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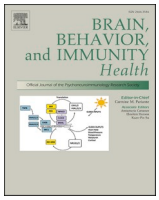

Efficacy of inflammation-based stratification for add-on celecoxib or minocycline in major depressive disorder: Protocol of the INSTA-MD double-blind placebo-controlled randomised clinical trial

C. Wessa [a,b,1], J. Janssens [a,1], V. Coppens [a,b], K. El Abdellati [a], E. Vergaelen [c,d], S. van den Ameele [a,e], C. Baeken [f,g,h], D. Zeeuws [f,i], Y. Milaneschi [j,k], F. Lamers [j,k], B. Penninx [j,k], S. Claes [c,d], M. Morrens [a,b], L. De Picker [a,b,*]

[a] *Collaborative Antwerp Psychiatric Research Institute, University of Antwerp, Belgium*
[b] *Scientific Initiative for Neuropsychiatric and Psychopharmacological Studies, University Psychiatric Centre Duffel, Belgium*
[c] *Catholic University Leuven, Belgium*
[d] *University Psychiatric Centre KU Leuven, Belgium*
[e] *UVC Brugmann, Brussels, Belgium*
[f] *Department of Psychiatry, Universitair Ziekenhuis Brussel, Brussels, Belgium*
[g] *Faculty of Medicine and Health Sciences, Department of Head and Skin, Ghent Experimental Psychiatry (GHEP) lab, Ghent University, Ghent, Belgium*
[h] *Eindhoven University of Technology, Department of Electrical Engineering, Eindhoven, the Netherlands*
[i] *Center for Neurosciences (C4N), Vrije Universiteit Brussel (VUB), Brussels, Belgium*
[j] *Department of Psychiatry, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands*
[k] *Amsterdam Public Health, Mental Health Program, Amsterdam, the Netherlands*

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ABSTRACT

Introduction: Different lines of evidence confirm the involvement of the immune system in the pathophysiology of major depressive disorder. Up to 30% of depressed patients present with an immune-mediated subtype, characterized by peripheral inflammation (high-sensitive C-reactive protein (hsCRP) $\geq$ 3 mg/l) and an atypical symptom profile with fatigue, anhedonia, increased appetite, and hypersomnia. This immune-mediated subtype of MDD is associated with poorer response to first-line antidepressant treatment. Consequently, strategies for immune-targeted augmentation should be prioritised towards patients with this subtype. Meta-analyses have shown modest but heterogeneous treatment effects with immune-targeted augmentation in unstratified MDD cohorts, with celecoxib and minocycline as most promising first-line treatment options. However, no study has prospectively evaluated the effectiveness of *a priori* stratification by baseline inflammation levels for add-on celecoxib or minocycline in MDD.

Methods: The INSTA-MD trial is a multicentre, 12-week, randomised, double-blind, placebo-controlled, parallel-group stratified clinical trial of adjunctive minocycline or celecoxib to treatment-as-usual for patients with MDD. Two hundred forty adult patients with Major Depressive Disorder who failed to remit with one or two trials of antidepressant treatment will be enrolled and allocated to high-hsCRP (hsCRP $\geq$3 mg/L) or low-hsCRP (hsCRP $<$3 mg/L) strata, where disproportional stratified sampling will ensure equally sized strata. Participants in each hsCRP stratum will be randomised to augment their ongoing antidepressant treatment with either adjunctive minocycline, celecoxib or placebo for a duration of 12 weeks, resulting in six treatment arms of each 40 participants. The primary objective is to evaluate the efficacy of immune-targeted augmentation with minocycline or celecoxib versus placebo, and the use of baseline hsCRP stratification to predict treatment response. Additionally, we will perform a head-to-head analysis between the two active compounds. The primary outcome measure is change in the Hamilton Depression Rating Scale (HDRS-17) total score. Secondary outcome measures will be response and remission rates, and change in inflammation-specific symptoms, adverse events and therapy acceptability (adherence). Further exploratory analyses will be performed with an array of peripheral inflammatory biomarkers, metabolic outcomes and physiological data.

* Corresponding author. CollaborativeAntwerp Psychiatric Research Institute, University of Antwerp, Belgium.
E-mail address: livia.depicker@uantwerpen.be (L. De Picker).
[1] Shared first authors.

