




RESEARCH PROTOCOL

PSY-PGx 

PROTOCOL TITLE 'A New Intervention for Implementation of Pharmacogenetics in Psychiatry'

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Protocol Title: A New Intervention for Implementation of Pharmacogenetics in Psychiatry

Version 1.1 dated 17 October 2024

I agree to the conditions relating to this study as set out in the above named protocol. I fully understand that any changes instituted by the Investigator(s) without previous discussion with the appropriate sponsor personnel would constitute a violation of the protocol, including any ancillary studies or procedures performed on study subjects (other than those procedures necessary for the well-being of the subjects).

I acknowledge that I have read the above named protocol and agree to carry out all of its terms in accordance with the applicable regulations and law, to follow ICH GCP guidelines for good clinical practice, to obtain the required regulatory approvals prior to implementation, to allow direct access to source documents, and agree to inspection by auditors from regulatory authorities, as required by ICH GCP.

To be signed by Principal Investigator.

Full name of Principal Investigator	
Signature	
Date	

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
AE	Adverse Event
ALAT	Alanine-Aminotransferase
ASAT	Aspartat-Aminotransferase
AR	Adverse Reaction
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
COV	Close-out visit
CPIC	Clinical pharmacogenetics implementation consortium
CV	Curriculum Vitae
CYP2C19	Cytochrome P450 2C19
CYP2D6	Cytochrome P450 2D6
DALY	Disability-adjusted life year
DAU	Dosing as Usual
DPWG	Dutch Pharmacogenetic Working Group
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EQ-5D-5L	5-level EQ-5D questionnaire
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
FAIR	Findable, Accessible, Interoperable and Re-usable principles
FAST	Functioning Assessment short test
FCRB	Fundacio Clinic per a la Recerca Biomedica

FFUB	Farmaceutski Fakultet Univerzitetu Boegradu
FIBSER	Frequency, Intensity and Burden of Side Effects Rating Scale
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
GGT	Gamma-Glutamate-Transferase
IB	Investigator's Brochure
IC	Informed Consent
ICH	International Conference on Harmonisation
ICT	Information and Communication Technology
IM	Intermediate Metaboliser
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IMV	Interim Monitoring Visit
ITF	Innovative Task Force
ITT	Intention to Treat
Hb	Haemoglobin
KCL	King's College London
LMUM	Ludwig-Maximilians-University Munich
IPPG	Institute of Psychiatric Phenomics and Genomics
MCV	Mean Corpuscular Volume
MDD	Major Depressive Disorder
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
MI	Multiple Imputation
ML	Maximum Likelihood
MUMC	Maastricht University Medical Centre
NM	Normal Metaboliser
PANSS	Positive and Negative Symptom Scale
PGB/ PsyQ	Parnassia Group
PGx	Pharmacogenetic

PI(s)	Principal Investigator(s)
PM	Poor Metaboliser
PPP	Purchasing Power Parity
RAS-DS	Recovery assessment Scale - Domains and Stages
RCT	Randomised Controlled Trial
(S)AE	(Serious) Adverse Event
SIGH-A	Structured Interview Guide for the Hamilton Anxiety Scale
SIGH-D	Structured Interview Guide for the Hamilton Depression Scale
SIV	Site Initiation Visit
SPC	Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor but referred to as a subsidising party.
SUNY	SUNY Upstate Medical University New York
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDM	Therapeutic drug monitoring
TRL	Technology Readiness Level
TSH	Thyroid Stimulating Hormon
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
UBB	Universitatea Babes Bolyai (Babes Bolyai University)
UKU-SERS	Udvalg for Kliniske Undersøgelser – Side Effects Rating Scale
UM	Ultra-rapid Metaboliser
USA	United States of America
USD	United States Dollars
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen
2FA	Two-factor authentication

PROTOCOL SYNOPSIS

Protocol code	PSY-PGx
Version and date	Version 1.1, 10 October 2024
Title of the study	'A New Intervention for Implementation of Pharmacogenetics in Psychiatry'
EUCT No.	2023-509680-25-00
Sponsor	Parnassia
Sites	<p>Multicenter clinical trial, 9 participating sites:</p> <p>Maastricht University (MUMC): Department of Psychiatry and Neuropsychology, Maastricht University, Netherlands</p> <p>Parnassia Group (PGB): PsyQ/ Parnassia Psychiatric Institute, Department of Psychiatry, Amsterdam, Netherlands</p> <p>Farmaceutski Fakultet Univerzitetau Boegradu (FFUB): Faculty of Pharmacy, University of Belgrade, Serbia</p> <p>Universitatea Babes Bolyai (UBB): Department of Clinical Psychology and Psychotherapy, Babeş-Bolyai University, Romania</p> <p>SUNY Upstate Medical University (SUNY): Department of Psychiatry and Behavioural Sciences, SUNY Upstate Medical University, Syracuse, NY, United States</p> <p>King's College London (KCL): Institute of Psychiatry, Psychology & Neuroscience, King's College, London, UK</p> <p>Universitätsklinikum Bonn (UKB):* Department of Psychiatry and Psychotherapy, University Hospital Bonn, Germany</p> <p>Ludwig-Maximilians-University (LMUM):* Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, Ludwig-Maximilian University, Munich, Germany</p> <p>Hospital Clínic de Barcelona (HC):*</p>

	<p>Department of Psychiatry and Psychology, Hospital Clínic de Barcelona, Spain</p> <p>According to local requirements of each participating country, this study is considered a clinical trial in Germany and Spain*. In the other participating sites the study is a research project.</p>
Study period	Each patient will be followed for 24 weeks.
Primary objective	The primary objective of this study is to compare individualized medication dosing based on pharmacogenetics in psychiatric patients with dosing as usual.
Secondary objective	Secondary objectives of this study include evaluation of the impact of pharmacogenetic testing on clinical response, side effects, general wellbeing, and psychosocial functioning.
Further objectives	<p>1) deep phenotyping of patients during the clinical trial to identify other factors besides pharmacogenetics that may influence individual medication response, including passive monitoring of behavioural aspects by means of a mobile phone application,</p> <p>2) investigate other genetic factors related to medication response including genetic variants related to drug absorption, distribution, metabolism and elimination.</p>
Study population	<p>All participants must be inpatients or outpatients with a primary diagnosis of one of the following:</p> <ol style="list-style-type: none"> Mood disorder (major depressive disorder and bipolar disorder (currently depressive episode)): diagnosed via psychiatric evaluation, by means of the Mini-International Neuropsychiatric Interview (MINI)*. Anxiety disorder (for example panic disorder, social phobia, specific phobia, agoraphobia, generalised anxiety disorder) assessed via psychiatric evaluation using the MINI*. Psychotic disorder (schizophrenia and schizoaffective disorder): diagnosed via psychiatric evaluation using the MINI*. <p>* SCID-I diagnosis in agreement with DSM-5 criteria, diagnosed with MINI.</p>
Selection criteria	<p>Inclusion criteria</p> <p>In order to be eligible to participate in this study, a subject must meet all of the following criteria:</p>

	<ol style="list-style-type: none"> 1. Suffer from a depressive episode (major depressive disorder and bipolar disorder (currently depressive episode)) (as assessed by the MINI in agreement with DSM-5 criteria) of at least moderate severity (assessed using the Structured Interview Guide for the Hamilton Depression Scale (SIGH-D) with a score of 14 or higher) and/or suffer from an anxiety disorder (for example panic disorder, social phobia, specific phobia, agoraphobia, generalised anxiety disorder) (as assessed by the MINI in agreement with DSM-5 criteria) of at least moderate severity (assessed using the Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A) with a score of 18 or higher) and/or suffer from a psychotic disorder (schizophrenia and schizoaffective disorder) (as assessed by the MINI in agreement with DSM-5 criteria) of at least moderate severity (assessed using the Positive and Negative Symptom Scale (PANSS) with a score of 75 or higher). 2. Have had an inadequate response to at least 1 psychotropic treatment during their life-time. Inadequate response is defined as insufficient efficacy of a psychotropic treatment when dosed high enough and maintained long enough, or discontinuation of a psychotropic treatment due to AEs or intolerability. 3. Are about to switch (or have switched within the last 2 weeks prior to first contact with an investigator) to sertraline or escitalopram (for patients with mood or anxiety disorders), or to aripiprazole or risperidone (for patients with psychotic disorders) due to an inadequate response to or intolerance of the current/previous medication. 4. Currently receiving inpatient or outpatient psychiatric treatment. 5. Be able to understand the requirements of the study and provide written informed consent to participate in this study; a signed
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	<p>and dated informed consent form (ICF) will be obtained from each patient before any procedure of the study.</p> <ol style="list-style-type: none"> 6. To give written consent to the use and disclosure of clinical data from their medical records for the purpose of this study. 7. Age between ≥ 18 and < 65 years. 8. Women of child-bearing potential* must have a negative pregnancy test in serum/urine before the inclusion in the study and agree to use highly effective contraceptive methods during the study. Highly effective contraceptive methods will include: intrauterine device, bilateral tubal occlusion, vasectomized partner and sexual abstinence. <p>Hormonal contraceptive methods is accepted because there are no additional risk for this trial.</p> <p>* A woman will be considered of childbearing potential, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as 0 menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.</p> <p>Exclusion criteria:</p> <p>Any potential subject who meets any of the following criteria will be excluded from participation in this study:</p> <ol style="list-style-type: none"> 1. Patients with a history of prior pharmacogenomic testing 2. Patients with no prior use of psychotropic medication (medication-naïve patients) 3. Severe somatic comorbidities as reported in the subject's medical history or based on clinical chemistry/electrocardiography (ECG) results up to six months
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	<p>ago. If any of these comorbidities is detected on the basis of physical examination and/or clinical chemistry and/or ECG at the screening visit, participation is not possible.</p> <ul style="list-style-type: none"> • Liver disease defined as follows: Alanine-Aminotransferase (ALAT) >70u/L • Renal disease defined as: Estimated glomerular filtration rate (eGFR) < 60mL/min/1.73m² • Uncontrolled diabetes considering screening blood tests (Blood glucose > 11.1 mmol/L or two timestwice fasting glucose > 7.0 mmol/L) • Cardiac disease defined as: prolonged QT-interval. <p>4. Alcohol and/or substance abuse and/or dependence (except nicotine) , allowing mild substance/ alcohol use disorder (as assessed by the MINI in agreement with DSM-5 criteria).</p> <p>5. Polypharmacy defined as the routine use of five or more medications including over-the-counter, prescription and/or traditional and complementary medicines used by a patient (WHO 2019) , excluding the study medication.</p> <p>6. Pregnant or breastfeeding women</p>
Study design	International multi-centre 24 week randomised clinical trial, participant- and rater-blinded, two-arm, parallel-group controlled.
Number of subjects	2500 patients
Investigational product	aripiprazole and risperidone for psychotic disorders sertraline and escitalopram for mood- and anxiety disorders
Pharmaceutical form	Pharmaceutical form will be different depending the country's authorisation.
Dosage	<p>PSY-PGx group: This is the intervention group. All patients will be treated according to a personalised medication recommendation based on the results of pharmacogenetic testing</p> <p>Dosing as usual (DAU) group: This is the control group. In this group, prescribing physicians will also prescribe one of the predefined drugs according to guides treatments.</p>

Duration of treatment	24 weeks.
Primary outcome measures	Primary endpoint will be patient recovery at 24 weeks, as assessed using the patient recovery assessment scale (RAS, RAS-DS,).
Secondary and exploratory outcome measures	<p>Secondary outcomes that will be examined are measures obtained over a 24-week period after inclusion. Clinical effect (response or remission), side effects, general well-being and psychosocial functioning will be assessed using the following scales:</p> <p><u>A. Response, defined as a 50% point reduction in the following scales:</u></p> <ol style="list-style-type: none"> 1. Structured interview Guide for the Hamilton Depression Scale³³ (SIGH-D) for depressive disorder 2. Structured interview Guide for the Hamilton Anxiety Scale¹ (SIGH-A) for anxiety disorder 3. Positive and Negative Symptom Scale² (PANSS) for psychotic disorder <p><u>B. Symptomatic Remission, defined as:</u></p> <ol style="list-style-type: none"> 1. SIGH-D score of 7 or less. 2. SIGH-A score of 7 or less. 3. PANSS score of 57 or less. <p><u>C. Side effects:</u></p> <ol style="list-style-type: none"> 1. Frequency, Intensity and Burden of side effects ratings³ (FIBSER). 2. Udvalg for Kliniske Undersogelse – Side Effects Rating Scale⁴ (UKU-SERS). <p><u>D. General wellbeing and psychosocial functioning:</u></p> <ol style="list-style-type: none"> 1. The 5-level EQ-5D version⁵ (EQ-5D-5L). 2. Functioning Assessment short test⁶ (FAST).
Statistical methods and planned analyses	<p>An independent statistician who is masked to treatment allocation will perform the statistical analyses. Patient characteristics will be summarized for all groups together and by diagnostic group and treatment arm as means or percentages, depending on the type of measurement. We will analyse the data as randomized (ITT). All analyses will be performed separately for each diagnostic group as different questionnaires will be used to assess different questionnaires. We will use mixed effects models adjusted for a number of important covariates (gender, age, ethnicity), that are plausibly predictive of missingness. The model should be robust for missingness at random. The model corrects for this and will yield valid results if missingness can be predicted depending on the diagnostic group to which one belongs. Reasons for drop-out will be documented. The descriptive analysis will summarize</p>

