised patients. We will repeat the analyses in the per-protocol sample. The primary analysis will compare MADRS changes from baseline to week 12 between SIM+ES and PL+ES by Gaussian linear models for repeated measures (so-called MMRM) with intervention, centre, time (week 1, 2, 4, 8 and 12), and intervention-by-time interaction as factors and baseline MADRS score as covariate. The error terms are assumed to follow a multivariate normal distribution with unstructured covariance. Least squares mean changes from baseline will be reported for both groups with 95% CI as well as the difference between the least squares SIM+ES group means with 95% CI and p-value testing the null hypothesis of no treatment effect. Although the model described above is robust to a certain extend to missing data, sensitivity analyses will be performed as supporting analyses including multiple imputation and last-observation-carried-forward. The latter will mainly be performed to facilitate comparison with previous trials.

The analyses of all secondary endpoints and safety parameters will have an exploratory character and will therefore not be adjusted for multiple testing. The secondary efficacy endpoints MADRS-response and MADRS-remission, and MADRS-MCID within 12 weeks will be analysed by logistic regression models with intervention and centre as factors and baseline MADRS as covariate. The treatment effects will be reported as ORs with 95% CI and p-values testing the null hypotheses of no treatment effect. The analyses of continuous secondary efficacy endpoint as well as SOFAS, and EQ-5D-3L will follow the same lines as the primary outcome. All details of the statistical analyses including definitions of the analyses populations will be specified in the statistical analysis plan, which will be finalised before database lock and unblinding. All statistical analyses will be carried out using SAS software or the R package.

Patient and public involvement

A patient representative from the German Depression League ('Deutsche Depres-sionsliga'), the umbrella organisation of depression self-help groups in Germany

was involved during the development of the study protocol. She will also be part of the Data and Safety Monitoring Board (DSMB) to represent the patient perspective.

ETHICS AND DISSEMINATION

This trial will be conducted in accordance with the current guidelines of International Conference on Harmonisation-Good Clinical Practice (ICH-GCP). GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. Informed consent will be obtained for screening and for participation in the study. Study protocol, patient information and consent form have been approved by the relevant Ethics Committees and the relevant federal authority (Bundesinstitut für Arzneimittel und Medizinprodukte—BfArM). The Ethics Committee will immediately be informed (by the sponsor/sponsor representative) of all changes to the protocol (according to GCP-V § 10) and of all events that could affect a patient's safety. The Ethics Committee will also be informed of all suspected SUSARs and of regular or premature termination of the study. We prospectively registered our study in the clinicaltrials.gov database and German Clinical Trials Register. The study results will be published irrespective of the study outcome in peer-reviewed journals and at (inter-)national conferences.

Study management

The sponsor/sponsor representative of the clinical study will have overall responsibility for the study. The PI together with each investigator of the study site will take clinical responsibility for the research team at each site. To enhance monitoring of study, we will seek advice from a DSMB comprised of methods and clinical experts in psychiatry and one patient representative. Thereby, the patients' perspective will be present at all DSMB meetings. Further details about DSMB including its charter are available on request.

Authorised representatives of the sponsor, a regulatory authority or an Independent Ethics Committee may visit the centre to perform audits or inspections, including source data verification. The purpose of a sponsor audit or inspection is to systematically and independently examine all study related activities and documents to determine whether these activities were conducted, and data were recorded, analysed and accurately reported according to the protocol, GCP, ICH guidelines and any applicable regulatory requirements.

Perspectives

According to a meta-analysis of small, RCTs, a beneficial antidepressive effect of simvastatin is to be expected.[14] Many depressed patients with comorbid obesity might additionally benefit from simvastatin in terms of primary prevention of cardiovascular disease. The potential benefits of the study by far outweigh the risks associated with escitalopram and simvastatin. If successful, our trial would have immediate impact on clinical practice because escitalopram and simvastatin are available as inexpensive generic drugs with established safety.

Ethics approval

The study has been approved by a German ethics committee - Ethik-Kommission des Landes Berlin (Reference: 19/0226 - EK 11) on 22 January 2020.

