



Simvastatin augmentation for recent-onset psychotic disorder: A study protocol



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ABSTRACT

Background: There is ample evidence that inflammatory processes play a role in the pathophysiology of schizophrenia. Randomized controlled trials have shown benefit of some (but not all) anti-inflammatory drugs on symptom severity. So far, these drugs have been given for a relatively short period. Simvastatin combines well-established vascular protection with reduction of the inflammatory status of the brain, thus offering an attractive potential to further improve treatment of schizophrenia and related disorders.

Methods/design: We are currently undertaking a double-blind placebo-controlled trial, including 250 patients (18–50 years of age) whom are diagnosed with a schizophrenia spectrum disorder. Onset of their first psychosis should be no longer than three years ago. Patients are randomized 1:1 to either 40 mg simvastatin or placebo daily during one year, next to their regular antipsychotic treatment. Primary outcome measures are symptom severity and cognitive decline as measured by the Positive and Negative Syndrome Scale (PANSS) and Brief Assessment of Cognition in Schizophrenia (BACS), at baseline and end of treatment. Secondary aims are to establish an attenuation of brain tissue loss and an improvement in general functioning, presence and severity of metabolic syndrome and degree of movement disorders. Lastly, immunological and metabolic parameters are assessed in blood samples to possibly predict treatment response.

Discussion: We hypothesize simvastatin to lower symptom severity and to prevent or reduce excessive brain tissue loss and cognitive decline, compared to placebo. We expect that simvastatin will be well-tolerated and lead to decreased prevalence of metabolic syndrome.

Trial registration: ClinicalTrials.gov NCT01999309; EudraCT-number 2013-000834-36.

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1. Introduction

Although the introduction of antipsychotic medications in the 1950s has substantially improved clinical symptoms of schizophrenia [32], the disease is still causing considerable morbidity and mortality [28]. Different lines of evidence now suggest that low-grade inflammation in the central nervous system is involved in the pathogenesis of schizophrenia, possibly affecting a specific subgroup of patients. These include the increased risk of schizophrenia patients and their relatives for specific auto-immune diseases [6], clinical similarities between the course of schizophrenia and auto-immune disease [23] and decreased prevalence of schizophrenia in men who have used non-steroidal anti-inflammatory drugs (NSAIDs) [24] or glucocorticosteroids [25] for somatic disorders. Furthermore, an infectious cause or trigger is

suggested by the observed association between schizophrenia and pre- and perinatal infections [10], as well as by seroconversion to certain pathogens in patients with schizophrenia [33].

The case of this increased inflammation is most likely both genetic and environmental. A large pooled data-set of single nucleotide polymorphism (SNP)-based genome-wide association studies followed up the most significant association signals [31]. One of the most remarkable findings was a significant association with several markers spanning the major histocompatibility complex (MHC) region on chromosome 6p21.3–22.1. This genetic deviation in the MHC region is consistent with an immune component to schizophrenia risk. Furthermore, recent studies suggest that negative environmental influences such as childhood trauma and drug abuse affect the brain by increasing the inflammatory response [1,7].

On a cellular level, inflammation of the central nervous system is suggested by an increased number of activated microglia cells in the brains of patients with recent-onset psychoses as visualized by positron electron tomography [14,34]. In an activated state, microglia cells can

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produce free radicals, pro-inflammatory components and other neurotoxic substances, causing cell death in their proximity [27], while at rest microglia are an important source of growth factors. The activation of microglia cells provides a possible route by which an increased pro-inflammatory state in the brain could cause increased grey matter loss and more severe negative and cognitive symptoms.

In support of this line of thought, cross-sectional studies showed a negative correlation between an inflammatory parameter in the blood (C-reactive protein; CRP) and cognitive performance in people with schizophrenia [12,13]. CRP and other inflammatory markers (including S100B, interleukin [IL]-6 and IL-8) have also been associated with severity of negative symptoms [26]. Furthermore, MRI studies showed larger cerebral volume decreases in poor outcome patients, characterized by more symptoms and lower levels of daily life functioning [35,36]. This more pronounced brain volume loss occurs mainly in the first years of illness [4,8] and may be related to increased inflammatory status in the brain. A recent meta-analysis [38] including 26 double-blind randomized controlled trials evaluated the efficacy of anti-inflammatory agents, showing promising results. Aspirin addition was found to have beneficial effects (mean weighted effect size [ES]: 0.3, $n = 270$), as well as estrogens (ES: 0.51, $n = 262$), and N-acetylcysteine (ES: 0.45, $n = 140$).