	<p>patient characteristics at baseline and all RAS-DS as well as other outcomes.</p> <p>After inclusion of 50% of patients an interim analysis will be performed. If the research question can already be answered with these patient numbers, the study can be prematurely terminated. Another possibility is that even with inclusion of the proposed number of patients the chance of finding statistical or clinically significant or relevant differences is small (futility analysis).</p> <p>A separate futility analysis will be conducted for each diagnostic group. Members from the research team will conduct these analyses and the Data Safety Monitoring Board (DSMB) will evaluate the actual data and advise.</p>
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1. INTRODUCTION AND RATIONALE

1.1 Background on mental disorders

Mental disorders are noncommunicable diseases which pose a major health challenge in Europe in the 21st century. An estimated 38.2% of the European population, representing 165 million people, suffer from a mental disorder, and this number is expected to increase over time⁷⁻⁹. The direct and indirect costs of psychiatric disorders in Europe are estimated at hundreds of billions of PPP (Purchasing Power Parity) and these costs are particularly high for anxiety, psychotic and mood disorders¹⁰. The majority of people with mental disorders experience onset early in life. In moderate or severe cases, spontaneous remission rarely occurs, pharmaceutical treatment is effective in about only one third of patients, and there is an increased risk of additional diseases, including obesity, cardiovascular disease and diabetes. As a result, the life expectancy of people with mental disorders is reduced by up to 20 years⁹. For most mental disorders, the specific individual treatment needs are not well defined, and therefore it seems essential to conduct studies that include a broader range of information regarding personalised treatment.

The fundamental understanding of the disease mechanisms underlying psychiatric disorders has stagnated in recent decades. As a result, new drugs with new therapeutic targets are lacking, leaving existing drugs as the only treatment alternatives. However, the use of these drugs is associated with frequent treatment failure, and many patients are condemned to a long and arduous process of trial-and-error pharmacotherapy until they receive effective and tolerable treatment; moreover, the number of therapy-resistant patients is considerable^{11,12}.

1.2 Background on pharmacogenetic testing

Effective treatments for mental disorders are available, but their efficacy is limited by low compliance due to frequent side effects, partly due to patient heterogeneity in genes encoding for drug-metabolising enzymes. The most commonly reported side effects are headache, gastrointestinal problems, dry mouth or hypersalivation, blunting of affect, agitation or increased suicidal behaviour. Another problem is that of somatic comorbidity, such as weight gain, hypercholesterolemia, cardiac side effects (e.g., QTc interval prolongation), and sexual side effects. These problems are often so severe that people do not adhere to the medication (e.g., skip doses) or decide to discontinue it. Recent studies have shown that genotyping of genes encoding drug-metabolising enzymes can identify which patient benefits from which treatment¹¹⁻¹³. In this sense, pharmacogenetic (PGx) testing can help reduce uncertainty in the treatment selection process by determining the person-specific genetic factors that predict clinical response and adverse effects associated with genetic variants affecting drug-metabolising enzymes, drug transporters or drug targets, with differences in metabolism being by far the most important¹¹⁻¹³.

Among the most commonly prescribed antidepressants and antipsychotics worldwide are escitalopram, sertraline (antidepressants), risperidone, and aripiprazole (antipsychotics). For

these drugs, common genetic variants of the drug-metabolising enzymes such as e.g. cytochrome P450 2C19 (CYP2C19) and cytochrome P450 2D6 (CYP2D6) influence medication response.

Pharmacogenetic polymorphisms affecting drug metabolism are common. Test methods for these have existed for many years and have become increasingly comprehensive and informative. The results of such tests are usually translated into metaboliser status:

- Normal metaboliser (NM); normal enzyme activity,
- Intermediate metaboliser (IM): reduced enzyme activity,
- Poor metaboliser (PM): almost no/no enzyme activity,
- Ultrarapid metaboliser status (UM): increased enzyme activity.

In 2005, the Dutch Pharmacogenetic Working Group (DPWG) formulated a dosage recommendation based on pharmacogenetic metaboliser status¹⁴⁻¹⁶. This advice has been adopted worldwide with subtle differences¹⁷. However, it is not routinely used in clinical settings as it is challenging to translate the results to the complexities of a real-life patient setting. The global implementation of pharmacogenetics in psychiatry has also been hampered by the fact that the seven prospective clinical trials that demonstrated clinical benefit in terms of reduction of psychiatric symptoms and/or fewer adverse effects were based on mostly small samples, were all (partly) industry sponsored, used commercial pharmacogenetic combinatorial panels, and used algorithms that were non-disclosed¹⁸⁻²⁴.

1.3 Study Rationale

The clinical study presented in this study protocol, embedded within the HORIZON 2020-funded international multi-centre PSY-PGx project (www.psy-pgx.org), will be the first international, non-commercial, prospective pharmacogenetic study to investigate the impact of genetic factors including the clinically relevant genotypes CYP2C19 and CYP2D6 when prescribing a number of commonly used psychiatric medications in real-life patient settings. In this clinical study we will compare individualized prescribing of medication based on pharmacogenetics in psychiatric patients with treatment as usual (i.e., dosing largely based on trial-and-error), assessing patient recovery as the primary endpoint. This result will be analysed and incorporated in already available dosage guidelines. A potential benefit of the study consists of patients receiving medication that is better matched to their individual pharmacogenetic profile, which is likely to lead to fewer side effects or greater efficacy of pharmacotherapy. In addition to pharmacogenetic information, other patient characteristics such as gender, age, comorbidity, comedication and behaviour will be examined to determine their influence on patient outcomes.

2. OBJECTIVES

Primary Objective: The primary objective of this study is to compare individualised medication dosing based on pharmacogenetics in psychiatric patients with dosing as usual (i.e. dosing largely based on trial-and-error). The primary endpoint for this comparison will be patient recovery in response to psychotropic treatment from baseline to the end of week 24 of the study. Earlier prospective pharmacogenetic studies in psychiatric patients have only assessed until 12 weeks, this study will follow-up until 24 weeks as it is known that recovery from more severe psychiatric disease episodes, where medication is indicated, usually takes longer.

Primary hypothesis: We hypothesize that patients in the pharmacogenetics group experience better efficacy of the prescribed medication and fewer side effects compared to the dosing as usual group, which we expect to be reflected in better patient recovery as assessed by the patients themselves.

Secondary Objective(s): Secondary objectives of this study include evaluation of the impact of pharmacogenetic testing on clinical response, side effects, general wellbeing, and psychosocial functioning.

Secondary hypothesis: We hypothesize that patients in the pharmacogenetics group experience greater symptom improvement, response and remission and fewer side effects compared to the dosing as usual group. In addition, we expect this to be reflected in better general wellbeing and psychosocial functioning.

Further objectives include 1) deep phenotyping of patients during the clinical trial to identify other factors besides pharmacogenetics that may influence individual medication response, including passive monitoring of behavioural aspects by means of a mobile phone application, 2) investigate other genetic factors related to medication response including genetic variants related to drug absorption, distribution, metabolism and elimination. We aim to collect data from individual patients with anxiety, mood, and psychotic disorders recruited in 9 centres across 6 European countries and the USA, before changing dose or type of psychopharmacological treatment, to identify additional personal factors that may influence medication response, such as (in)efficacy or emergence of side effects and comorbidities.

3. STUDY DESIGN

This protocol describes an international multi-centre randomised clinical trial (RCT) into fine-tuning medication dosage prescription in psychiatric patients suffering from a mood-, anxiety, or psychotic disorder. This will be achieved by conducting a 24-week randomised, participant- and rater-blinded, two-arm, parallel-group controlled trial of pharmacogenetic-informed pharmacotherapy. A timeline is provided in Figure 1 below.

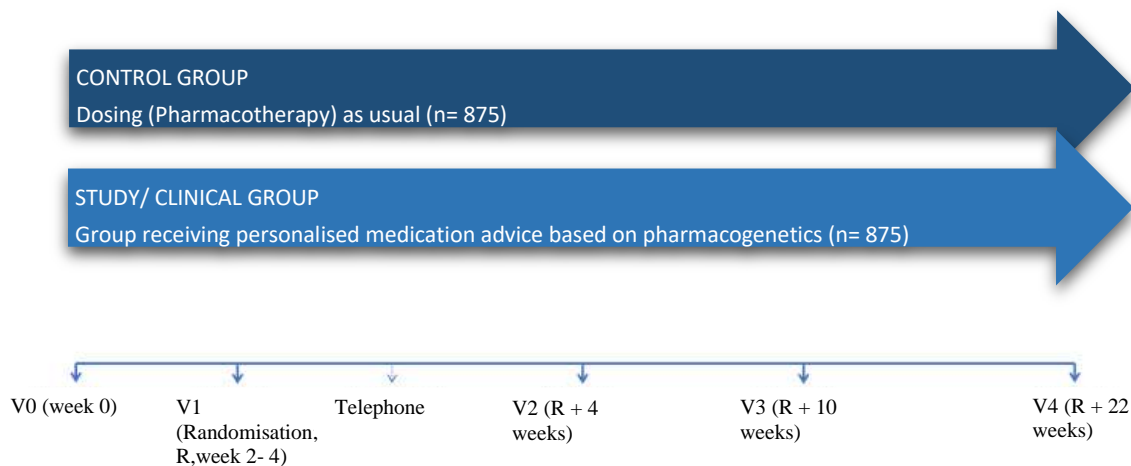


Figure 1: Study timeline

During the study five visits and a phone call will take place. At visit 0, baseline assessments will be performed and blood samples taken to determine the pharmacogenetic profile. Visit 1, which will take place 2-4 weeks after V0, is the randomisation visit (via CASTOR), where patients will be assigned to the dosing as usual (DAU) group, or the PSY-PGx Group, where medication (dose) will be prescribed based on their genetic profile, according to the predefined dosing schedule (see Table 2 and Section 6.2). The drugs used in the study are sertraline or escitalopram for mood and anxiety disorders, and risperidone or aripiprazole for psychotic disorders. For these psychiatric drugs, the relationship between for example CYP2C19/CYP2D6 genotype and drug levels was quantified with sufficient accuracy to be used as a scientific basis for CYP2D6/CYP2C19 genotype-based dosage recommendations²⁵.

Two weeks after randomisation, a telephone phone call will be made to the patient. The aim of this phone call, which will be conducted by a researcher and will last no longer than about five minutes, is to motivate the patient to continue taking the medication and to answer any questions they might have. In clinical practice this short phone call has proven to be very useful in maintaining medication adherence and motivation. No assessments are made during this phone call.

During V2 (4 weeks post-randomisation), V3 (10 weeks post-randomisation) and V4 (22 weeks post-randomisation), medication efficacy will be assessed, mainly using the patient recovery assessment scale (RAS-DS) for all disorder groups. After the study, patients in the DAU and PGx groups will also be given their pharmacogenetic profile, which will make it possible to personalise their medication if necessary.

4. STUDY POPULATION

4.1 Population (base)

All participants aged 18 or older will be recruited from the inpatient and outpatient facilities of the 9 participating sites: Parnassia Groep BV (PGB), Ludwig-Maximilians-Universität München (LMUM), University Hospital Bonn (UKB), Farmaceutski Fakultet Univerzitetau Beogradu (FFUB), King's College London (KCL), Hospital Clinic de Barcelona (HC), Maastricht University Medical Centre + (MUMC+), Universitatea Babeş-Bolyai (UBB), and SUNY Upstate Medical School, Syracuse, NY, USA (SUNY).

According to local requirements of each participating country, this study is considered a clinical trial in Germany (Ludwig-Maximilians-Universität München and University Hospital Bonn) and Spain (Hospital Clinic de Barcelona). For the other participating sites the study is considered a research project.

The study approval was requested at each country according to the specific requirements.

All participants must be inpatients or outpatients with a primary diagnosis of one of the following:

1. **Mood disorder (major depressive disorder and bipolar disorder (currently depressive episode))**: diagnosed via psychiatric evaluation, by means of the Mini-International Neuropsychiatric Interview (MINI)*.
2. **Anxiety disorder (for example panic disorder, social phobia, specific phobia, agoraphobia, generalised anxiety disorder)** assessed via psychiatric evaluation using the MINI*.
3. **Psychotic disorder (schizophrenia and schizoaffective disorder)**: diagnosed via psychiatric evaluation using the MINI*.