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Contributors CO designed the study, obtained funding, developed protocol and study materials, obtained necessary approvals for the study and critically revised this manuscript. WRC contributed to protocol and study materials and drafted the manuscript. JN contributed to study materials. SM and SL helped with study approvals and preparing the study protocol. MK, DoP, SR, BE, HJG, UH, KH, TH, DJ, KJ, KGK, JPK, THCK, GL, DaP, AR, DS, MS, SS and AW contributed to study design and critically revised the manuscript. TF contributed to study design, obtained funding, developed the protocol and revised this manuscript. SMG contributed to study design, obtained funding, developed protocol and study materials and critically revised this manuscript.

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Otte et al. Simvastatin add-on to Escitalopram in patients with comorbid obesity and major depression (SIMCODE): study protocol of a multicenter, randomized, double-blind, placebo-controlled trial

Supplementary Table 1: SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Adressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	-
Funding	4	Sources and types of financial, material, and other support	25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	25
	5b	Name and contact information for the trial sponsor	25
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	-

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10, 19, 25
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
	6b	Explanation for choice of comparators	8
Objectives	7	Specific objectives or hypotheses	7-8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10; Table S2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	16
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14; Table 1 & 2
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 2; Figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13-14; Figure 1
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	15
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	15
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	15-16
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15-16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	15-16
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14, 16; Table 2; data collection forms are available upon request
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Supplementary materials page 3

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17; data management procedures are available upon request
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17-18; the statistical analysis plan will be finalized before database lock and unblinding
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17-18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17-18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	19
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13-14; supplementary materials page 3-4

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16; supplementary materials page 1-2
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18-19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	26-27
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available upon request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	14

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.

Supplementary Materials

1. Safety

The most prominent risk of Escitalopram is QTc-Prolongation in the ECG that can lead to ventricular arrhythmia (torsade des pointes). To exclude patients with QTc-prolongation an ECG will be conducted at screening. Furthermore, additional safety ECG will be conducted at every visit. Importantly, a recent extensive literature review on parallel SSRI and statin use concluded the following: “Escitalopram, Citalopram, and Paroxetine are almost certain to be safe with all statins”[1].

Simvastatin is offered in an “add-on” design, thus there will be no untreated patients in this trial. Invasive interventions beyond ordinary sampling of peripheral venous blood will not be performed within this trial, therefore the risks associated with trial participation are mainly attributable to Simvastatin that has already been shown in depressed patients to be safe and well tolerated in combination with an SSRI[2]. It has been suggested that both for the lipid-lowering effects and for the pleiotropic effects of statins a high dose is more effective than a low dose[3-5]. Especially in studies examining effects of statins on diseases of the central nervous system such as multiple sclerosis and mild cognitive disorder a high dose of Simvastatin (60 – 80 mg/d) has been administered[6-8]. One of the most important side effects of Simvastatin is dose-dependent risk of myopathy. The combined incidence for myopathy/rhabdomyolysis under Simvastatin was 0.03% for 20 mg/d, 0.08% for 40 mg/d and markedly went up to 0.61% for 80 mg/d according to latest version of German Summary of Product Characteristics. To minimize the risk of Simvastatin and examine the pleiotropic effects of Simvastatin in depression, we will use it in a medium dose (40 mg/d) and not a high dose (80 mg/d). In addition to assessing safety laboratory values including creatine kinase (CK) at screening, baseline, at week 4, week 8 and week 12, it will be explicitly

asked during each visit if the patient experienced unexplained muscle pain or dark urine as a sign of rhabdomyolysis. Furthermore, we will not include particularly vulnerable patients (e.g. patients with renal impairment, untreated hypothyroidism or history of muscle toxicity under statins or fibrates) to our study.

For women of childbearing potential, a highly sensitive serum human chorionic gonadotropin (hCG) test will be conducted at screening visit, baseline, week 4, week 8 and at the end-of-study. Highly effective contraception in women (defined as pearl index < 1), or complete abstinence of intercourse (during study participation) is required for study participation (see exclusion criteria in *table S2*).

2. Definitions of AE, SAE, and SUSAR

Adverse event (AE): An AE is an untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE could be diseases, signs or symptoms which occur or worsen after enrolment of the patient in the clinical trial. All AEs reported by the subject or observed by the Investigators will be recorded at each visit and evaluated to determine whether it constitutes a serious adverse event.