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Expected impact: The aim of INSTA-MD is to advance the use of immune-targeted precision psychiatry, by supporting the implementation of targeted hsCRP screening and treatment of immune-mediated MDD as a cost-effective intervention in primary care settings. Based on previous studies, we expect immune-targeted augmentation with minocycline or celecoxib to yield a superior remission rate of 15–30% compared to treatment as usual for immune-mediated cases of MDD. By treating immune-related depression early in the treatment algorithm with repurposed first-line anti-inflammatory treatments, we can significantly improve the outcomes of these patients, and reduce the global societal and economic burden of depression.
Ethics and dissemination: This protocol has been approved by the Medical Ethics Review Board (CTR - 04/08/2023)
Registration details: Trial registration number NCT05644301 (Clinical trial.gov), EU-CT 2022-501692-35-00.

1. Introduction

1.1. The immune-mediated subtype of depression

Major Depressive Disorder (MDD) is one of the most prevalent mental disorders with devastating consequences for the individual as well as society. Core symptoms include lowered mood, loss of interest or pleasure, insomnia and recurrent suicidal ideation. MDD is a highly and increasingly impactful mental health disorder, disrupting the lives of over 36 million European citizens, and expected to lead the World Health Organization (WHO) ranking of disease burden by 2030 (Liu et al., 2024).

Over the past two decades evidence has accumulated confirming the involvement of the immune system in the pathophysiology of mood disorders. Several alterations of the innate and adaptive immune system have been associated with MDD, and recent evidence clearly demonstrates immune activation can cause new-onset depressive episodes (Capuron et al., 2000; Khandaker et al., 2014; Marrie et al., 2017; Medina-Rodriguez et al., 2018; Milaneschi et al., 2021; Perry et al., 2021; Udina et al., 2012). In a series of meta-analyses (Bai et al., 2020; Goldsmith et al., 2016; Zhang et al., 2023) CRP, IL-6, TNFα, TGFβ and IL-1β were identified as the most consistent peripheral immune markers related to MDD. Of note, plasma and CSF CRP levels were strongly intercorrelated ($r = 0.855$; $n = 89$) in a recent MDD patient sample (Felger et al., 2018). Additionally, pretreatment concentrations of CRP and IL-6 in MDD patients have been identified as predictors of poor treatment outcomes with first-line antidepressants, leading to higher rates of chronicity (Arteaga-Henriquez et al., 2019; Carvalho et al., 2013). Despite strong evidence for immune alterations in MDD, they are not observed in all patients. In a recent meta-analysis of 11.813 depressed patients, 27% displayed evidence of low-grade inflammation (CRP >3 mg/L) (Osimo et al., 2019). This corresponds to findings from the Netherlands Study of Depression and Anxiety (NESDA; $n = 1098$) and the UK Biobank ($n = 26{,}894$), where respectively 28.3% and 21.2% of a depressed patients had a CRP of 3 mg/L or higher (Milaneschi et al., 2021; Pitharouli et al., 2021). This suggests low grade inflammation is only present in around 30% of MDD patients displaying one or more immune-mediated subtypes of MDD (Drevets et al., 2022). Compared to other types of MDD, the immune-mediated subtype of MDD has been associated with higher atypical depressive (hyperphagia, weight gain, hypersomnia and fatigue), psychomotor and cognitive symptom scores, as well as unfavourable metabolic parameters (obesity, hypertension, hypercholesterolemia, insulin resistance) (Foley et al., 2021; Kaser et al., 2022; Milaneschi et al., 2020).

Following the recognition of the causal and predictive role of immune dysregulation in the pathophysiology and treatment response of MDD, a range of anti-inflammatory compounds have been investigated for immune-targeted augmentation in MDD. Out of these compounds, minocycline and celecoxib are the most extensively studied and most promising compounds for first-line immune-targeted augmentation in terms of efficacy, acceptability and cost-effectiveness (Simon et al., 2023).