* SCID-I diagnosis in agreement with DSM-5 criteria, diagnosed with MINI.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. Suffer from a depressive episode (**major depressive disorder and bipolar disorder (currently depressive episode)**) (as assessed by the MINI in agreement with DSM-5 criteria) of at least moderate severity (assessed using the Structured Interview Guide for the Hamilton Depression Scale (SIGH-D) with a score of 14 or higher)

and/or

suffer from an anxiety disorder (**for example panic disorder, social phobia, specific phobia, agoraphobia, generalised anxiety disorder**) (as assessed by the MINI in

agreement with DSM-5 criteria) of at least moderate severity (assessed using the Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A) with a score of 18 or higher)

and/or

suffer from a psychotic disorder (**schizophrenia and schizoaffective disorder**) (as assessed by the MINI in agreement with DSM-5 criteria) of at least moderate severity (assessed using the Positive and Negative Symptom Scale (PANSS) with a score of 75 or higher).

2. Have had an inadequate response to at least 1 psychotropic treatment during their life-time. Inadequate response is defined as insufficient efficacy of a psychotropic treatment when dosed high enough and maintained long enough, or discontinuation of a psychotropic treatment due to AEs or intolerability.
3. Are about to switch (or have switched within the last 2 weeks prior to first contact with an investigator) to sertraline or escitalopram (for patients with mood or anxiety disorders), or to aripiprazole or risperidone (for patients with psychotic disorders) due to an inadequate response to or intolerance of the current/ previous medication.
4. Currently receiving inpatient or outpatient psychiatric treatment.
5. Be able to understand the requirements of the study and provide written informed consent to participate in this study; a signed and dated informed consent form (ICF) will be obtained from each patient before any procedure of the study.
6. To give written consent to the use and disclosure of clinical data from their medical records for the purpose of this study.
7. Age between ≥ 18 and < 65 years.
8. Women of child-bearing potential* must have a negative pregnancy test in serum/urine before the inclusion in the study and agree to use highly effective contraceptive methods during the study. Highly effective contraceptive methods will include: intrauterine device, bilateral tubal occlusion, vasectomized partner and sexual abstinence.

Hormonal contraceptive methods is accepted because there are no additional risk for this trial.

* A woman will be considered of childbearing potential, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as 0 menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12

months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.

4.3 Exclusion criteria

Any potential subject who meets any of the following criteria will be excluded from participation in this study:

1. Patients with a history of prior pharmacogenomic testing
2. Patients with no prior use of psychotropic medication (medication-naïve patients)
3. Severe somatic comorbidities as reported in the subject's medical history or based on clinical chemistry/electrocardiography (ECG) results up to six months ago. If any of these comorbidities is detected on the basis of physical examination and/or clinical chemistry and/or ECG at the screening visit, participation is not possible.
 - Liver disease defined as follows: Alanine-Aminotransferase (ALAT) >70u/L
 - Renal disease defined as: Estimated glomerular filtration rate (eGFR) < 60mL/min/1.73m²
 - Uncontrolled diabetes considering screen blood tests (Blood glucose > 11.1 mmol/L or two timestwice fasting glucose > 7.0 mmol/L)
 - Cardiac disease defined as: prolonged QT-interval.
4. Alcohol and/or substance abuse and/or dependence (except nicotine) , allowing mild substance/ alcohol use disorder (as assessed by the MINI in agreement with DSM-5 criteria).
5. Polypharmacy defined as the routine use of five or more medications including over-the-counter, prescription and/or traditional and complementary medicines used by a patient (WHO 2019) , excluding the study medication.
6. Pregnant or breastfeeding women

4.4 Sample size calculation

We aim to recruit a total of 2500 patients for the study, taking into consideration a total drop-out of 30%, over a period of 2 years. The number of patients to be recruited for each diagnostic group in each of the participating centres is detailed in Table 1 below.

Centre	Mood disorders	Anxiety Disorders	Psychotic Disorders	Total
PGB	255	100	50	405
LMUM	175	80	50	305
UKB	175	80	50	305
FFUB	125	70	50	245
KCL	150	70	50	270
HC	100	70	40	210
MUMC +(incl regional partners)	125	70	50	245

Centre	Mood disorders	Anxiety Disorders	Psychotic Disorders	Total
UBB	150	70	50	270
SUNY	125	70	50	245
Total	1250	750	500	2500

Table 1: Number of patients to be recruited per centre.

Based on previous prospective pharmacogenetic studies in psychiatry, we assume a dropout rate of 10% after screening and an additional dropout rate of 20% after randomization. This means that at least 1750 patients will be followed up (n = 875 for mood disorder, n= 525 for anxiety disorder, and n = 350 for psychotic disorder).

The numbers of patients to be recruited per diagnosis were selected on the basis of (a) the willingness to participate per diagnosis: clinical experience shows that depressed patients are more willing to participate in clinical trials than psychotic patients, and (b) the estimated number of patients that each research centre indicated it could recruit over a 2-year recruitment period. These numbers of patients are considered sufficient as all registration studies for the drugs to be used in this study were no larger than n=200 per group. In comparison, the largest prospective pharmacogenetic clinical trial conducted in psychiatry to date included a total sample of 1799 patients²⁴. Including all patients in a trans-diagnostic independent group's comparison (t-test) with a power of 90%, and alpha at 5%, an effect size (ES) as small as 0.15 (Cohen's d) could be detected. Assessment of the outcomes within each diagnostic group, with adjustment of the alpha level for multiple comparisons would give 90% power to detect a between-groups difference of 0.23 (small) for mood disorders, 0.3 (small to moderate) for anxiety disorders and 0.36 (moderate) for psychotic disorders.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

The antipsychotics aripiprazole and risperidone have been selected for the treatment of psychotic disorders, and antidepressants sertraline and escitalopram for mood- and anxiety disorders. These psychiatric drugs were chosen because they are commonly used in all countries participating in the clinical trial and because at present there is sufficient scientific evidence for genotype-based dosage recommendations²⁵. For these drugs, doses are advised to be adjusted according to DPWG and CPIC recommendations and we expect to find clinical effects when comparing prescribing standard doses (DAU group) to personalised doses (PSY-PGx group).

After inclusion, all participants will be randomly assigned (CASTOR) to one of the following branches, stratified by diagnosis:

- 1) PSY-PGx group:** This is the intervention group. All patients will be treated according to a personalised medication recommendation based on the results of pharmacogenetic testing, following the dosing guideline (Table 2). Prescribing physicians will prescribe one of the predefined drugs and will be unblinded for genotype and the resulting metabolism phenotype.
- 2) Dosing as usual (DAU) group:** This is the control group. In this group, prescribing physicians will also prescribe one of the predefined drugs, but will remain blinded to their patients' genotype and resulting metabolism phenotype for the duration of their participation in the study. After the study, patients in the control group will also be given their pharmacogenetic profile, which will make it possible to personalise their medication if necessary.

From randomisation onwards, prescribing physicians in both treatment groups may alter a patient's psychotropic medication regimen in terms of the type of medication, dose, schedule, or number of medications if necessary. If necessary, medication can be started in the lowest dose before randomization. Until randomisation, patients will continue to use their current medication. The medication and dosages used will be recorded at each visit.

Prescribing physicians will be de-blinded for genotype and the resulting metabolism phenotype only in those cases where patients were allocated into the PSY-PGx group. This will not affect the assessment of therapeutic response, as both assessors and patients will be blinded to the group allocation. The prescribing physicians will not perform any study assessments and assessors and prescribing physicians will not switch roles. Treatment will be

with medication that is already commonly prescribed worldwide in clinically applied dosages, and whose efficacy and safety have been well established (see Section 9.2).

CYP2C19 me- tabolizer	Genotype	Escitalopram daily dose	Sertraline daily dose	CYP2D6	Genotype	Risperidone daily dose	Aripiprazole daily dose
Poor (PM)	Null/Null	5 mg	50 mg	Poor (PM)	Null/Null	3-4 mg	15-20 mg
Intermediate (IM)	Wt/Null Inc/Null	5-10 mg	100 mg	Intermediate (IM)	Null/Red Red/Red	4-5 mg	20-25 mg
				Intermediate (IM+)	Wt/Null	5-6 mg	25-30 mg
Normal (NM)	Wt/Wt	15-20 mg	100-150 mg	Normal (NM)	Wt/Wt	6 mg	30 mg
Ultrarapid (UM)	Wt/Inc Inc/Inc	15-20 mg	100-150 mg	Ultrarapid (UM)	Wt/Wt x 2	6 mg	30 mg

Table 2: Predefined dosing schedule according genotype (based on data from²⁵⁻²⁷)

5.2 Use of co-intervention (if applicable)

No polypharmacy is allowed, defined as the routine use of 5 or more medications including over-the-counter, prescription and/or traditional and complementary medicines used by a patient²⁸, excluding the study medication.

5.3 Concomitant medication

As detailed in the exclusion criteria 5 polypharmacy is not accepted (defined as the routine use of five or more medications including over-the-counter, prescription and/or traditional and complementary medicines used by a patient (WHO 2019) , excluding the study medication).

For these reason, all medications continued at the start of the study or started during the treatment must be documented and recorded in the eCRF.

5.4 Escape medication (if applicable)

N/A

6. INVESTIGATIONAL PRODUCT

The study treatment for patients are:

For psychotic disorders: antipsychotics **aripiprazole** and **risperidone**

For mood- and anxiety disorders and antidepressants **sertraline** and **escitalopram**.

Dose and pharmaceutical form will be different depending the country's authorisation.

The information about Safety and efficacy for the investigational medical products are described in section "4. Clinical particulars" of the Summary of product characteristics (SmPC) of each one.

6.1 Name and description of the investigational products

6.1.1 ARIPIPRAZOLE

Aripiprazole is indicated for:

- treatment of schizophrenia in adults and in adolescents aged 15 years and older.
- treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.
- treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

ATC Code: N05AX12

Manufacturer: depending on the country's authorisation

Summary of known potential risks and benefits

Its use is contraindicated when there is hypersensitivity to the active substance or any of the excipients listed in section 6.1 from safety data sheet.

Special warnings and precautions for use can be consulted in section 4.4 from safety data sheet.

List of interaction with other medicinal products can be consulted in section 4.5 from safety data sheet.

Is not recommended in pregnancy, it should not be used during pregnancy unless clearly necessary. If discontinuation during pregnancy is necessary, it should not be done abruptly. For more information consult section 4.6 from safety data sheet.

List of adverse reaction and undesirable effects can be consulted in section 4.8 of safety data sheet.

Route of administration, dose, dosing regimen and treatment period

Route of administration: oral

Dosing regime and method of administration: detailed at section 5.1 of the protocol.

Treatment period: 24 weeks

6.1.2 RISPERIDONE

Risperidone is indicated for:

- treatment of schizophrenia.
- treatment of moderate to severe manic episodes associated with bipolar disorders.
- short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.
- short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of 55 aggressive or other disruptive behaviours require pharmacologic treatment. Pharmacological treatment should be an integral part of a more comprehensive treatment programme, including psychosocial and educational intervention. It is recommended that risperidone be prescribed by a specialist in child neurology and child and adolescent psychiatry or physicians well familiar with the treatment of conduct disorder of children and adolescents.

Risperidone is classified as an antipsychotics The main characteristics of risperidone are detailed in the safety data sheet.

ATC code: N05AX08

Manufacturer: depending on the country's authorisation

Summary of known potential risks and benefits

Its use is contraindicated when there is hypersensitivity to the active substance or any of the excipients included in section 6.1 from safety data sheet.

Special warnings and precautions for use can be consulted in section 4.4 from safety data sheet.

List of interaction with other medicinal products can be consulted in section 4.5 from safety data sheet.

Is not recommended in pregnancy, it should not be used during pregnancy unless clearly necessary. If discontinuation during pregnancy is necessary, it should not be done abruptly. For more information consult section 4.6 from safety data sheet.

List of adverse reaction and undesirable effects can be consulted in section 4.8 of safety data sheet.

Route of administration, dose, dosing regimen and treatment period

Route of administration: oral

Dosing regime and method of administration: detailed at section 5.1 of the protocol.

Treatment period: 24 weeks

6.1.3 SERTRALINE

Sertraline is indicated for the treatment of:

- Major depressive episodes.
- Prevention of recurrence of major depressive episodes.
- Panic disorder, with or without agoraphobia.
- Obsessive compulsive disorder (OCD) in adults and paediatric patients aged 6-17 years.
- Social anxiety disorder.
- Post traumatic stress disorder (PTSD)

Sertraline is a selective serotonin reuptake inhibitor (SSRI). The main characteristics of sertraline are detailed in the safety data sheet.