This mounting body of evidence suggests that anti-inflammatory drugs can be viewed as potential candidates for new augmentation therapies, although at this stage it is unknown if increased pro-inflammatory status is characteristic for all patients with schizophrenia or just for a specific subset of them. A recent post-mortem study showed clear signs of increased inflammation in some 40% of patients [15], which parallels findings in peripheral blood also showing increased inflammation in 35% of patients [29]. Thus, augmentation with an anti-inflammatory component may be particularly beneficial for this subgroup.

Sierra et al. [30] compared nine statins for their potential as a neuroprotective agent and concluded that simvastatin is the best candidate for the prevention of neurodegenerative conditions due to its high capacity to penetrate the blood–brain-barrier, strong cholesterol lowering effect on neurons and (in vitro) protection against neural cell death. However, statins have anti-inflammatory effects that are independent of their ability to lower cholesterol. Individuals with schizophrenia already have high levels of cardiovascular risk factors [18]. Statin treatment that combines anti-inflammatory with cardioprotective properties may therefore have particular potential as adjuvant therapy in patients with recent-onset schizophrenia.

1.1. Aims

We hypothesize that simvastatin addition will have a beneficial effect in patients with early-stage psychotic disorder on the following outcome variables:

- Primary: Symptom severity and cognitive performance;
- Secondary: Brain volume loss, global functioning, movement disorders, and metabolic and inflammatory parameters.

2. Methods

2.1. Overview

This is a randomized, double-blind, placebo-controlled study of simvastatin addition 40 mg/day for patients with recent-onset psychosis. A placebo-controlled design was chosen in order to differentiate between clinical effects of simvastatin and effects associated with experimental treatment, such as induced expectations of participants. Randomization is applied to minimize bias. A total of 250 patients with a DSM-IV diagnosis of schizophrenia, schizoaffective or schizophreniform disorder, or psychotic disorder NOS (not otherwise specified) will be included in a period of three years, between 18 and 50 years of age and onset of

first psychosis no longer than three years ago. Multiple psychosis-related diagnoses are allowed within this study, as recent scientific developments substantiate that these diagnoses share an underlying pathophysiology. This scientific development is illustrated by the editorial comment by NIMH director Thomas Insel (<http://www.nimh.nih.gov/about/director/2013/transforming-diagnosis.shtml>).

Patients will be recruited from both inpatient and outpatient settings throughout the Netherlands. The patients will be identified and first approached by their treating psychiatrist and the multidisciplinary teams. When patients are eligible to participate after the screening procedure, they will be randomized to simvastatin or placebo. Clinical and cognitive assessment will be done during the baseline visit, in addition to an MRI scan, after which the patient will start with the study medication. Patients will continue with their antipsychotic medication as usual during the trial. Study assessments will be conducted by members of the study team, while the treating psychiatrist will remain in charge of the overall treatment. Any changes in type or dosage of antipsychotic medication will be recorded on each study visit. During the course of the study the patient will also have additional support from the study team and continued support from their mental health care team.

2.2. Allocation

All 250 patients will be randomized 1:1 to either 40 mg simvastatin or placebo daily, with a treatment period of 12 months while continuing their antipsychotic medication as prescribed by their treating physician. A web-based application will be used, and stratification will be applied for center and gender. Trial treatment randomization codes will not be available to the study staff, but will be conveyed to the pharmacy in the University Medical Centre Utrecht in case emergency debinding is needed. Emergency unblinding is only allowed in case of serious concerns about patient safety.

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 need to utilize a proper method of contraception.