1.2. Efficacy of celecoxib (CXB) and minocycline (MCO) in immune-mediated MDD

To date, twelve clinical trials have been completed, with more currently ongoing, investigating the augmentation of first-line antidepressant agents with CXB or MCO. For an overview of the individual trials, refer to Tables S1 and S2 in the supplementary material. Two recent meta-analyses (Bai et al., 2020; Kohler-Forsberg et al., 2019) confirmed the antidepressant efficacy of add-on CXB and MCO for MDD, with SMD effect sizes for both compounds ranging from −0.76 to −0.87 in favour of CXB and MCO compared to placebo. In contrast, in the subsequent 6-week trials of Baune et al. (2021) and Simon et al. (2021), no evidence was found to support the efficacy of add-on CXB. Similarly, subsequent clinical trials investigating adjunctive MCO therapy in MDD have been conducted (total $N = 228$) (Attwells et al., 2021; Hellmann-Regen et al., 2022; Nettis et al., 2021). None of these demonstrated a significant altered course of depression severity when compared to placebo in an unstratified cohort. However, despite the evidence suggesting that immune-targeted augmentation may only be effective in approximately 30% of MDD patients with an immune-mediated subtype, previous CXB and MCO trials have failed to enrich their study designs for this subtype, naturally resulting in insufficient power to convincingly demonstrate the efficacy of anti-inflammatory treatment. Moreover, these interventions may mostly affect certain symptom domains not captured using composite scores on standardised depression severity scales (Wessa et al., 2023).

The efficacy and safety of administering anti-inflammatories in individuals without detectable inflammation are occasionally questioned. Key concerns are the potential side effects without therapeutic benefit and the dampening of necessary immune responses. However, Celecoxib and Minocycline are repurposed compounds that are routinely used for approved indications that do not require the presence of inflammation. No detrimental effects have been proven across studies, meta-analyses indicate no higher risk of adverse events in Celecoxib and/or Minocycline compared to placebo (Bai et al., 2020; Kohler-Forsberg et al., 2019), and show benefits even without preselecting patient based on (overt) inflammation. This indicates further research is needed to fully understand the risk-benefit profile in patients with and without inflammation (Leboyer et al., 2024).

1.3. High sensitive C-reactive protein (hsCRP) as a stratification tool

The potential of using hsCRP to identify immune-mediated MDD responsive to immune-targeted augmentation has been demonstrated by three clinical trials. Raison et al. (2013) and Nettis et al. (2021) found that hsCRP stratification predicted treatment response with infliximab (hsCRP ≥ 5mg/L, $N = 22$) or MCO (hsCRP ≥3 mg/l, $N = 18$), although in both cases the hsCRP-stratification was performed post-hoc and the number of patients in the high-CRP arms was small or unbalanced (Nettis et al., 2021). Furthermore, a pre-stratified clinical trial by Porcu et al. (2018) with add-on N-acetylcysteine revealed antidepressant efficacy only in the subsample with hsCRP ≥3 mg/l ($N = 27$).

In contrast, Baune et al. (2021) found no impact of pre-treatment

hsCRP strata on CXB efficacy, but the trial was unbalanced as well (N = 39 with hsCRP ≥3 mg/l, N = 80 with hsCRP <3 mg/l). Similarly, Hellman-Regen et al. (Hellmann-Regen et al., 2022) found that post-hoc stratification for baseline hsCRP-levels did not support the hypothesis of MCO treatment being more effective in participants with higher-grade baseline inflammation (N = 83 with hsCRP > median, N = 84 with hsCRP < median, with median hsCRP = 1.21 mg/l in the MCO group and 0.60 mg/l in the placebo group).

Following the FDA's guidance on enrichment strategies for clinical trials (Services USDoHaH et al., 2019) and recent recommendations from numerous experts in the field of (immuno-)psychiatry (Leboyer et al., 2024), new trial designs are advised to use biomarkers such as hsCRP (either on its own or in combination with symptom-based predictors) to stratify prior to randomisation and/or enrich the trial sample for the target population. A good example is the ongoing INFLAMED RCT (Zwiep et al., 2023) where add-on CXB will be tested in an MDD cohort enriched for patients with an immunometabolic depression subtype characterized by CRP >1 mg/l and atypical symptoms.

In conclusion, to advance the use of immune-targeted precision medicine in MDD, clinical trials should identify clinical and/or blood-based markers of treatment response to immune-targeted pharmacological interventions by employing pre-stratified, balanced clinical trial designs (Figure A) (Leboyer et al., 2024). Head-to-head comparisons of different anti-inflammatories are also needed to determine the most effective compound(s).