ATC-code: N06 AB06

Manufacturer: depending on the country's authorisation

Summary of known potential risks and benefits

Its use is contraindicated when there is hypersensitivity to the active substance or any of the excipients included in section 6.1 from safety data sheet. Concomitant treatment with irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serotonin syndrome with symptoms such as agitation, tremor and hyperthermia. Sertraline must not be initiated for at least 14 days after discontinuation of treatment with an irreversible MAOI. Sertraline must be discontinued for at least 7 days before starting treatment with an irreversible MAOI (see section 4.5).

Special warnings and precautions for use can be consulted in section 4.4 from safety data sheet.

List of interaction with other medicinal products can be consulted in section 4.5 from safety data sheet.

Sertraline is not recommended in pregnancy, unless the clinical condition of the woman is such that the benefit of the treatment is expected to outweigh the potential risk. For more information consult section 4.6 from safety data sheet.

List of adverse reaction and undesirable effects can be consulted in section 4.8 of safety data sheet.

Route of administration, dose, dosing regimen and treatment period

Route of administration: oral

Dosing regimen and treatment period: detailed at section 5.1 of the protocol.

Treatment period: 24 weeks

6.1.4 ESCITALOPRAM

Escitalopram is indicated for:

- the treatment of major depressive episodes
- panic disorder with or without agoraphobia
- obsessive compulsive disorder (OCD)
- social anxiety disorder
- generalized anxiety disorder

Escitalopram is a selective serotonin reuptake inhibitor (SSRI). The main characteristics of escitalopram are detailed in the safety data sheet.

ATC-code: N06 AB06

Manufacturer: May vary depending on the country.

Summary of known potential risks and benefits

Its use is contraindicated when there is hypersensitivity to the active substance or any of the excipients included in section 6.1 from safety data sheet. Concomitant treatment with irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serotonin syndrome with symptoms such as agitation, tremor and hyperthermia.

Escitalopram is also contraindicated in patients with prolonged QT and to use it with other medications that prolong QT. (see section 4.5).

Special warnings and precautions for use can be consulted in section 4.4 from safety data sheet.

List of interaction with other medicinal products can be consulted in section 4.5 from safety data sheet.

Escitalopram is not recommended in pregnancy, unless the clinical condition of the woman is such that the benefit of the treatment is expected to outweigh the potential risk. For more information consult section 4.6 from safety data sheet.

List of adverse reaction and undesirable effects can be consulted in section 4.8 of safety data sheet.

Route of administration, dose, dosing regimen and treatment period

Route of administration: oral

Dosing regimen and treatment period: detailed at section 5.1 of the protocol.

Treatment period: 24 weeks

6.2 Labeling of investigational products

The study is considered a low-intervention clinical trial in which patients will receive an investigational medicinal product that is covered by a marketing authorization.

The drug will be delivered and administered using the usual clinical circuits of the participating sites. For this reason, it is not considered necessary the labeling of investigational products.

6.3 Drug accountability

Adherence will be asked to patients at each study visit and analysed at the end of the study using TDM. The information will be recorded in medical records and in the eCRF.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

Clinical symptom score: Primary endpoint will be patient recovery at 24 weeks, as assessed using the patient recovery assessment scale^{29,30} (RAS, RAS-DS,). Psychometric research showed the RAS total score to have adequate test-retest reliability and internal consistency³¹. Moreover, analysis of the concurrent validity showed the RAS total score to be positively associated with empowerment and quality of life and inversely associated with psychiatric symptoms. Recovery has been a challenging construct to conceptualize because it seems to consist of, and be related to, so many constructs, including hope, empowerment, meaning of life, and quality of life, all of which were examined in this study. Overall, the RAS appears to have solid psychometric and conceptual features that make it useful in mental health services research³¹. Recent psychometric studies provide further evidence for the feasibility and psychometric strengths of the RAS-DS. The results of these study further support the construct validity of the RAS-DS and its ability to detect change over time^{30,32}.

7.1.2 Secondary study parameters/endpoints (if applicable)

Secondary outcomes that will be examined are measures obtained over a 24-week period after inclusion. Clinical effect (response or remission), side effects, general well-being and psychosocial functioning will be assessed using the following scales:

A. Response, defined as a 50% point reduction in the following scales:

1. Structured interview Guide for the Hamilton Depression Scale³³ (SIGH-D) for depressive disorder
2. Structured interview Guide for the Hamilton Anxiety Scale¹ (SIGH-A) for anxiety disorder
3. Positive and Negative Symptom Scale² (PANSS) for psychotic disorder

B. Symptomatic Remission, defined as:

1. SIGH-D score of 7 or less.
2. SIGH-A score of 7 or less.
3. PANSS score of 57 or less.

C. Side effects:

1. Frequency, Intensity and Burden of side effects ratings³ (FIBSER).
2. Udvalg for Kliniske Undersogelse – Side Effects Rating Scale⁴ (UKU-SERS).

D. General wellbeing and psychosocial functioning:

1. The 5-level EQ-5D version⁵ (EQ-5D-5L).
2. Functioning Assessment short test⁶ (FAST).

7.1.3 Other study parameters (if applicable)

Passive behavioral monitoring will be conducted using the BeHAPP mobile application³⁴⁻³⁶. The app was developed in academia (RUG) for use in scientific research, and has been used previously in several international scientific research projects. It is an easy-to-use app and the research subject only has to install it on the his/her mobile phone and make sure the mobile is charged in time, no other actions are required by the participant. The BEHAPP mobile application will be used to collect passive, social behavioural data as additional outcome measure that has been shown to be of value in predicting relapse/recurrence. Once the application is installed and initialised, it passively collects (meta)data on phone call activity, Bluetooth devices and WiFi access points in the participant's immediate environment, location updates and mobile application usage. Given such a sensitive operational context and equally sensitive data-catalogue, BEHAPP recognizes privacy and security as the primary design goal in all platform developments and operations. To achieve a high level of security and trust, the platform uses a combination of measures on both the organizational and technical levels^{35,36}.

A brief overview of the data flow:

1. Data is collected on the smartphones of participants and immediately encrypted on device.
2. The data is sent over to our central infrastructure through a secure connection.
3. The public zone dispatches the data to the private zone, it does not have the capability to inspect / retrieve or decrypt data.
4. The private zone redirects the data to the correct study and site database.
5. A researcher, if authorized for a specific study, can request to load and decrypt a participant's data and subsequently analyze it. Behapp's custom tools make sure that the decrypted data view is only held in volatile memory (RAM).

More details can be found in *D6_Productgegevens BeHapp mobiele applicatie*, and on the website <https://behapp.org>.

7.2 Randomisation, blinding and treatment allocation

Participants will be randomised to “dosing as usual” (DAU) or “treatment guided by pharmacogenetic testing” (PSY-PGx) using a 1:1 allocation after genotyping. Randomisation is stratified according to diagnosis (mood, anxiety and psychotic disorder), and is done via the eCRF system (CASTOR). Randomisation is performed by a non-blinded member of the study team after receiving phenotype information. Patients and assessors will be blinded throughout the study. Assessors and prescribers will not switch roles. At the end of the trial, we will ask the patient and the assessor in which group they think they are assigned to, to check whether blinding has been effective.

As all medication used is registered and will not be used off-label, there is no need for (emergency) unblinding during the study.

7.3 Study procedures

Patients will be approached at the local inclusion sites (see also Section 11.2). All participants will be asked to sign an informed consent form prior to participation, with the investigators co-signing.

After inclusion, the baseline assessments will be performed. Patients will be randomised (V1) no more than four weeks later. To compare pharmacotherapy prescribed as usual with personalised treatment using pharmacogenetic information, all enrolled patient will be followed-up for a 24-week period and will be assessed at baseline (V0), and 4 weeks after randomisation at Visit 2 (V2), 10 weeks after randomisation at Visit 3 (V3), and 22 weeks after randomisation at Visit 4 (V4). The 4 weeks between inclusion and randomisation is the time needed for genotyping in the central genotyping facility in Bonn and transferring the phenotype into the eCRF in CASTOR. This does not mean a delay in treatment, as we only include participants who are already being treated, for whom the medication was previously insufficiently effective or who have previously stopped medication due to side effects. Also if necessary medication can be started in the lowest dose. To evaluate the initial response to treatment, and motivate the patient to continue taking the medication, a brief telephone call will be made two weeks after randomisation. The estimated window for the follow up visits and the telephone call is ± 2 days, always in relation to visit V1 during which randomisation takes place.

A pregnancy test in serum or urine should be done before the inclusion, prior to start treatment and at the end of treatment.

All assessments to be carried out at each time point are listed in Table 3 and described in detail below.

Assessments	V0	V1 *	V2 **	V3 ***	V4 ****
Duration of visit	2 hours	10 minutes	1 hour	1 hour	1.5 hour
Psychiatric assessment and MINI	+				
Patient Characteristics	Age, gender, demographics, diet, smoking, drugs of abuse, alcohol, comorbidity, family history		Smoking, drugs, alcohol		Smoking, drugs, alcohol
Medication	Medication history (including inefficacy and side effects), treatment duration, dosages, current medication, family history of medication	Check current medication	Check current medication	Check current medication	Check current medication

Clinical Modulators	Long duration of illness episode, higher baseline severity, moderate to severe suicidal ideation, high level of anxiety	Re-assess clinical modulators such as suicidal ideation and anxiety levels	Re-assess clinical modulators such as suicidal ideation and anxiety levels	Re-assess clinical modulators such as suicidal ideation and anxiety levels	Re-assess clinical modulators such as suicidal ideation and anxiety levels
Somatic Measurements	Hip-waist circumference, height, weight, blood pressure, pulse, ECG		Hip-waist circumference, weight, blood pressure, pulse, ECG	Hip-waist circumference, weight, blood pressure, pulse	Hip-waist circumference, weight, blood pressure, pulse
Blood measurements	Genotyping, clinical chemistry. Therapeutic drug monitoring (TDM), (section 8.3.3)		Clinical chemistry, Therapeutic drug monitoring (TDM)		
Questionnaires	SIGH-D, SIGH-A or PANSS (depending on diagnosis), FIBSER, UKU, EQ-5D-5L, FAST, RAS-DS		SIGH-D, SIGH-A or PANSS (depending on diagnosis), FIBSER, UKU, EQ-5D-5L, FAST, RAS-DS	SIGH-D, SIGH-A or PANSS (depending on diagnosis), FIBSER, UKU, EQ-5D-5L, FAST, RAS-DS	SIGH-D, SIGH-A or PANSS (depending on diagnosis), FIBSER, UKU, EQ-5D-5L, FAST, RAS-DS
Pregnancy test	Pregnancy test in serum or urine (selection criteria)	Pregnancy test in serum or urine			Pregnancy test in serum or urine
IT data -BEHAPP app for passive monitoring	Throughout the duration of the trial period (i.e. from consent until V4)				

Table 3: Visit schedule. *max. four weeks after baseline (by V1); **visit window ± 2 days *** ± 5 days, **** ± 7 days compared compared to the randomisation visit (V1). Two weeks after randomization, a brief phone call will be carried out to evaluate initial response to treatment and motivate the patient to continue taking the medication.

7.3.1 Psychiatric assessment and patient characteristics

All participants will be interviewed to gather the following data (Table 3):

- Psychiatric assessment using the MINI version 7.0.2 for DSM-5³⁷
- Age, gender, demographics, medication, diet, smoking, alcohol use, drugs, and comorbidities
- Medication history (including inefficacy and side effects, duration of treatment, dosages)
- Family history of psychiatric illness (also of medications and inefficacies and/or side effects)
- Clinical modulators: longer duration of illness episode, higher baseline severity, moderate to severe suicidal ideation, high level of anxiety

7.3.2 Patient questionnaires

The following domains will be examined by administering various scales and questionnaires at V0, V2, V3, and V4 (Table 3). Symptom severity will be assessed using the SIGH-D (mood disorders), SIGH-A (anxiety disorders), or PANSS (psychotic disorders). Assessors will be trained with a (physical and digital) training programme and will need to score above a predefined threshold level (depending on the questionnaire) to become certified and this will be centrally documented at the sponsor site. Interrater variability will be assessed. All assessors will be blind to patient allocation.

- Clinical recovery will be assessed by means of the Recovery Assessment Scale (RAS-DS).
- Secondary endpoints: Well-being and quality of life will be assessed by means of the EuroQol 5 Dimensions-5 levels questionnaire (EQ-5D-5L); psychosocial functioning by means of the Functioning Assessment Short Test (FAST). Clinical symptomatology will be evaluated using the SIGH-D (for patients with mood disorders), SIGH-A (in the case of patients with anxiety disorders), and the PANSS (for psychotic patients).
- Side effects will be evaluated using both the Frequency, Intensity and Burden of side effects ratings (FIBSER) and the Udvalg for Kliniske Undersogelse – Side Effects Rating Scale (UKU-SERS).