2.4. Exclusion criteria

1. Fulfillment of criteria for statin prescription; according to the Dutch Heart Foundation (Hartstichting), statin treatment is indicated when the total cholesterol level is >8 mmol/l (www.hartstichting.nl);
2. Presence of any of the contra-indications or warnings for the use of simvastatin as reported in the SPC;
3. Chronic use of glucocorticosteroids (temporary use is permitted, if stopped at least 1 month before start of treatment trial);
4. Chronic use of non-steroidal anti-inflammatory drugs (temporary use is permitted, if stopped at least 1 month before start of treatment trial);
5. Current use of statins or other lipid-lowering drugs;
6. Pregnancy or breast-feeding (urine pregnancy test will be performed for sexually active females with child bearing potential);
7. In case of familial risk for muscular disorders or previously experienced muscle toxicity when taking medication similar to simvastatin, creatine kinase (CK) levels will also be checked (as recommended by the Dutch Farmacotherapeutisch Kompas, www.farmacotherapeutischkompas.nl). In addition, levels of aspartate aminotransferase (ASAT), alanine aminotransferase

(ALAT), gamma-glutamyltranspeptidase (γ -GT) and creatinine will be checked when a history of alcohol abuse, liver or kidney disorders is reported;

8. Use of comedication that either inhibits or induces the live enzyme CYP3A4, which is responsible for the degradation of simvastatin. Inhibitors of CYP3A4 include itraconazole, ketoconazole, posaconazole, fluconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, telaprevir, boceprevir, imatinib, ticagrelor, and voriconazole; inducers of CYP3A4 include carbamazepine, efavirenz, nevirapin, and etravirine (can be washed out before start of trial);
9. Use of comedication that may increase the risk for myalgia, rhabdomyolysis and myopathy, including colchicine, bosentan, fenobarbital, phenytoin, hypericum, rifabutin, rifampicin, fibrates (e.g. gemfibrozil), fusidic acid, and carbamazepine (can be washed out before start of trial).

For patients, the MRI scan requires additional exclusion criteria to be eligible to participate in this part of the study (if these additional criteria are not met, patients can participate in the study but not in the MRI component):

10. Ferrous objects in or around the body (e.g. braces, glasses, pacemaker, metal fragments);
11. Claustrophobia.

2.5. Interval assessments

A total of 8 visits will be conducted throughout a period of one year (see Table 1). During the screening visit, informed consent will be signed and in- and exclusion criteria will be checked. If the patient is eligible for participation, the patient will be randomized. An experienced researcher will interview the patients at each visit using the PANSS questionnaires. Furthermore, side effects will be checked, assessment of GAF score and study medication count will be conducted during each visit. Cognitive testing and MRI scanning will take place at the baseline visit and at the end of the experimental treatment after one year. With regard to metabolic and immunological measurements, blood will be drawn at the baseline visit, after 1, 6 and 12 months and at follow-up (24 months) in addition to measurements of waist circumference, body mass index (BMI) and blood pressure. Patients are examined for movement disorders at baseline, 6 months and 12 months, and the questionnaire on childhood trauma will be filled in at baseline.

2.6. Training and inter-rater reliability

All involved researchers will be trained in the PANSS interview by using instructional videos and group-wise assessment of a test video. Researchers have to pass an exam before he/she can perform PANSS ratings for this study. Proper conduct of the CASH interview, movement disorders scales, and cognitive testing will also be trained by experts. Study members will be carefully selected and comprehensively informed and trained regarding Good Clinical Practice (GCP).

2.7. Treatment

During the study, all patients will continue their antipsychotic medication as prescribed by their treating physician. The study medication will be ingested in the evening at a fixed dosage of 40 mg, which is within the registered dose range of 5–80 mg/daily. Patients will ingest the study medication in the form of identical tablets (e.g. simvastatin and placebo). No dosage modifications will take place.

2.8. Outcome variables

2.8.1. Primary outcome variables

2.8.1.1. Clinical outcome measure. Symptom severity will be evaluated using the Positive and Negative Syndrome Scale (PANSS [total score]; [21]). We expect to find lower symptom severity as measured with the Positive and Negative Symptom Scale (PANSS) with an average of at least 7.5 points compared to baseline, over the course of one year.

2.8.1.2. Cognitive outcome measures. 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

Table 1
Schedule of assessments.