1.4. Inflammation-based stratification for immune-targeted augmentation in major depressive disorder (INSTA-MD)

INSTA-MD encompasses a double-blind, placebo-controlled, parallel-group stratified RCT of adjunctive MCO or CXB to treatment-as-usual for patients with MDD. In total, 240 patients will be enrolled and allocated to the low or high-hsCRP stratum based on their hsCRP levels at screening (low = hsCRP <3 mg/L; high = hsCRP ≥3 mg/L). Participants will be randomised to augment their ongoing antidepressant treatment with either minocycline, celecoxib or placebo for a duration of 12 weeks.

As our study is explicitly designed to evaluate the benefit of hsCRP-stratification, we will use disproportionate stratified sampling to enrich our study with high-hsCRP patients.

1.5. Objectives

The primary objective is to evaluate the efficacy of a 12-week immune-targeted augmentation with minocycline or celecoxib versus placebo in a cohort of patients with Major Depressive Disorder as measured by the Hamilton Depression Rating Scale (HDRS-17 (Hamilton, 1960)). The primary analysis will be a linear regression model with the change in HAMD-17-score between baseline and 12-week endpoint as outcome, and treatment and hsCRP-arm (high, low) as predictors.

We aim to compare the respective acceptability (adherence), treatment response and remission rates of both compounds. The linear regression model of the primary analysis will be studied in depth to evaluate the use of hsCRP as a predictor of treatment response and other relevant confounding variables such as gender and age. A mixed model analysis will determine the longitudinal effects of MCO and CXB versus placebo on the primary and secondary outcomes (Supplementary S3) over the different timepoints. Logistic regression analyses of alternate biomarkers will determine which (combination of) blood biomarkers best predict treatment response to MCO and/or CXB. The primary linear regression analysis can be repeated following post-hoc stratification based on the most promising alternative biomarker candidates from these exploratory assessments.

We hypothesise that the effect sizes of treatment with Celecoxib or Minocycline compared to Placebo will be significantly higher in the high-hsCRP stratum compared to the low-hsCRP stratum.

2. Methods

2.1. Study design and procedures

INSTA-MD is a multi-centre, 12-week, randomised, double-blind, placebo-controlled, parallel-group stratified clinical trial in which patients with MDD will receive adjunctive MCO, CXB or placebo. We will enrol 240 patients with a current major depressive episode according to DSM-5 criteria, who have not responded to one or two adequate trials of antidepressant medication, and apply disproportional stratified sampling to obtain equally-sized strata of patients with low blood levels of hsCRP (<3mg/L) and high blood levels of hsCRP (≥3mg/L), resulting in 6 treatment arms of each 40 participants (Figure B). Participants in each hsCRP stratum will be randomised to augment their ongoing antidepressant treatment with either minocycline (200 mg/day given as 100mg twice daily), or celecoxib (400 mg/day, given as 200 mg twice