Serious Adverse Event (SAE): A SAE is an untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, or requires a higher benzodiazepine regimen or prescription of antipsychotics (“rescue medication”).

Suspected Unexpected Serious Adverse Reactions (SUSAR): A SUSAR is any suspected adverse reaction related to the study treatment that is both serious and unexpected.

3.1 Premature termination of the individual patient

Patients are free to withdraw from participation in the study without specifying any reasons. An Investigator may discontinue or withdraw a participant from the study if any clinical adverse event, laboratory abnormality, or other medical condition occurs such that continued participation in the study would not be in the best interest of the participant. In particular the following AE, laboratory abnormality, or other medical condition will lead to immediate discontinuation of the individual participant: report of any unexplained muscle pain, tenderness or weakness if accompanied by malaise or fever, hyperbilirubinemia or jaundice, interstitial lung disease, QTc prolongation ≥ 500 ms or ≥ 60 ms increase from baseline, seizures, activation of mania/hypomania, abnormal bleeding event (e.g. ecchymoses, purpura), serotonin syndrome, angle closure glaucoma, clinically significant worsening of depression severity operationalized as a change score of 6 or 7 (“much worse” or “very much worse”) in the Clinicians’ Global Impression of Improvement scale (CGI-I) in two successive visits, clinically significant laboratory abnormalities, acute suicidal ideation (MADRS item 10 > 4), and pregnancy. In the case of premature termination, the reason for withdrawal will be documented and the patient will be followed for safety and efficacy until the end of the study (week 12).

3.2 Premature termination of the clinical study

According to the German Summary of Product Characteristics for Simvastatin, the combined incidence for myopathy/rhabdomyolysis in 41.413 patients treated for at least 4 years was 0.08% for 40mg/d Simvastatin. Severe symptomatic hyponatremia (serum sodium [S_{Na}] <125 mmol/L) is a rare but potentially fatal complication of Escitalopram. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness and can be as severe as hallucination, syncope, seizure, coma, respiratory arrest, and death.

Therefore, the whole study may be discontinued at the occurrence of "myopathy/rhabdomyolysis" as defined by the German Summary of Product Characteristics for Simvastatin [muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN)] in more than 5 participants or "severe symptomatic hyponatremia" (serum sodium [S_{Na}] <125 mmol/L) in more than 5 participants. In addition, an early discontinuation of the trial may be decided if new scientific data during the course of the trial changes the risk-benefit-balance significantly. If such data emerges, recruitment and treatment of currently treated patients will be paused immediately. A final decision on continuation or termination of the trial will then made by the Sponsor based on the recommendation of the Data and Safety Monitoring Board (DSMB).

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Table S2: SIMCODE study inclusion and exclusion criteria

Inclusion criteria
- Written informed consent is present
- The patient has the capacity to give consent (He/she is able to understand the nature and anticipated effects/side effects of the proposed medical intervention)
- The patient has a major depressive episode according to DSM 5 (Diagnostic and Statistical Manual of Mental Disorders 5th Edition)
- The patient has a score of ≥ 18 in the Montgomery-Asberg Depression Rating Scale (MADRS)
- The patient has a body mass index ≥ 30
- The patient's age is between 18 and 65 years (≥ 18 und ≤ 65)
- The patient has not given childbirth within the 6 months prior to study entry and is not breastfeeding
- In case of non-psychotropic medication: The patient received stable pharmacological medication for at least 14 days prior to study entry (any changes in medication dose or frequency of therapy must be answered with no)
- The patient did not take antidepressants during the last 7 days prior to study entry (discontinuation of effective medication to enable study participation is prohibited)
- The patient did not receive prior treatment with Escitalopram in index episode
- The patient had less than three (<3) trials with antidepressants in index episode
- The patient does not have a history of non-response to Escitalopram
- The patient did not receive treatment with ketamine, electroconvulsive therapy (ECT) or other stimulatory treatments in index episode
- The patient does not meet any of the following criteria: schizophrenia, schizoaffective disorder, bipolar disorder
- The patient is not diagnosed with dementia and does not have moderate or severe impairment of general cognitive function according to clinical impression
- The patient does not have clinically relevant elevated liver enzymes [GOT or GPT > 3 x upper limit normal (ULN)] and does not have elevated Carbohydrate Deficient Transferrin (CDT) ≥ 2.4 %