7.3.3 Blood samples

This project will collect blood twice, once at baseline (V0) and once at V2. At the baseline visit, 20ml of blood will be collected. At V2, 10 ml will be collected.

1. Genotyping:

Genotyping is a core element in the current study. The samples will be obtained by taking blood from the patients according to a standard medical procedure (venipuncture) and only once per patient (V0).

Once the blood sample is collected, it will be pseudonymized and transported from the clinical centres to the central genotyping facility in Bonn. After genotyping, the prescribing clinician will receive the results latest at four weeks after the first visit. To meet this deadline, samples must be sent to the central genotyping facility on the day of blood collection or at the latest the next working day.

In the central genotyping laboratory, all logistic requirements are in place to ensure that the incoming samples are analysed promptly so that the time interval of four weeks between blood collection and generation of the pharmacogenetic report is met.

Genotyping will be performed using state of the art genome-wide microarrays with specific PGx content that contain detailed information on many genotypes relevant for pharmacogenetics with genome-wide coverage. The genotypes tested will include all relevant

common and some rare functional variant alleles. These currently include CYP2C19 loss of function (CYP2C19Null) alleles are CYP2C19*2, *3, *4, *5, *6, *8, and the allele which increases CYP2C19 expression (CYP2C19Inc) is *17. CYP2D6 loss of function (CYP2D6Null) alleles are *3, *4, *5, *6, *7, *8, *11, *12, *14, *18, *19, *20, *29, *38, and *42. Alleles reducing the function of CYP2D6 (CYP2D6Red) are *9, *10, *17, and *41, whereas CYP2D6 multiplication (CYP2D6xN) leads to the increase of CYP2D6 activity. Interpretations and validation of the results of the genotyping will be performed continuously in the central laboratory. The categorization and dosing recommendations are provided to the prescribing physician as described in table 2. These dose range recommendations are based on recently published results from over 5,000 patients²⁵ (see Table 2).

2. Clinical chemistry

At V0 and V2 time points, a blood extraction will be carried out in order to perform laboratory tests (biochemistry including sodium, glucose, creatinine, glucose, ALAT/ASAT, GGT, fatty lipids, prolactin, TSH, Hb/MCV, vitamin B12 and D, folic acid). For baseline (V0), results from previous routine laboratory tests, not older than 6 months, may be used.

3. Therapeutic drug monitoring (TDM)

At the V0 and V2 time point, one sample of the blood extraction will be used to measure the steady state blood concentration of the prescribed medication, using validated analytical methods. The V0 blood sample is used as blank serum for control.

7.3.4 Other somatic and medical measures

Hip-waist circumference, height, weight, blood pressure, and pulse rate will be collected at all time-point visits (V0-V2-V3-V4), while an electrocardiogram (ECG) will be performed at V0 and V2.

7.3.5 Passive monitoring via ICT tool

The BEHAPP mobile application (table 4), which performs passive behavioural monitoring of patients, has been and is currently used for research in psychiatric patients³⁴⁻³⁶. This app is currently not used in standard clinical practice. As part of our clinical trial, we will integrate patient data retrieved via the BEHAPP app for more extensive phenotyping of the patients to support the clinical trial to develop a personalised pharmacotherapy approach towards better and safer treatment outcomes in psychiatry. Monitoring behavioral data can assist in e.g. predicting relapse and guide future interventions in preventing relapse.

Patient can decide to participate in this passive monitoring without interfering in their participation in the study.


	
ICT Solution	BeHapp
Type	Mobile App
Website	https://behapp.org
Available languages	Google provided languages
Purpose	Data collection through passive monitoring of patients via app for patients
Functionalities/ Specifications	Smartphone application for assessment of typical and abnormal human behavioural phenotypes in their natural environment.
Innovation	A passive behavioural monitoring tool from which data has been successfully collected in a wide variety of brain disorders, including depression, schizophrenia and Alzheimer's Disease.
Use in PSY-PGx	Endpoint measures will be used to develop an implementation strategy of pharmacogenetics-based personalised medicine in psychiatry at an international level.
Technology Readiness Level (TRL)	<ul style="list-style-type: none"> Currently: TRL 7³⁴ Proof of concept data has been collected and analysed as part of IMI PRISM project. Initiated path forward to informally discuss a digital biomarker using this technology with the EMA innovative task force (ITF)
Previous tests	App has been applied in a variety of disease cohorts (Schizophrenia, Depression, and Alzheimer's disease) in a variety of national and EU funded projects (e.g., IMI PRISM, IMI ROADMAP, SMARD).

Table 4: BEHAPP as an integral part of the new PSY-PGx model of care

7.4 Consent withdrawal and study discontinuation

Consent withdrawal

A patient will prematurely discontinue the study in case of withdrawal of informed consent. All patients have the right to withdraw their consent at any time during the study without prejudice to them.

If the patient expresses the wish to quit the study, they will be asked to be followed up according to protocol, without following the medication strategy as dictated by the protocol.

Study discontinuation

The patient may also discontinue study participation in the following instances:

1. If the investigator considers in the interest of the subject (i.e intercurrent illness, occurrence of adverse events) that it is best for the patient to stop study medication.
2. The subject fails to comply with the protocol requirements or fails to cooperate with investigator.
3. If the patient considers it best to discontinue his/her participation in the study.
4. If a female subject becomes pregnant during the study and investigator consider that expected benefit not justifies the potential risk (please see section 8.6)

All follow-up terminations of study patients and their reasons must be reported immediately to monitor and sponsor and be duly documented in both the subject's eCRF and source document.

Specific criteria for treatment discontinuation

- Criteria for permanent treatment discontinuation: according to the physician's decision
- Criteria for transient treatment discontinuation: according to the physician's decision

All treatment discontinuation and reasons for doing so must be reported immediately to the monitor and the sponsor, and be duly documented in both the subject's CRF and source document.

All patients will complete the follow-up period despite being discontinued the study treatment.

7.5 Replacement of individual subjects after withdrawal

A 20% dropout rate is taken into account. Withdrawn patients will not be replaced by new participants. If the patient expresses the wish to quit the study, they will be asked to be followed up according to protocol, without following the medication strategy as dictated by the protocol.

7.6 Premature termination of the study

Premature termination of the study will occur if subjects are considered to be exposed to an unacceptably high risk in the investigators opinion or when advised by the DSMB and accepted by the sponsor. Premature termination will be reported to the local Ethics Committee and competent authorities within in accordance with country-specific required timelines. (See section 7.3 Consent withdrawal and study discontinuation).

In case the entire study is discontinued, this will not affect the patient's treatment, as patients will be treated as usual in routine daily practice. However, no protocol procedures will be conducted anymore as routine care is considered sufficient. For the provisions regarding the premature termination of the study, we refer to the clinical trial agreement.

8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC/EC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC/EC. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and SUSARs

There is no risk for additional AEs as treatment in the study is performed with approved and well-known medications. The drugs that will be investigated are the antipsychotics aripiprazole and risperidone and the antidepressants sertraline and escitalopram. These drugs have already been registered and prescribed for years all over the world. It is not the efficacy of the drugs that is the subject of study, but fine-tuning dosage according to pharmacogenetic individual patient characteristics. The registration studies for these drugs have been conducted years ago, therefore AEs are expected to be similar as those described in the product specification. For specific details please see the SmPC of the different drugs:

- Aripiprazole: <https://www.ema.europa.eu/en/medicines/human/EPAR/aripiprazole-sandoz>
- Risperidone: https://www.ema.europa.eu/en/documents/referral/risperdal-article-30-referral-annex-i-ii-iii-iv_en-0.pdf
- Sertraline: https://www.ema.europa.eu/en/documents/referral/zoloft-article-30-referral-annex-i-ii-iii-iv_en.pdf
- Escitalopram: <https://www.ema.europa.eu/en/medicines/human/referrals/escitalopram>

Since this new study intervention concerns usage of pharmacogenetic information to fine-tune dosage of the aforementioned medications, we expect that medication (dose) selection will potentially improve safety and efficacy. In this regard, we expect that the safety and tolerability will be better than what has been originally reported in studies carried out to obtain their approval. One might think that a dosing lower or higher might be a risk, but as a different metabolizer status will result in different blood levels: a poor metabolizer will be dosed lower to avoid high blood levels with a higher risk of side effects and an ultrarapid metabolizer will be dosed higher to avoid undertreatment, as has been shown previously^{26,27}. Close monitoring will ensure timely intervention and will minimise the risks.

8.2.1 Definitions

Adverse event (AE): an AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not

necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (Definition per International Conference on Harmonization [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Serious adverse event (SAE): an SAE is any untoward medical occurrence that at any dose: Results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a suspected transmission of any infectious agent via a medicinal product, is medically important (according to the treating physician), other important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (e.g., death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following: hospitalizations not intended to treat an acute illness or AE (e.g., social reasons such as pending placement in long-term care facility), surgery or procedure planned before entry into the study.

Adverse reaction (AR): An AR is an AE suspected to be causally related to a medicinal product. An ADR is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (i.e. the relationship cannot be ruled out). Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include overdose, misuse, abuse and medication errors.

Unexpected Adverse Reaction (UAR): Any adverse reaction, whose nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an

unauthorized investigational product or summary of product characteristics for an authorized product).

Suspected Unexpected Serious Adverse Reaction (SUSAR): An adverse reaction that is both serious and unexpected.

8.3 Assessment of intensity and causality

8.3.1 Intensity

An assessment of intensity grade will be made using the general categorical descriptors outlined in the WHO Toxicity Grading Scale (see appendix 1). The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

8.3.2 Causality

- AE related: The relationship in time of the AE with the study drug indicates a possible causal relationship and it cannot be explained by factors such as the patient's clinical condition or therapeutic interventions.
- AE unrelated: The relationship in time of the AE with the study drug indicates an unlikely causal relationship, or other factors (concomitant medication or conditions) or other therapeutic interventions provide a satisfactory explanation for the AE.

8.4 Collection and follow up of adverse events

AEs may be recorded at each visit based on careful clinical observation of the subject, laboratory tests or spontaneously reports identified by the participant discovered as a result of general questioning by the study staff. All AEs will be recorded on the medical history and in the eCRF. The investigator will also decide whether the adverse event is, based on his/her judgment, related or not to the study product—this decision should also be noted in the medical history and eCRF.

The following will be recorded for each event: description, severity (grade 1, 2, 3,4 and 5), duration (start and end dates), intensity, causal relationship with the drug (according to the previously attributability criteria), actions taken and outcome, using choices given on the subject's medical history. The investigator should report the underlying condition when a surgical or medical procedure is required as the event term, and the procedure as an action taken. For a preexisting AE that has worsened in terms of severity or frequency, the meaning of the change should be specified.

For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets criteria for classification as a serious adverse event (SAE) requiring immediate notification (see section 8.4.1). Follow-up of the AE

is required if the AE persists until the event resolves or stabilizes at a level acceptable to the Investigator.

The degree of severity of an adverse event provides a qualitative assessment of the extent or intensity of an adverse event elicited by the investigator or reported by the subject. Severity does not reflect the clinical seriousness of the event, only the grade or extent of the complaint or incidence.

Adverse events must be recorded on an specific form in the eCRF. The investigator must provide information on the adverse event, preferably with a diagnosis, or at least with signs and symptoms; start and stop dates (and start and stop time if the adverse event lasts less than 24 hours); intensity; causal relationship to intervention drug; action taken and outcome. If the adverse event is an overdose, the nature of the overdose must be stated (for example, medication error, accidental overdose, or intentional overdose) and the investigator shall notify sponsor or whoever assumes the tasks delegated by the sponsor, within 24 hours from the time of knowing about the event. The reporting circuit and form will be the same as for the SAE.

The SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs: the event resolves, the event stabilizes, the event returns to baseline, if a baseline value/status is available, the event can be attributed to agents other than the study drug or to factors unrelated to study conduct, it becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts). Information on adverse events that are not serious or unexpected and on those considered unrelated to the study treatment will be collected in tabular form at the end of the clinical trial or at the time of interim analyses when these are planned.

The sponsor, or whoever assumes the tasks delegated by the sponsor, will keep a record of all AEs reported by investigators. These records will be submitted to the competent authorities when requested.

8.5 Procedure for expedited reporting of serious adverse events (SAE) and serious unexpected adverse reactions

8.5.1 Serious Adverse Events (SAEs)

The principal investigator or delegates will report immediately any SAE occurring during the study to the Sponsor regardless of their degree of causal relationship with the investigational product. Any such serious adverse event due to any cause, whether or not related to the study medication, occurring from signing of informed consent and up to the last visit of the study,

must be reported within 24 hours of occurrence or when the investigator becomes aware of the event.