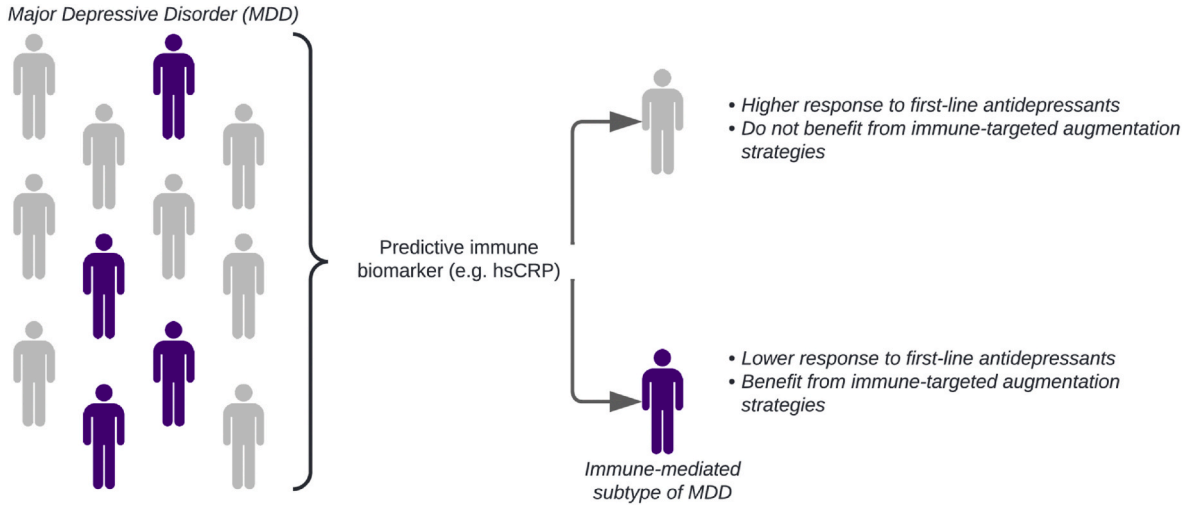

Figure A. Patient stratification based on predictive immune biomarkers: It is hypothesized that baseline predictive blood-based immune biomarkers can accurately identify the immune-mediated subgroup of MDD (present in approximately $^{1}/_{3}$ of patients), which can lead to the development of more precise, tailored treatment strategies.

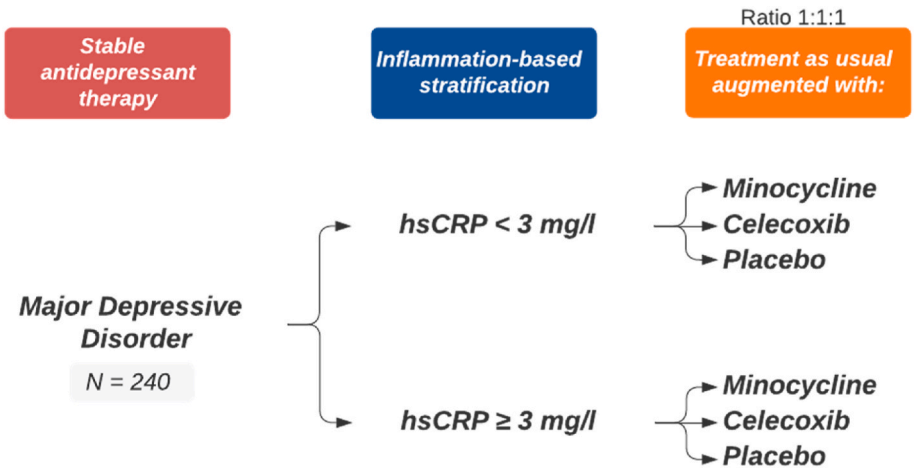

Figure B. INSTA-MD design: hsCRP = high sensitive C-reactive protein.

daily) or placebo for 12 consecutive weeks. Recruitments are expected to be concluded in December 2025.

2.1.1. Sample size and power analysis

We designed our study to be sufficiently powered to detect clinically meaningful treatment effects between each of the active compounds versus the placebo treatment arm both in the overall (unstratified) sample and in the high-hsCRP stratum separately.

For the unstratified cohort, we conducted a power analysis in R 4.1.2 using the respective effect sizes for HDRS-17 score change and remission rates of recent meta-analyses of RCTs of CXB or MCO versus placebo in unstratified cohorts of MDD patients, updated with the findings of the most recent studies (Supplementary S4). For the mean change in HDRS-17 score between baseline and endpoint, we assumed a Cohen's d effect size of 0.79 for MCO and 0.52 for CXB (Bai et al., 2020) and an α of 0.025, as we have 2 comparisons (MCO versus placebo and CXB versus placebo). Using an independent sample T-test, we obtain 80% power to detect differences of these magnitudes with a minimum sample size of 32 (MCO) and 72 (CXB) in each treatment arm. Based on earlier studies, we expect a drop-out rate of 10% (Abbasi et al., 2012; Emadi-Kouchak et al., 2016). As we prefer to maintain a 1:1:1 allocation ratio, we will enrol a total of 240 patients, with 80 patients in each treatment arm. Furthermore, our design also aims to enrol the same number of patients in each hsCRP-based stratum, thereby enriching our study with high-hsCRP patients. We will thus enrol 120 patients in both the low-hsCRP and high-hsCRP strata, and 40 patients within each treatment arm of the strata. Of note, we can expect to find larger effect sizes in the high-hsCRP stratum. For this stratum, sample size of n = 32 in each treatment arm generates an 80% power to detect a treatment effect of d = 0.79.

2.2. Eligibility criteria and consent

Recruitment of participants will be locally coordinated by three recruitment hubs (University Psychiatric Centre Duffel, University Psychiatric Centre Catholic University Leuven, University Hospital Brussels). Interested patients can apply by completing an online prescreening questionnaire or by contacting the centre directly. Each potential participant will be scheduled for a physical screening in one of the hubs and evaluated for eligibility based on the criteria found in Table 1 below.