Assessment	Visit 1 screening	Visit 2 (baseline)	Check-up (2 weeks, call)	Visit 3 (1 month)	Visit 4 (3 months)	Visit 5 (6 months)	Visit 6 (9 months)	Visit 7 (12 months)	Early termination	Follow-up (24 months)
In- and exclusion criteria	x									
Consent	x									
Lab screening	x									
Drug treatment history	x			x	x	x	x	x	x	x
Withdrawal criteria				x	x	x	x	x	x	
CASH	x									
PANSS		x		x	x	x	x	x	x	x
Cognitive assessment		x						x	x	x
MRI scan		x						x	x	
GAF		x		x	x	x	x	x	x	x
Physical examination		x		x		x	x	x	x	x
Movement disorders		x				x		x	x	x
Blood samples		x		x		x		x	x	x
CTQ-SF		x								
CDSS		x				x		x	x	x
Drug/alcohol use	x					x		x	x	
Side effects simvastatin			x	x	x	x	x	x	x	
Compliance monitoring				x	x	x	x	x	x	

Abbreviations: CASH = Comprehensive Assessment of Symptoms and History; PANSS = Positive and Negative Symptoms Scales; MRI = Magnetic Resonance Imaging; GAF = Global Assessment of Functioning; CTQ-SF = Childhood Trauma Questionnaire—Short Form; CDSS = Calgary Depression Scale for Schizophrenia.

2.8.2. Secondary outcome variables

2.8.2.1. Magnetic Resonance Imaging outcome measures. Changes in brain abnormalities and brain tissue loss will be investigated by means of Magnetic Resonance Imaging (MRI). Specifically, we will measure changes in: 1) global grey matter volumes cerebral, cortical and ventricle areas as measured with MRI; 2) widespread white matter integrity changes throughout the frontal, temporal, parietal and occipital lobes as measured with Diffusion Tensor Imaging (DTI) and Magnetic Transfer Ratio (MTR) scans; 3) quantitative MRI by using mcDESPOT scans which will provide an additional higher spatial resolution scan to investigate the global effects of simvastatin on the brain. We will compare the effect of simvastatin versus placebo, both given in addition to antipsychotic medication, with regard to changes in the primary outcome variables alluded above.

2.8.2.2. Clinical outcome measures. Secondary study parameters are the PANSS subscales: the positive scale, negative scale and general psychopathology scale. General functioning will be evaluated using the Global Assessment of Functioning scale (GAF; [19]), and the presence and severity of metabolic syndrome will be 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). The presence and severity of movement disorders will be evaluated using St. Hans Rating Scale (SHRS; [16]) and the Barnes Akathisia Rating Scale (BARS; [5]).

2.8.3. Other objectives

Various immunological and metabolic parameters will be assessed in blood samples to examine whether these parameters predict treatment response to simvastatin augmentation. Therefore, serum, peripheral blood mononuclear cells (PBMC) and RNA will be collected. The following markers will be investigated: triglycerides, HDL-C, fasting glucose, cholesterol, LDL and CRP. In addition, experience of childhood trauma will be assessed using the Childhood Trauma Questionnaire—Short Form (CTQ-SF; [9]). The severity of depression will be evaluated using the Calgary Depression Scale for Schizophrenia (CDSS; [2]). Finally, safety data will be evaluated by comparing incidences (number and % of subjects with at least one occurrence) of key SAEs and SUSARs between both groups (e.g. hospitalisations).

2.9. Safety assessment

2.9.1. Medical history

Medical history and current medication use will be checked at each visit to assess in- and exclusion criteria with regard to contraindications. Blood will be screened for cholesterol in order to conclude whether a patient can participate or whether statin treatment for high cholesterol (>8 mmol/L) needs to be part of the regular medical treatment.

2.9.2. Physical and blood examinations

In case a patient reports side effects of simvastatin use, physical examination will be conducted and blood will be drawn to conclude whether participation needs to be terminated.

2.9.3. Adverse events (AE)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product. All adverse events reported by the subject or observed by the investigator or his staff will be recorded. During each visit, side effects or healthy issues will be checked. The patient will be asked by an open question if he experienced any side effects or healthy problems since the last visit, moreover it will be explicitly asked if the

patient experienced unexplained muscle pain or dark urine, as these include the most common side effects of simvastatin. Serious adverse events (SAEs) will be reported according to the protocol and recorded in the case report form.