SAEs forms should be sent immediately to the study coordinator of the sponsor site. Moreover, as SAEs should be added to Castor, the study coordinators will receive an automatic email via this system.

The initial report of SAE should be written and as complete as possible including details of the current disease and SAE and assessment of the causal relationship between the AE and the investigational product. Reporting will be made using the Serious Adverse Event Report Form (see Appendix 2) within 24 hours from first knowledge by the investigator, completing all information on the form in the following two days.

The information missing at the time of the initial report must be reported in the SAE follow-up form.

For SAEs, the investigator will provide the Sponsor with all documentation related to the event (additional laboratory tests, discharge reports, etc.).

The investigator must also follow up SAEs and similarly report information related to the event until it has subsided, returned to baseline, can be attributed to products other than the study medication or to factors unrelated to conduct of the study, it is unlikely to obtain additional information, or in case of permanent impairment, until the condition stabilizes.

In the event of fatal or life-threatening, the investigator should be required to provide with all additional information requested by the study coordinator, the EC and regulatory authorities.

Sponsor shall keep detailed records of all the SAEs or the events of special interest which are notified by the investigators.

In the case of documenting medication errors or overdose, the sponsor will carry out the necessary actions for its management and prevention (specify when necessary).

8.5.2 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Any suspicion of a serious adverse reaction (SUSAR) must be notified by the sponsor to competent authorities through the Eudravigilance platform within a maximum period of 15 calendar days, 7 calendar days in the event of serious and unexpected fatal or life-threatening adverse reactions, all in compliance with Royal Decree 1090/2015 and Regulation (EU) No. 536/2014 of the European Parliament and of the Council, of April 16 2014. Investigator will notify it using the Serious Adverse Event Report Form specifying that it is considered a SUSAR.

8.6 Pregnancy

The investigator shall notify any pregnancy that occurs during the course of the study to Sponsor within 24 hours of knowing about the event through the Serious Adverse Event Report Form specifying that it is a pregnancy. If patient agree and investigator consider that expected benefit clearly justifies the potential risk, patient can continue the study procedures/medication.

8.7 Serious breach

Sponsor will notify any serious breach occurred in the study no later than 7 days from becoming aware of the breach. Serious breach is defined as a breach that may significantly compromise the safety and rights of the trial subjects or the reliability and robustness of the data obtained in the clinical trial. Serious breaches will be notified through CTIS portal as indicated in the Q&A document in Chapter V of Eudralex Volume 10.

8.8 Expedited reporting of other relevant safety information

Sponsor will notify regulatory authorities, as soon as possible and no later than 15 days after having knowledge of it, any information that could alter the benefit/risk relationship of the investigational medicinal product (e.g. an increase in the rate of occurrence of the expected SAR, SUSARs that occur after the completion of the clinical trial, new events related to the conduct of the trial or the development of the investigational medicinal product, any recommendation of the Data Monitoring Committee where relevant for the safety of subjects, etc.).

8.9 Annual safety report

During the course of the study, the Sponsor will prepare periodic safety reports annually following the recommendations outlined in the ICH E2F guidelines, and they must be submitted to the regulatory authorities and the ECs involved following the timetable established in the legislation.

8.10 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study.

8.11 Data Safety Monitoring Board (DSMB) / Safety Committee

To provide independent oversight of safety, efficacy, and study conduct, a Data Safety Monitoring Board (DSMB) will be instituted. The Data Safety Monitoring Board (DSMB) is a group of experts that monitors the main safety and tolerability outcome measures and the

overall conduct of the trial with the aim of protecting the safety and interests of the trial participants.

The DSMB will meet at least once per year during the study to ensure that participant safety is carefully monitored. The first meeting will be held before the start of the study. If necessary, the DSMB will convene additional ad hoc meetings. The membership, frequency, method and the aspects to be reviewed, will be specified in the DSMB-Charter.

Following each meeting, the DSMB will recommend continuation, modification, or discontinuation of the study based on observed safety issues. A separate DSMB charter will describe the activities of this committee in more detail.

The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

The DSMB consists of:

[REDACTED]

9. STATISTICAL ANALYSIS

An independent statistician who is masked to treatment allocation will perform the statistical analyses. Patient characteristics will be summarized for all groups together and by diagnostic group and treatment arm as means or percentages, depending on the type of measurement. We will analyse the data as randomized (ITT). All analyses will be performed separately for each diagnostic group as different questionnaires will be used to assess different questionnaires. We will use mixed effects models adjusted for a number of important covariates (gender, age, ethnicity) , that are plausibly predictive of missingness. The model should be robust for missingness at random. The model corrects for this and will yield valid results if missingness can be predicted depending on the diagnostic group to which one belongs. Reasons for drop-out will be documented. The descriptive analysis will summarize patient characteristics at baseline and all RAS-DS as well as other outcomes (see below).

9.1 Primary study parameter(s)

Primary endpoint will be patient recovery, as assessed using the Patient Recovery Assessment (RAS-DS). For the primary analysis, mixed effects model with a main effect for group and time (continuously) and the interaction group x time will be used. The model will include random intercept for subject and a random slope for time. If the interaction is significant, it means that there is a different time trend in the 2 groups.

9.2 Secondary study parameter(s)

Analyses of primary outcomes will be performed using group x time interaction to assess differences in time trends between groups. Secondary analyses will be conducted using 3-way interaction group x time x diagnosis to assess differences in time trends across diagnoses. If interaction is significant, we will follow up with pairwise contrasts to see in which diagnosis groups there is a difference in time trend.

9.3 Other study parameters

Passive behavioural monitoring as assessed with the BeHAPP app³⁴⁻³⁶ (<https://behapp.org>). Other potential relevant genetic variants related to medication response will be included in the statistical model above.

9.4 Interim analysis (if applicable)

After inclusion of 50% of patients an interim analysis will be performed. If the research question can already be answered with these patient numbers, the study can be prematurely terminated. Another possibility is that even with inclusion of the proposed number of patients the chance of finding statistical or clinical significant or relevant differences is small (futility analysis).

A separate futility analysis will be conducted for each diagnostic group. Members from the research team will conduct these analyses and the DSMB will evaluate the actual data and advise.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The proposed clinical trial will be conducted according to the principles of the Declaration of Helsinki (current version: Fortaleza, Brazil, October 2013) or the applicable guidelines on GCP, and all applicable local laws, rules, and regulations and in accordance with the Medical Research Involving Human Subjects Act (WMO). The study will be conducted according to this clinical protocol and will be governed by the following directives and guidelines:

- EU General Data Protection Regulation (GDPR) (2016/679)
- EU Cyber Security Regulations and international security standards

Requirements for ethical review as set forth in Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice (GCP) in the conduct of clinical trials on medicinal products for human use or other relevant local regulations for institutional review will be followed. The Protocol, informed consent form, Investigator's Brochure and other required documents must be approved by the Ethics Committee before enrolment of subjects in the study. The letter of approval from the Ethics Committee, as well as a list of documents reviewed, will be filed in the Investigator Site File (ISF) and a copy will be filed in the trial master file (TMF) held by the Sponsor.

The Sponsor and his delegates, in collaboration with the investigator, will be responsible for reporting to the Ethics Committee all changes in research activity, including protocol amendments, updates of Investigator's Brochures, annual safety reports, all unanticipated problems involving risks to human subjects, and study termination.

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. Protocol amendments must not be implemented without prior Ethics Committee approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the Ethics Committee and relevant competent authority.

Documentation of amendment approval by the investigator and Ethics Committee must be provided to the sponsor. During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any

departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

10.2 Responsibilities of the investigators

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements. Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki (and updated according to its last version, Fortaleza, Brazil, 2013), and that the study data are credible.

In addition, the investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, before and during the course of the study.

The investigator is also responsible for ensuring the privacy, health, and welfare of the subjects during and after the study. The investigator(s) must be familiar with the background and requirements of the study and with the properties of the investigational product as described in the Investigator's Brochure.

Before the start of the study, the investigator (or sponsor where required) will provide the Ethics Committee with current and complete copies of the following documents (as required by local regulations).

10.3 Recruitment and consent

Subjects will be recruited primarily through mental health care institutions/ clinics and general practitioners where they are routinely monitored. Patients will be made aware of the study by the treating physician during their visit. The physician will ask the subject permission to transfer contact details to the research team. When interested, the potential participant will be contacted by telephone or email by a member of the research team who will explain the study procedure and complete screening. Advantages and disadvantages of the study will be explained. In case a subject meets the inclusion criteria, the patient information will be sent by email. All potential participants will be given one week for their contemplation of participation. There are no consequences attached to the decision not to participate in the study. This will be explicitly mentioned to all potential participants. For any questions, involving the study the principal investigator, the coordinating investigators, as well as the independent physician can be contacted. After one week for contemplation of participation a member of the research team will contact the participant again to check whether he/she

would still like to participate in the study and to make an appointment for the test day. On the first visit, the study procedure will be explained again, and the participant can ask additional questions. If the subject has no more questions, he/she will be asked to sign the informed consent form in presence of the member of the research team. After signing the informed consent form, study procedures will take place. A copy of the informed consent form and patient information sheet will be handed out to the participant.

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing Ethics Committee and be in a language that the patient can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki (updated according to its last version, Fortaleza, Brazil, 2013), current ICH and GCP guidelines, applicable regulatory and country-specific requirements, and sponsor policy. Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort that the 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. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

10.4 Patient Confidentiality

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. Patient data will

be anonymized to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

Subjects will be codified with a study code that prevents their identity from being deduced. The PI and duly authorized collaborators will compromise to maintain personal data strictly confidential, according to the corresponding country-specific requirements. The link between the numeric code and real personal data from subjects will be rigorously kept by the PI. The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, Ethics Committee review, and regulatory inspection.

In the case report form, the patient will only be identified by the assigned study code. The name of patients will not appear in any publication or report of the study results. The participation of the patient in the trial will be noted in their medical records. The investigator will complete a list which will include the names of the patients participating in the trial, the number of inclusion in the study, and their medical history. Only investigators and the staff responsible for guaranteeing data quality and data analysis will have access to the clinical documentation of the participants.

Duly authorized persons by the sponsor and the health authorities and the Ethics Committee may audit or inspect the trial. Personal information will not be publicly available, in compliance with General Data Protection Regulation (GDPR) (EU) 2016/679 of 27th April 2016).

In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

Only data collected for the study that does not bear any information that could directly identify the patient will be transferred to third parties or other countries. Should this transfer occur, it will be for the same purposes as the study and guarantee confidentiality with at least the level of protection afforded by applicable regulations in Spain.

Patients will be informed that their clinical data will be incorporated into an automated study-specific file after and the results of the clinical trials and different studies conducted with samples can be communicated at scientific meetings, medical conferences or publications. However, patient's identity or identifiable data will never be disclosed.

10.5 Benefits and risks assessment, group relatedness

For an individual, a potential direct benefit of participation to this study consists of receiving pharmacogenetic information on metabolizer status. The risk for the subject participating in this study is low. Patients may experience some discomfort from the measurements for the study (e.g., venipuncture). Furthermore, abnormalities in psychiatric questionnaires, blood chemistry and ECG can potentially be found. If an abnormality is found, we will inform the participant and the general practitioner. The current study will not impede treatment of participants. We will only include participants currently receiving inpatient or outpatient treatment. From randomisation onwards, prescribing physicians in both treatment groups will be able to modify a patient's psychotropic medication regimen in terms of the type of medication, dose, schedule, or number of medications if necessary. Until randomisation, patients will continue to use their current medication. Most procedures carried out as part of the study e.g., taking blood samples, are also part of routine clinical diagnostics and treatment.

Additional procedures specific to this study are:

- Patients in this study will need to undergo one additional venipuncture for genotyping.
- Prescribing physicians will prescribe one of the predefined drugs: aripiprazole or risperidone for the treatment of psychotic disorders, and sertraline or escitalopram for mood and anxiety disorders.
- Patients in the intervention group will be treated according to a personalised medication recommendation based on the results of pharmacogenetic testing.
- Completion of additional questionnaires about psychological recovery, health and side effects of the medication.
- Passive monitoring via the BeHapp app.

All in all, there is a moderate additional burden associated with study participation.

10.6 Compensation for injury

In Spain and Germany, it is considered a low-intervention because complies with the following conditions:

- a) the investigational medicinal products, excluding placebos, are authorised;
- b) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and
- c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.

The participating centres are responsible for liability insurance. For submissions at local competent authorities the insurance and coverage should be listed. The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.7 Financing

[REDACTED]

10.8 Incentives (if applicable)

Patients will not be reimbursed for participating in this study, but all travel expenses to the research centre will be reimbursed. Moreover, the additional testing for the study (genotyping, clinical chemistry, therapeutic drug monitoring, ECG) will be free of charge for patients. All medication prescribed to participants will be covered by their own health insurance ('eigen risico').