Continued Table S2: SIMCODE study inclusion and exclusion criteria

Inclusion criteria
- The patient does not meet the criteria for alcohol use disorder (DSM-5: 303.90; ICD-10: F10.20) or substance use disorder (DSM-5: 304; ICD-10: F11.20 – F19.20) in M.I.N.I. for DSM-5 and a urine/serum drug screening is negative (except for benzodiazepines and opiates)
- The patient does not have a history of suicide attempt
- The patient does not have diagnosed epilepsy or increased bleeding diathesis or a history of angle closure glaucoma or other glaucoma
- The patient did not have bariatric surgery prior to study entry
- The patient does not have a known allergy or contraindication against Escitalopram or Simvastatin
- The patient does not meet any of the following criteria: hereditary muscle disease, known history of rhabdomyolysis, elevated creatine kinase (CK) outside of the sex-specific reference intervals, history of muscular symptoms under treatment with statins or fibrates
- The patient does not have elevated TSH level outside of the age- and sex-specific reference intervals.
- The patient does not have insulin-dependent diabetes mellitus
- The patient does not have uncontrolled hepatic disorder, renal or cardiovascular disease
- The patient does not have untreated hypothyroidism
- The patient does not have a history of myocardial infarction or stroke
- The patient does not have symptomatic peripheral arterial disease
- The patient does not have monogenic familial hypercholesterolemia
- The patient does not have clinically significant laboratory abnormalities
- The patient did not participate in other interventional trials during the 6 months before and at the time of this trial
- The patient is not an employee of the Investigator study site, or a family member of the employees or the Investigator, or otherwise dependent on the Sponsor, the Investigator or the Investigator study site

Continued Table S2: SIMCODE study inclusion and exclusion criteria

Exclusion criteria
- The patient has current use of statins (for visits 2-6 applies: except for IMP Simvastatin) - The patient has current use of antidepressants (for visits 2-6 applies: except for standard medication Escitalopram) - The patient has acute suicidal tendencies (MADRS Item 10 > 4) - The patient uses potent CYP3A4-inhibitors (e.g. clarithromycin, erythromycin, HIV protease inhibitors) - The patient uses potent CYP3A4 inductors (Carbamazepine, Efavirenz, Nevirapine, Etravirine). - The patient uses Fibrates, Amiodarone, Amlodipine, Verapamil, Fluconazol, Diltiazem, Fusidic acid, Niacin or Lomitapide or BCRP-Inhibtors (e.g. Elbasvir or Grazoprevir) - The patient uses Gemfibrozil, Ciclosporin or Danazol - The patient has known hypersensitivity to other ingredients of Simvastatin and Escitalopram [butylated hydroxyanisole, microcrystalline celluose, citric acid, starch, lactose, magnesium stearate, hypromellose, talc, titanium dioxide, iron oxies, colloidal silicon dioxide, croscarmellose sodium, polyethylene glycol] - The patient uses medication that is associated with QTc-prolongation [antiarrhythmica class IA and III, antipsychotics (e.g. Haloperidol), phenothiazines, tricyclic antidepressants, antibiotics (e.g. Moxifloxacin), and certain antihistaminergic drugs (e.g. Astemizol, Mizolastine)] - The patient has clinically significant abnormalities in 12-lead ECG (e.g. QTc-prolongation ≥ 500 ms or increase ≥ 60 ms from baseline visit) - The patient is pregnant - The patient with childbearing potential is not willing to use an acceptable form of contraception (defined as Pearl index < 1) - The patient has current use of psychotropic medication (e.g. antipsychotics, anticonvulsants, lithium or St. John's Wort) except for benzodiazepines, non-benzodiazepines and opiates - The patient uses nonselective, irreversible monoamine oxidase (MAO) inhibitor (e.g. Tranylcypromine) or selective, reversible inhibitor of monoamine oxidase A (e.g. Moclobemide) or the nonselective, reversible monoamine oxidase inhibitor Linezolid - The patient is unwilling to consent to saving, processing and propagation of pseudonymized medical data for study reasons - The patient is legally detained in an official institution