2.10. Power calculation and statistical analysis

An expected difference between groups of at least 7.5 points on the Positive and Negative Syndrome Scale (PANSS) questionnaire is considered relevant. In order to be able to detect this difference, 113 participants in each group will have to be evaluated to have 80% power at a two-sided alpha of 5%. The expected standard deviation of the total PANSS score used for this sample size calculation is based on similar data of the Eufest trial [20] and set to 20. This sample size calculation assumes the primary analysis will be a *t*-test comparing the two treatment groups on mean change from baseline to 12 months of treatment. However, the primary analysis will actually be based on a linear model including at least treatment arm and baseline PANSS score as covariates. If the correlation between baseline PANSS and PANSS at 12 months follow-up is 0.4 or higher, which is not unreasonable, the statistical evaluation is approximately at least $(0.4)^2$ more efficient, in that 16% less patients are required. This greater efficiency can partly compensate for the anticipated drop-out, which is expected to be between 20 and 30% given the relative long duration of the study. It is thus expected that 125 patients in each arm will suffice, resulting in a total of 250 participants in this study.

Intention To Treat analyses will be conducted. Descriptive statistics of continuous outcomes will be presented by treatment arm and include sample size, mean, median, standard deviation, minimum and maximum. For categorical outcomes, the number and percentage of subjects in each category will be presented by treatment arm. All statistical analyses will be performed using SPSS for Windows (version 20) or other widely accepted statistical or graphical software. The primary analysis will include PANSS scores at 1, 3, 6, 9 and 12 months follow-up in a repeated measurements model. The model will be a mixed model for repeated measurements including at least time point, treatment group, the interaction between time point and treatment, sex, age and severity as fixed factors, baseline PANSS score as covariate and subject as random intercept factor. An cAR(1) structure will be used to model the residual covariance matrix. The primary analysis will be to test the contrast between simvastatin addition and control at 12 months of treatment. This will be presented with a 95% confidence interval for the difference between the treatment arms. In addition, post-hoc analyses will be conducted to investigate possible differences at individual time points. The analyses on neurocognitive functioning will be similar, although only scores after 12 months of treatment are included. The BACS total composite score will be evaluated, as well as post-hoc analyses to evaluate the six individual subtasks (as suggested by [22]). The raw test scores of the subtasks will be converted into z-scores. The total composite score will be calculated by averaging the standardized scores from the individuals subtests of the BACS. The secondary analyses on continuous measures (including the PANSS positive, negative and general psychopathology scales, in addition to MRI data) will be similar to the primary analyses (but note that the number of time points is different here). Secondary analyses on dichotomous data (e.g. on presence of metabolic syndrome and movement disorders) will be conducted using logistic regression analysis. The analyses on other study parameters, including data from the 24-month follow-up visit, on continuous and dichotomous measures will also be similar to the primary and secondary analyses (but again with a different number of time points). For safety data, incidences (number and % of subjects with at least one occurrence) of key SAEs and AEs will be presented

per group. For exploratory purposes, confidence intervals comparing both groups will be provided.

2.11. Study procedures

2.11.1. Recruitment

Patients diagnosed with schizophrenia, schizoaffective or schizophreniform disorder (DSM-IV 295.*) or psychosis NOS (298.9) will be invited to participate by their treating physician. Psychiatrists associated in the Dutch Psychosis Consortium collaborate on several treatment trials, including this one.

2.11.2. Screening visit

Participation in the study is preceded by an informative meeting with the study investigator, during which the participant must be informed about the entire course of the study, potential individual benefits and personal risks. Here it must be emphasized that participation is absolutely voluntary. Patients are given sufficient time to read all the provided information, counsel partners or relatives, and clarify any questions with the investigator. Participation requires written consent before any (screening) procedure takes place. This consent can be revoked at any time without citing reasons and without any consequences. A copy of the consent form and patient information will be given to the participant. After the informed consent procedure has been completed, in- and exclusion criteria will be checked to assess the patient's eligibility for participation. In case of familial risk for muscular disorders or previously experienced muscle toxicity when taking medication similar to simvastatin, creatine kinase (CK) levels will also be checked. In addition, levels of aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma-glutamyltranspeptidase (γ -GT) and creatinine will be checked when a history of alcohol abuse, liver or kidney disorders, is reported. In addition, total cholesterol level will be measured to determine whether the reference level of 8 mmol/l is exceeded, in which case the patient cannot be included in the study and is referred to the general physician as statin use is indicated (www.hartstichting.nl). These results will be evaluated by a physician before the baseline visit takes place.