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

A data management plan as well as a detailed data process flow have been set up in collaboration with the Data Management Work Package, led by the Scientific Coordinator, and MEMIC, the centre for data and information management at the Faculty of Health, Medicine and Life Sciences of Maastricht University, as a partner assisting with data management. This data management plan has been created according to a set and approved template that applies with the sponsor's regulations. As the PSY-PGx Consortium participates in the Open Research Data Pilot as part of Horizon 2020, the data management plan carefully describes the policy of data preservation and re-use according to the findable, accessible, interoperable, and re-usable (FAIR) principles.

11.1.1 Data Protection

Most jurisdictions have comprehensive and similar Data Protection Acts, which include genetic data either explicitly or implicitly in a category of 'special or sensitive personal data', which is afforded higher privacy protections. Generally speaking, consent of the subject must be sought to process the genetic data in any way. It should be noted that the General Data Protection Regulation 2016/679 ('GDPR'), which came into force in May 2018, has had an effect on many of the statutes discussed in this section. The key point is that genetic data must now be more heavily protected than was the case until recently across all the surveyed jurisdictions (JCR 2018). Data privacy is critical and will be ensured throughout the project. First, the GDPR comprises the basis for the data and information security in this project. The parties will collaborate to ensure compliance with the EU General Data Protection Regulation (GDPR) (2016/679) and any local legislation. The BEHAPP app is also fully GDPR compliant³⁵. The processing, communication and transfer of personal data of all participants will be adjusted to compliance with Regulation EU 2016/679 of the European Parliament and the Council of 27 April 2016 on the protection of natural persons as to the processing of personal data and the free circulation of data, being mandatory as of May 25, 2018. The legal basis that justifies the processing of your data is the consent given in this act, in accordance with the provisions of the Article 9 of the EU Regulation 2016/679.

The data collected for the study will be collected only identified by a code, so that no information will be included to identify the participants. Data will be processed with the only purpose of carry out all activities related to the clinical trial in compliance with pharmacovigilance regulations (for the drug safety control). The legal basis for the processing of the data is the participant consent and Article 9.2 of the Regulation. Only the study doctor and his collaborators have the right to access the source data (clinical history) and will be able to relate the data collected in the study with the patient's medical history.

The identity of the participants will not be available to any other person except for a medical

emergency or legal requirement. Health authorities, the Research Ethics Committee and personnel authorized by the Sponsor of the study, may have access to the personal data identified when necessary to verify data and study procedures, but always maintaining confidentiality in accordance with current legislation.

Only encrypted data will be transferred to third parties and to other countries, which in no case will contain information that can identify the participant directly (such as name and surnames, initials, address, social security number, etc.). In the event that this assignment occurred, it would be for the same purpose of the study described and guaranteeing confidentiality.

If a transfer of encrypted data is carried out outside the EU, either in entities related to the hospital where the patient participates, to service providers or to researchers who collaborate with them, the data of the participants will be protected by safeguards such as contracts or other mechanisms established by the data protection authorities.

The sponsor of the trial commits to carry out the data processing according to EU Regulation 2016/679 and, therefore, to keep a record of the processing activities to carry out and to make a risk assessment of the data processing, to establish what measures will be applied and how it will be done.

In addition to the rights already covered by the previous legislation (access, modification, opposition and cancellation of data, deletion in the new Regulation) participants can now limit the processing of data collected for the project that has to be rectified, request a copy or move to a third party (portability). To exercise these rights, the participant should be directed to the principal investigator of the study or the Data Protection Delegate of their site. The participant also has the right to contact the Data Protection Agency if not satisfied.

The data cannot be deleted even if a patient discontinues the study, to guarantee the validity of the investigation and comply with the legal duties and the medication authorization requirements.

The Investigator and the Sponsor are obliged to keep the data collected for the study according to local legislation. Subsequently, personal information will only be kept by the site for the care of their health and by the sponsor for other scientific research purposes if the patient has given their consent to do so, and if the law and applicable ethical requirements so permit.

In accordance with the provisions of recital 33 of the regulations and the corresponding provisions of each country involved in the study regulations, the data may be preserved in such a way that the clinical data are kept separate from the identifiers, to be used in future

investigations, applying all technical precautions necessary to avoid their re-identification, and in accordance with all ethical and legal requirements.

11.1.2 Clinical and sociodemographic data.

The data generated during the study, will be collected in a data management system, an eCRF in CASTOR, which is a safe environment that is set-up according to GDPR standards. This is also described in the Data Management Plan that has been set-up by the Scientific Coordinator of the PSY-PGx Project and MEMIC in the digital Data Management system of University Maastricht.

Source data will be only accessible for the investigators. The data of all subjects will be coded by using letters and numbers. Coding will not constitute of initials, date of birth, addresses or any subject related details. Only the local principal investigator and study investigators will have access to the key of the codes and the key of codes will not leave the participating center. The data will be monitored by the Clinical Trial Centre Maastricht (CTCM). They may have access to the data. Also other authorities such as the IGJ, the DSMB and members of the research team may have access to the data to check quality of the data. All the paper data will be stored in a locked closet in a locked room. The key is safeguarded by the coordinating investigator. The data will be saved for fifteen years. This is necessary for new analyses aiming at answering research objectives. If the participants give consent, the data may be used for future studies investigating pharmacogenetics in psychiatry. The handling of personal data will comply with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation. (in Dutch: Uitvoeringswet AVG, UAVG).

The Sponsor or his delegates must ensure that data are recorded in the eCRF correctly and completely by authorized personnel. The investigator has to confirm the integrity of the data transferred to the eCRF by signature.

Direct access to source data/documents

Investigators will ensure access to the source documents of the staff responsible for guaranteeing data quality and data analysis. In addition, access to documentation will be provided, if necessary, to the staff duly authorized by the sponsor (study monitors), to regulatory authorities and to Ethics Committee if they request to inspect the study. Source documents will be stored in the Investigators's File. These documents will be kept according to local requirements (country specific), after which they will be destroyed.

Data management

The Investigator must ensure the accuracy, completeness, legibility and timelines of data reported in the CRF and all required reports. Any change or correction to the CRF must be dated, initialled and explained (if necessary).

Archiving and storage of data

The investigator is responsible for maintaining all records which enable the conduct of the clinical trial at the site to be fully documented, in compliance with ICH GCP filing standard. Timeliness and completeness of the documentation will be regularly checked by the clinical monitor. The documentation of the clinical trial including all the relevant correspondence should be kept by the investigator for the minimum period required by applicable regulatory and country-specific requirements. All completed study related documents (e.g. eCRF, Informed consent forms, drug accountability logs, staff signature lists, Subject identification log, ...) must be archived by 25 years.

Audit and inspection

The investigators agree to comply with the requirements of the sponsor and the relevant authority for an audit or an inspection of the study. The audit can apply to all stages of the study, from development of the protocol to publication of the results and filing the data used or produced in the study.

11.1.3 ICT data

The BEHAPP mobile application will be used to collect passive behavioural data. This app collects behavioural data from personal digital devices for use in (medical) scientific research contexts. Given such a sensitive operating context and equally sensitive data-catalogue, BEHAPP recognizes privacy and security as the primary design goal in all platform developments and operations. To achieve a high level of security and trust the platform employs a combination of measures on both an organizational and technical level^{35,36}:

A brief overview of the data flow:

1. Data is collected on the smartphones of participants and immediately encrypted on device.
2. The data is sent over to our central infrastructure through a secure connection.
3. The public zone dispatches the data to the private zone, it does not have the capability to inspect / retrieve or decrypt data.
4. The private zone redirects the data to the correct study and site database.
5. A researcher, if authorized for a specific study, can request to load and decrypt a participant's data and subsequently analyze it. Behapp's custom tools make sure that the decrypted data view is only held in volatile memory (RAM).

More details can be found in *D6_Productgegevens BeHapp mobiele applicatie*.

11.1.4 Blood samples

Biological samples (EDTA-blood) will be collected for genetic analysis as well as for therapeutic drug monitoring (TDM). Bloods for genetic analysis will be sent to the Institute of Human Genetics (University Hospital Bonn) in Germany, which is the central genotyping facility of the

study. TDM samples will be frozen and stored locally and sent to University of Belgrade – Faculty of Pharmacy, Belgrade, Serbia, at the end of the study after the last TDM collection has taken place. All blood samples will be pseudonymized. These data will be stored and kept for 25 years, according to local regulations. If participants provide their consent, these data and samples can be used for further research. The handling of all biological samples will comply with the EU General Data Protection Regulation. This also applies to the samples that will be sent to the University of Belgrade, as is convened in the Data Transfer Agreement. The GDPR requires in its Article 46 that controllers/processors shall put in place appropriate safeguards for transfers of personal data to third countries or international organisations. To that end, the GDPR diversifies the appropriate safeguards that may be used by organisations under Article 46 for framing transfers to third countries by introducing amongst others, codes of conduct as a new transfer mechanism (Articles 40-3 and 46-2-e). In this respect, as provided by Article 40-3, once approved by the competent supervisory authority (hereafter “competent SA”) and having been granted general validity within the Union by the Commission, a code of conduct may also be adhered to and used by controllers or processors not subject to the GDPR located in third countries for the purpose of providing appropriate safeguards to data transferred to third countries. Such controllers and processors are required to make binding and enforceable commitments, via contractual or other legally binding instruments, to apply the appropriate safeguards provided by the code including with regard to the rights of data subjects as required by Article 40-3. As regards the Code members located outside the EU, there is a need to ensure that their commitment to adhere to a “specified level of data protection” guarantees that the level of data protection provided for in the GDPR is not undermined. This is a prerequisite for their eligibility to participate in the code of conduct as a transfer tool. To this end, a contract will be signed by the controller/processor in the third country (i.e. the data importer) with, for example, the entity transferring data under the code (i.e. data exporter).

11.2 Monitoring and Quality Assurance

According to ICH/GCP guidelines, the sponsor should ensure that the trial is adequately monitored.

The study and the data from all participating research sites will be monitored by the Clinical Trial Center Maastricht (CTCM). They may have access to the data.

The monitor will visit each investigational site during three types of visits: the Site Initiation Visit (SIV), the Interim Monitoring Visit (IMV) and the Close-Out Visit (COV). Before the inclusion of the first patient, a Site Initiation Visit (SIV) will take place. During this SIV, the investigator site will be checked, and all Standard Operating Procedures (SOPs) will be discussed. During the study, one Interim Monitoring Visit (IMV) will be performed by the CTCM. This IMV will be preceded by a control visit by a member of the coordinating

investigator's group. The study will end with a close-out visit (COV). Monitoring will be conducted following ICH-GCP guidelines. The monitor will randomly check:

- 20% of all Informed Consent Forms;
- 20% of all SAEs and SUSARs;
- 5% of all eCRFs will be verified with the source documents

According to Good Clinical Practice (GCP) guidelines, the main task of the clinical trial monitor is to ensure that:

- The rights and well-being of human subjects are protected
- Reported trial data are accurate, complete and verifiable from source documents
- The conduct of the trial is in compliance with the currently approved protocol, GCP and applicable regulatory requirements
- Personal data protection is in accordance with national or legal regulations

11.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC/EC has been given. All amendments will be notified to the METC/EC that gave a favourable opinion.

11.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC/EC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the of the end of the study to each country according local legislation. The end of the study is defined as the last patient's last visit.

The sponsor will notify the Regulatory Authority and METC/EC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited Regulatory Authority and METC/EC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC/EC.

11.6 Public disclosure and publication policy

The CCMO guideline "Publication policy" will be followed and the provisions concerning the publication of data included in the research contract will apply. The study protocol will be registered at www.clinicaltrials.gov.

12. STRUCTURED RISK ANALYSIS

12.1 Potential issues of concern

N/A

a. Level of knowledge about mechanism of action

The drugs that will be used are the antipsychotics aripiprazole and risperidone and the antidepressants sertraline and escitalopram. The registration studies for these drugs have been conducted years ago.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

The drugs used in this study have already been registered and prescribed for years all over the world. It is not the efficacy of the drugs that is the subject of study, but fine-tuning dosage according to pharmacogenetic individual patient characteristics.