Each subject must give written consent after the nature of the study has been fully explained. Before study enrolment, the investigator or an authorised member of the investigational staff must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time.

Table 1
In- and exclusion criteria for the INSTA-MD trial.

Inclusion	Exclusion
● Male or female, 18–65 years inclusive ● MDD diagnosis according to DSM-5 ● Score ≥14 on HDRS-17 ● Current episode has failed to remit to the current antidepressant treatment at the adequate dose, as defined in the Maudsley Prescribing Guidelines ● Stable on current treatment (minimum 4w) prior to baseline ● Tolerant to the current antidepressant and having no planned changes in their current therapy for the duration of the study ● If female, willing to use adequate contraceptive precautions and take pregnancy tests. ● Informed consent ● Physically healthy	● Primary diagnosis of bipolar disorder, psychotic spectrum disorder, obsessive-compulsive disorder, eating disorder, post-traumatic stress disorder, or alcohol and/or substance use dependence according to DSM-5 ● Positive urine test result(s) for drugs of abuse at screening ● Current MDD episode has failed to remit after 3 trials of antidepressant treatment ● Contra-indications for minocycline or celecoxib o History of peptic ulcer disease or gastrointestinal (GI) bleeding o Cardiovascular disease, thrombotic events or unstable coronary artery o Liver impairment o Renal impairment o NSAID and/or tetracycline and/or sulfonamide hypersensitivity o Chronic severe hypertension ● Received ECT <2 months prior to screening ● Blood donation in 30 days prior to screening ● Use of immunosuppressant or immunostimulant drugs within 21 days prior to screening ● Having an acute infection, an inflammatory bowel disorder, or Familial Adenomatous Polyposis ● Leucocytosis on screening and test days ● Serology positive for hep-B, hep-C or HIV antibodies ● Pregnancy or breastfeeding ● Currently enrolled in an intervention study

2.3. Outcomes

2.3.1. Clinical outcomes

The primary outcome is the reported change in severity of depression between baseline and endpoint measured as change in the Hamilton

depression rating scale (HDRS-17 (Hamilton, 1960)). Secondary outcomes include remission rates (HDRS-17 $\leq$ 7) at T6, the self-reported change in severity and symptom profiles as measured by the Inventory of Depressive Symptomatology – Self Rated score (IDS-SR30 (Rush AJC et al., 2006; Rush AJG et al., 1996)); sleep quality through the Pittsburgh Sleep Quality Index (PSQI (Buysse DJRI et al., 1988)), states of anxiety through the State-Trait Anxiety Inventory for adults (STAI (Spielberger, 2012)), overall functioning using the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0 (Ustun et al., 2010)) and the Checklist of Individual Strength (CIS (Vercoulen JHS et al., 1994)), and psychomotor retardation (CORE (Parker et al., 1993)). Therapy adherence will be evaluated using the Medication Adherence Rating Scale (MARS (Thompson and Sergejew, 2000)). The full list of outcome measures can be found in the supplementary material (S3), and an overview of the study procedures in Figure C.

2.3.2. Physiological data

MDD is associated with altered activity levels, altered sleep patterns (Brietzke et al., 2019; Ramsey et al., 2022) and altered autonomic activity such as decreased parasympathetic activity (Mueller et al., 2022; Schiweck et al., 2019) which is why physiological data will be measured using smartwatches and chest straps. Participants will be asked to wear these for 2 weeks at the beginning and the end of the study period to collect data on heart rate, heart rate variability, general activity level, and sleep patterns in daily life. Data collection will commence approximately 30 minutes prior to the first administration of the study medication. It is hypothesized that these physiological measures will improve as depressive symptoms reduce.

2.3.3. Biological data

Additionally, blood samples will be collected after an overnight fast at screening, baseline, weeks 2, 6 and 12 for biomarker and safety analysis, using EDTA tubes. After collection, samples will be processed according to the local laboratory procedures, which includes separating plasma and peripheral blood mononuclear cells (PBMCs). This will be aliquoted into multiple smaller volumes and will be stored at biobanks in a −80 °C freezer until analysis.