The Comprehensive Assessment of Symptoms and History (CASH) [3] will be administered to confirm the inclusion diagnosis. In addition, several demographical and clinical variables will be assessed with this instrument, including date of birth, sex, educational level, prior psychiatric disorders and duration of untreated psychosis. Furthermore, the use of concomitant medication, medical history and current medical conditions/adverse events will be recorded.

2.11.3. Baseline visit

At baseline, the patient will be randomised and the study medication will be dispensed for the first time at the end of the visit, see Table 1. PANSS and GAF will be administered, in addition to the CDSS and the BACS. With regard to metabolic and immunological measurements, the blood will be drawn at the baseline visit, in addition to measurement of waist circumference, body mass index and blood pressure. Patients are examined for movement disorders, namely tardive dyskinesia, parkinsonism, akathisia and tardive dystonia, using a standard protocol, described by van Harten and colleagues [37]. Childhood trauma will be evaluated by asking subjects to fill-in a retrospective self-report questionnaire (CTQ-SF). In addition, an MRI scan will be performed. At the end of the baseline visit, study medication will be dispensed and patients are instructed on how to use it. As a final check, no current use of contraindicated comedications is ascertained again. A study participation letter will be sent to the treating psychiatrist, general practitioner and pharmacy of the patient, mentioning these contraindicated comedications. Patients are instructed to contact the study center if muscle pain, weakness, cramps, or dark urine

occur. Lab procedures that will follow such a report are described in the section 'Patient withdrawal' below.

2.11.4. Treatment visits

After the screening and baseline visits, visits will be conducted at 1, 3, 6 and 9 months and at the end (12 months) of treatment, during which an experienced researcher will interview patients using the PANSS and the GAF questionnaires (see Table 1). Cognitive testing and brain volume assessments will again take place at the end (12 months) of the study. Depression scores (CDSS) will be assessed at 6 and 12 months. Blood will be drawn after 1, 6 and 12 months of the experimental treatment, in addition to measurements of waist circumference, body mass index and blood pressure. Patients are examined for movement disorders at 6 and 12 months after baseline. During each visit, the occurrence of side effects will be checked, in addition to use of contraindicated co-medications. In case of drop-out, an early termination visit similar to the end of treatment visit will be performed to finalize participation. If the patient is not willing to complete all measures, priority will be given to the PANSS.

2.11.5. Follow-up visit

A follow-up visit will take place 24 months after baseline in order to examine any long-term effects of simvastatin on the clinical status of participants as well as immune parameters (see Table 1). The PANSS and the GAF questionnaires will be administered. Cognitive functioning and depressive symptoms will be assessed, in addition to measurements of waist circumference, body mass index and blood pressure. Blood will be drawn and patients are examined for movement disorders. Medication use will be evaluated, next to side effects and hospitalisation in the past year.

2.11.6. Patient safety

The patients' day-to-day care is the responsibility of the treating physician. The safety profile of simvastatin is satisfactory, especially in a population of recent-onset patients, where the multiple interactions with other medications will be less often an issue due to the good somatic health status of such a relatively young population. Medical and safety concerns specifically related to participation in the study are the responsibility of the principal investigator (P.I.). The principal investigator and study members can at all times be contacted at the telephone number provided on the appointment card and letters patients receive during the study.

2.11.7. Patient withdrawal

Subjects can leave the study at any time for any reason if they wish to do so, without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Reasons to terminate a patient's participation include:

- The patient withdraws her/his consent
- Intolerance to the study drug: if a patient experiences unacceptable side effects, the patient may decide, or make a joint decision with the treating physician, to terminate study participation.
- The patient develops myopathy with increased creatine kinase (CK) levels. When unexplained muscle pain, weakness, cramps or dark urine occur, CK, CPK (creatine phosphokinase) and CRP (C-reactive protein) levels should be measured. If these levels are found to be significantly elevated ($>10 \times$ ULN, in the absence of strenuous exercise) or if pain does not subside with paracetamol use, treatment will be stopped.
- Use of glucocorticosteroids, non-steroidal anti-inflammatory drugs, statins or other lipid-lowering drugs
- Use of comedication that either inhibits or induces the live enzyme CYP3A4 (responsible for the degradation of simvastatin)

or use of comedication that may increase the risk for myalgia, rhabdomyolysis and myopathy.

In case a patient reports unexplained muscle pain, weakness, cramps, dark urine, or in case of suspected liver failure or toxicity, a blood sample will be drawn at the earliest opportunity to assess levels of CK, CPK (creatine phosphokinase), CRP (C-reactive protein), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma-glutamyltranspeptidase (γ -GT) and/or creatinine. If these levels are found to be significantly elevated ($CK > 10 \times ULN$, in the absence of strenuous exercise; ASAT, ALAT or γ -GT $> 3 \times ULN$ or in case of liver damage, hyperbilirubinemia and/or jaundice), or if pain does not subside with paracetamol use, treatment will be stopped.

- Abnormal level of triglycerides, HDL-C (high-density lipoprotein cholesterol), fasting glucose, cholesterol, LDL, CRP, which will be extensively monitored. In case of abnormal findings, the treating physician and general physician will be contacted. When medical interventions are needed, the patient will be withdrawn from the study and will receive medical treatment.
- The nature of the patient's treatment is changed to coercive treatment (based on judicial ruling)
- Emergence of one or more contraindications against the study drug as mentioned in the Summary of Product Characteristics
- Patient becomes pregnant.
- The investigator considers a patient's continued participation in the study to be unjustifiable on medical grounds (i.e., because of side effects or unusual risks).

If an individual patient is discontinued due to one of the above-mentioned reasons, this patient will be treated as usual in normal daily practice. The treating physician remains the primary caregiver during the study and will be contacted at the baseline visit and updated throughout the study. The treating physician will contact the study team in cases of important changes and will be responsible to apply for legal custody if appropriate. All patients leaving the study early, regardless of the reason, will be requested to return to the site for an early termination visit to finalize participation.

2.12. Ethical and regulatory standards

2.12.1. Medical Ethical Review Board

Ethical approval covering all participating sites was obtained from the research and ethics committee of the University Medical Center Utrecht (UMCU), the Netherlands, protocol number 13-249. The trial is registered in the ClinicalTrials.gov database (identifier NCT01999309) and the European Clinical Trials Database (EudraCT number 2013-000834-36).

2.12.2. Data and Safety Monitoring Board (DSMB)

It has been decided not to engage Data and Safety Monitoring Board in this study. The intervention concerns medication that has been available on the EU market for two decades. Its safety and efficacy are well-established. Simvastatin is well-tolerated and if side effects occur, these are usually minor and require no or minimal treatment. In addition, no interim analyses are planned. In the investigator's opinion, implementation of a DSMB will not have sufficient added value for the current study.

2.12.3. Declaration of Helsinki

This study will be performed according to the Declaration of Helsinki (64th WMA general assembly; October 2013) and the International Conference on Harmonisation – Good Clinical Practice (ICH-GCP). The definitions of adverse events and serious adverse events described in these guidelines will be used for the present study.

3. Discussion

This study will investigate the potential effect of simvastatin to further improve medical treatment of patients with schizophrenia and related disorders. A recent medical trial by Chataway and colleagues [11] demonstrated simvastatin to be effective in reducing annualized rates of whole brain atrophy in patients with progressive Multiple Sclerosis (MS), which further attributes to simvastatin as a new promising add-on treatment option for patients with brain diseases that have an inflammatory component. As such, we expect simvastatin to lower symptom severity, reduce brain tissue loss and cognitive decline when compared to placebo. Secondly, we expect to find increases in the general functioning using GAF score, reduced presence and severity of metabolic syndrome and reduced presence and severity of movement disorders. Lastly, we expect to find positive changes in immunological and metabolic biomarkers related to simvastatin augmentation.

3.1. Trial status

The study is active and currently recruiting patients. We anticipate completing recruitment by the end of 2016 and final assessments (including follow-up 12 months after study completion) by the end of 2017.

Transparency document

The [Transparency document](#) associated with this article can be found, in the online version.

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