The selected biomarkers include a non-limitative list depending on the state-of-the-art literature at time of the analysis. Current biomarkers of interest (Bai et al., 2020; Goldsmith et al., 2016; Zhang et al., 2023; Drevets et al., 2022) are inflammatory markers (IL-6, IL-1β, TNFα, IFNγ, IL-1R, IL-4, IL-7); kynurenine pathway metabolites (KYN, KYNA, QA, 3-HK); vascular and (neuro)trophic factors (VEGF, BDNF, D-dimer); as well as lipid profiles (cholesterol and triglycerides). PBMCs will be analysed for functional and morphological parameters. Additionally, participants may give their consent for the collection of one additional blood collection tube for DNA analysis.

2.4. Randomisation and allocation

Eligibility review and blood sampling for hsCRP levels will be performed at screening. Eligible subjects will be included and stratified in two groups using disproportional stratified sampling to enrol equally sized low-hsCRP and high-hsCRP strata. Immediately after stratification, a computer-generated code will be used to randomly assign the participants to CXB, MCO or placebo in a 1:1:1 ratio. A permuted block randomisation method (1:1:1) is used to ensure balance in sample size across groups over time (block size 3–6).

2.5. Statistical plan

All statistical analyses will be planned, executed and interpreted in collaboration with the core facility for statistical data analysis at the University of Antwerp.

The primary analysis will be a linear regression model with the change in depressive symptomatology on the HDRS-17 between baseline and endpoint as outcome and treatment, with hsCRP (high or low) as predictors. The primary estimands of relevance are the differences in HDRS-17 change scores between the MCO and placebo groups, and between the CXB and placebo groups, within both the overall population and the high-hsCRP subgroup. All analyses will be based on the intention-to-treat principle with all subjects included in the analysis as randomised.

As secondary analyses, the response and remission rates, and percentage of adverse events will be compared between the treatment arms using a Chi-square test. A further in-depth study of the linear regression model of the primary analysis in which we compare the MCO to the CXB arms and evaluate if the treatment effect differs between low and high hsCRP stratum. As a sensitivity analysis we will also look at this model with inclusion of other relevant confounding variables like sex and age. As we have repeated measures over time, a mixed model analysis will be considered to determine the longitudinal effects of active treatment (vs.

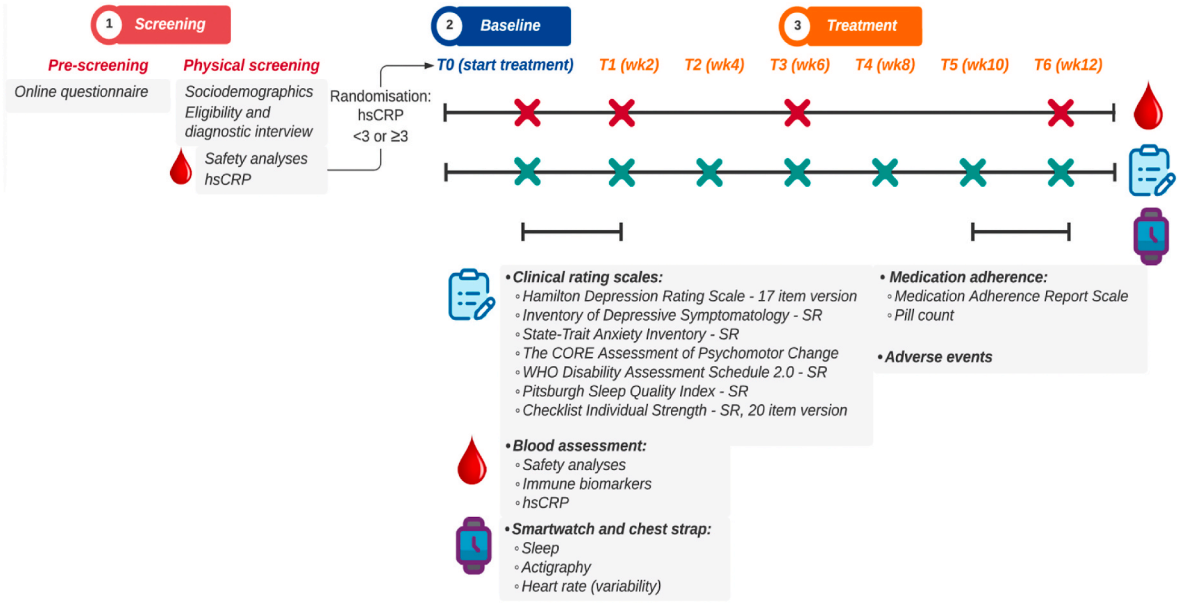

Figure C. INSTA-MD study procedures: hsCRP = high sensitive C-reactive protein, SR = self-report, wk = week.

placebo) on the primary and secondary outcomes over the different timepoints; logistic regression analysis of alternate biomarkers to determine which (combination of) blood biomarkers best predicts treatment response to MCO and/or CXB. A replication of the primary linear regression analysis following post-hoc stratification by the two most promising alternative biomarker candidates from the exploratory assessments will be performed.

3. Expected impact

Current first-line treatments for MDD are often ineffective, inaccessible, unavailable, or poorly tolerated. This highlights the urgent need for additional, readily accessible treatment options in primary care settings, which could profoundly benefit patients, carers, and society at large. INSTA-MD will evaluate the efficacy and acceptability of anti-inflammatory medication as first-line treatment for immune-targeted augmentation in MDD and identify the patient groups who benefit from this approach in addition to standard care. Implementing screening and treatment of immune-mediated MDD in primary care settings will be a pivotal step towards the clinical implementation of precision psychiatry. By targeting inflammation early in the therapeutic algorithm (typically between 8 and 24 weeks after MDD treatment onset), we can prevent patients with immune-related depression from progressing into long-term disability. Based on previous studies, we expect immune-targeted augmentation with MCO or CXB to yield a superior remission rate of 15–30% compared to treatment as usual for immune-mediated cases of MDD.

Additionally, MCO and CXB are available globally, and the hsCRP testing is a low-cost, routine lab test accessible to all medical practitioners in both outpatient and inpatient settings, making it an ideal screening tool for clinical practice worldwide. Additionally, these compounds have been available for years and come with a known pharmacological and safety profile, facilitating their repurposing and a rapid translation into clinical practice. We anticipate that subgroup identification and personalised treatment will not only support the implementation of precision psychiatry in the MDD population, but also provide broader transdiagnostic insights applicable to a wide range of mental health conditions.

3.1. *Registration, Ethics and monitoring*

The INSTA-MD trial is funded with a grant from the Flanders Research Foundation (FWO), grant number T001222N. The study is sponsored by University of Antwerp, Belgium and registered under trial registration number NCT05644301 (Clinical trial.gov), EU-CT 2022-501692-35-00. The trial has received ethics approval in accordance with CTR EU regulation 536/2014 (04/08/2023) and will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the International Council for Harmonisation (ICH) Harmonised Guideline for Good Clinical Practice (GCP), EU regulation 536/2014 and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations will be treated as "protocol deviation". Protocol Deviations with a direct impact on the safety of the subject also must be notified by the Sponsor to the national competent authority, the Federal Agency for Medicines, and Health Products (FAMHP). Similarly, Suspected Unexpected Serious Adverse Events will be reported through the EudraVigilance system. A yearly safety report will be published through the Clinical Trials Information System (CTIS).

Monitoring will be conducted after a site has included approximately five new patients to ensure protocol adherence, accurate data entry, and correct adverse event reporting, as well as to verify compliance with regulatory requirements, GCP, and GDPR guidelines. More frequent monitoring visits may be conducted as needed.

CRediT authorship contribution statement

C. Wessa: Writing – review & editing, Writing – original draft, Project administration. **J. Janssens:** Writing – original draft, Project administration. **V. Coppens:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition. **K. El Abdellati:** Writing – review & editing, Methodology. **E. Vergaelen:** Supervision, Project administration, Methodology, Funding acquisition. **S. van den Ameele:** Supervision, Project administration, Methodology, Funding acquisition. **C. Baeken:** Supervision, Project administration, Methodology, Funding acquisition. **D. Zeeuws:** Supervision, Project administration. **Y. Milaneschi:** Writing – review & editing, Methodology, Funding acquisition. **F. Lamers:** Writing – review & editing, Methodology, Funding acquisition. **B. Penninx:** Writing – review & editing, Methodology, Funding acquisition. **S. Claes:** Supervision, Project administration, Methodology, Funding acquisition. **M. Morrens:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition. **L. De Picker:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition.

Declaration of competing interest

The authors report no conflicts of interests.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100871.

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