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

N/A

d. Selectivity of the mechanism to target tissue in animals and/or human beings

N/A

e. Analysis of potential effect

Since this new study intervention concerns usage of pharmacogenetic information to fine-tune dosage of the aforementioned medications, we expect that medication (dose) selection will potentially improve safety and efficacy. In this regard, we expect that the safety and tolerability will be better than what has been originally reported in studies carried out to obtain their approval.

f. Pharmacokinetic considerations

For specific details please see the SmPC of the different drugs. (D2_SPC_Aripiprazol, D2_SPC_Risperidone, D2_SPC_Sertraline, D2_SPC_Escitalopram)

g. Study population

N/A Patients with a mood, anxiety or psychotic disorder. Patients will be aged 16 years and older. Patients with pre-existing liver disease, renal disease, cardiac disease or diabetes will be excluded.

h. Interaction with other products

N/A We expect lower levels of risk than in usual care; in the intervention group medication dosage will be adjusted to the individual CYP450 phenotype based on the most recent guidelines and therefore we expect lower levels of side effects and earlier response to treatment. No polypharmacy is allowed, defined as the routine use of 5 or more medications including over-the-counter, prescription and/or traditional and complementary medicines used by a patient²⁸.

i. Predictability of effect

N/A

j. Can effects be managed?

N/A

12.2 Synthesis

The burden and risks of participating in the study are moderate. Patients may experience some discomfort from the measurements for the study (e.g., venipuncture). Furthermore, abnormalities in psychiatric questionnaires, blood chemistry and ECG can potentially be found. If an abnormality is found, we will inform the participant and the general practitioner. All procedures performed in the context of the study such as taking blood samples, are also part of routine clinical diagnostics and treatment. Patients in this study will need to undergo one additional venipuncture for genotyping, so there is minimal additional burden associated with study participation.

Instead, we expect lower levels of risk: in the intervention group medication dosage will be adjusted to the individual CYP450 genotype based on the most recent guidelines and therefore we expect lower levels of side effects and earlier response to treatment. One might think that lower or higher dosing would pose a risk, but different metabolizer status will result in different blood levels. A poor metabolizer will be dosed lower to avoid high blood levels with a higher risk of side effects, while an ultrarapid metabolizer will be dosed higher to avoid undertreatment, as previously demonstrated^{26,27}. Close monitoring will ensure timely intervention if needed. After the study, patients in the DAU group will also receive their pharmacogenetic profile, giving them the same opportunity to personalise their medication if needed. We therefore believe that the potential benefits of the study outweigh the burdens and risks.

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**Appendix: WHO TOXICITY GRADING SCALE FOR DETERMINING
THE SEVERITY OF ADVERSE EVENTS**
WHO Toxicity Grading Scale for Determining The Severity of Adverse Events

HEMATOLOGY				
ITEM	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
Hemoglobin	9.5 - 10.5 gm/dl	8.0 - 9.4 gm/dl	6.5 - 7.9 gm/dl	< 6.5 gm/dl
Absolute Neutrophil Count	1000-1500/mm ³	750-999/mm ³	500-749/mm ³	<500/mm ³
Platelets	75000-99000/mm ³	50000-74999/mm ³	20000-49000/mm ³	<20000/mm ³
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Fibrinogen	0.75 - 0.99 X LLN	0.50 - 0.74 x LLN	0.25 - 0.49 x LLN	< 0.25 x LLN
Fibrin Split Product	20-40 mcg/ml	41-50 mcg/ml	51-60 mcg/ml	> 60 mcg/ml
Methemoglobin	5 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20 %
LIVER ENZYMES				
AST (SGOT)	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
ALT (SGPT)	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
GGT	1.25 -2.5 x ULN	1.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Alkaline Phosphatase	1.25 - 2. 5 x ULN	1.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
CHEMISTRIES				
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 or mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement Rx required or hospitalization required.	< 2.0 mEq/L or paresis or ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or mental status changes or coma

**Appendix: WHO TOXICITY GRADING SCALE FOR DETERMINING
THE SEVERITY OF ADVERSE EVENTS**


CHEMISTRIES (continued)				
Hyperglycemia (note if fasting)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or life threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL life-threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or life- threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive Rx or hospitalization required	< 1.0 mg/dL or life- threatening arrhythmia
Hyperbilirubinemia	1.1 - 1.5 x ULN	1.6 - 2.5 x ULN	2.6 - 5 x ULN	> 5 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Creatinine	1.1 x 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or required dialysis
URINALYSIS				
Proteinuria	1+ or < 0.3% or <3g/L or 200 mg - 1 gm loss/day	2 -3 + or 0.3 - 1.0% or 3-10 g/L 1- 2 gm loss/day	4+ or > 1.0% or > 10 g/L 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria	microscopic only	gross, no clots	gross+ clots	obstructive or required transfusion
CARDIAC DYSFUNCTION				
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; No Rx required	requires treatment
Hypertension	transient inc. > 20 mm; no Rx	recurrent, chronic, > 20 mm, Rx required	requires acute Rx; No hospitalization	requires hospitalization
Hypotension	transient orthostatic hypotension, No Rx	symptoms correctable with oral fluids Rx	requires IV fluids; no hospitalization required	requires hospitalization
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no Rx	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

**Appendix: WHO TOXICITY GRADING SCALE FOR DETERMINING
THE SEVERITY OF ADVERSE EVENTS**

RESPIRATORY				
Cough	transient- no Rx	treatment associated cough local Rx	uncontrolled	
Bronchospasm, Acute	transient; no Rx < 80% - 70% FEV ₁ (or peak flow)	requires Rx normalizes with bronchodilator; FEV ₁ 50% - 70% (or peak Flow)	no normalization with bronchodilator; FEV ₁ 25% - 50% (or peak flow retractions)	cyanosis: FEV ₁ < 25% (or peak flow) or intubated
GASTROINTESTINAL				
Stomatitis	mild discomfort; no limits on activity	some limits on eating/drinking	eating/talking very limited	requires IV fluids
Nausea	mild discomfort; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	severe discomfort; no significant intake; activities limited	minimal fluid intake
Vomiting	transient emesis	occasional/moderate vomiting	orthostatic hypotension or IV fluids required	hypotensive shock or hospitalization required for IV fluid therapy
Constipation	mild	moderate	severe	distensions w/vomiting
Diarrhea	transient 3-4 loose stools/day	5-7 loose stools/day	orthostatic hypotension or > 7 loose stools/day or required IV fluids	hypotensive shock or hospitalization for IV fluid therapy required
NEURO & NEUROMUSCULAR				
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Mood	mild anxiety or depression	moderate anxiety or depression and therapy required	severe anxiety or depression or mania; needs assistance	acute psychosis; incapacitated, requires hospitalization
Neuro Control (ADL = activities of daily living)	mild difficulty concentrating; no Rx; mild confusion/agitation; ADL unaffected	moderate confusion/agitation some limitation of ADL; minimal Rx	severe confusion/agitation needs assistance for ADL; therapy required	toxic psychosis; hospitalization
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis

**Appendix: WHO TOXICITY GRADING SCALE FOR DETERMINING
THE SEVERITY OF ADVERSE EVENTS**

OTHER PARAMETERS				
Fever: oral, > 12 hours	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Headache	mild, no Rx therapy	transient, moderate; Rx required	severe; responds to initial narcotic therapy	intractable; required repeated narcotic therapy
Fatigue	no decrease in ADL	normal activity decreased 25- 50%	normal activity decreased > 50% can't work	unable to care for self
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Local Reaction	tenderness or erythema	induration < 10 cm or phlebitis or inflammation	induration > 10 cm or ulceration	necrosis
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation, moist desquamation, or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens- Johnson or necrosis requiring surgery

 Clinical Trials Unit A1-PNT-FAR-01, v.1.0 I.T.1_v.3.0_23-02-2023	SERIOUS ADVERSE EVENT -SAE- NOTIFICATION FORM	Protocol code: PSY-PGx
		EuCT Num: 2023-509680-25-00
		SAE ID:


0. Classification report <input type="checkbox"/> SAE <input type="checkbox"/> AESI		
1. Report type <input type="checkbox"/> Initial <input type="checkbox"/> Follow up	3. Country: Spain	4. Patient code: _____
2. Date of report: ____/____/____ (dd/mm/yyyy)		5. Center code: _____

I. PATIENT PERSONAL DATA	
6. Sex: <input type="checkbox"/> Male <input type="checkbox"/> Female	7. Age: ____ Years
8. Weight: _____ Kg.	9. Height: _____ cm.

II. SERIOUS ADVERSE EVENT	
10. Description reaction(s) -including relevant test/lab data-:	11. Reaction onset: ____/____/____ (dd/mm/yyyy)
	12. Check the appropriate to adverse reaction: <input type="checkbox"/> Resulted in death <input type="checkbox"/> Life-theratening <input type="checkbox"/> Requieres inpatient hospitalization <input type="checkbox"/> Prolongation of existing hospitalization <input type="checkbox"/> Persistent or significant disability/incapacity <input type="checkbox"/> Congenital anomaly/birth defect <input type="checkbox"/> Important medical event
13. Action(s) taken: <input type="checkbox"/> None <input type="checkbox"/> Treatment cessation <input type="checkbox"/> Permanent treatment discontinuation <input type="checkbox"/> Concomitant treatment of the symptoms <input type="checkbox"/> Hospitalization <input type="checkbox"/> Prolongation of hospitalization <input type="checkbox"/> Other (specify): _____	14. Result / Outcome: <input type="checkbox"/> Unknwon <input type="checkbox"/> Total recovery → Date: __ _ _ _ _ (dd/mm/yyyy) <input type="checkbox"/> Partial recovery → Date: __ _ _ _ _ (dd/mm/yyyy) <input type="checkbox"/> Still ongoing <input type="checkbox"/> Clinical worsening of the patient <input type="checkbox"/> Death → Date: __ _ _ _ _ (dd/mm/yyyy) Cause of death: _____

III. TRIAL MEDICATION (Register each investigational medicinal product)					
15. Suspect drugs(s)	16. Daily dose(s)	17. Route(s) of administration	18. Date of onset (dd/mm/yyyy)	19. Termination date (dd/mm/yyyy)	20. Causal relationship with the trial medication (indicar según 20a)
<input type="checkbox"/>	<input type="checkbox"/>		_ _ _ _	_ _ _ _ <input type="checkbox"/> ongoing	
<input type="checkbox"/>	<input type="checkbox"/>		_ _ _ _	_ _ _ _ <input type="checkbox"/> ongoing	
20a. Causal relationship: 1 related 2 probable 3 possible 4 unlikely 5 not related 6 NA (not applicable)					
21. Did the reaction abate after stopping drug? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA					
22. Did the reaction abate after reducing the dose? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA					
23. Did the reaction reappear after reintroduction? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA					
IV. UNBLINDED					
24. Unblinded for the patient is justified by SAE <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA					
If yes, it must be explained:					

IV. CONCOMITANT DRUG(S) INFORMATION <input type="checkbox"/> NA					
25. Concomitant drugs	26. Daily dose	27. Date of onset (dd/mm/yyyy)	28. Termination date (dd/mm/yyyy)	29. Causal relationship according 20a section	30. Indications
		_ _ _ _	_ _ _ _ <input type="checkbox"/> ongoing		
		_ _ _ _	_ _ _ _ <input type="checkbox"/> ongoing		
		_ _ _ _	_ _ _ _ <input type="checkbox"/> ongoing		
		_ _ _ _	_ _ _ _ <input type="checkbox"/> ongoing		

 Clinical Trials Unit A1-PNT-FAR-01, v.1.0 I.T.1_v.3.0_23-02-2023	SERIOUS ADVERSE EVENT -SAE- NOTIFICATION FORM	Protocol code: PSY-PGx
		EuCT Num: 2023-509680-25-00
		SAE ID:

V. RELEVANT TEST/LAB DATA <input type="checkbox"/> NA			
31. Lab variable	32. Result (units)	33. Lower range – Upper range	34. Collected date (dd/mm/yyyy)
			_ _ _ _ _ _ _
			_ _ _ _ _ _ _
			_ _ _ _ _ _ _
			_ _ _ _ _ _ _

VI. RELEVANT MEDICAL RECORDS DATA <input type="checkbox"/> NA			
35. Medical/surgical specifications	36. Date of onset (dd/mm/yyyy)	37. Termination date (dd/mm/yyyy)	38. Ongoing
	_ _ _ _ _ _ _	_ _ _ _ _ _ _	<input type="checkbox"/> Yes <input type="checkbox"/> No
	_ _ _ _ _ _ _	_ _ _ _ _ _ _	<input type="checkbox"/> Yes <input type="checkbox"/> No
	_ _ _ _ _ _ _	_ _ _ _ _ _ _	<input type="checkbox"/> Yes <input type="checkbox"/> No
	_ _ _ _ _ _ _	_ _ _ _ _ _ _	<input type="checkbox"/> Yes <input type="checkbox"/> No
39. Other relevant history (e.g. diagnostics, allergics, pregnancy with last month of period, etc): <input type="checkbox"/> NA			
40. Report attached: <input type="checkbox"/> Yes <input type="checkbox"/> No (nº of pages: __)			

VII. INVESTIGATOR INFORMATION	
41. Name of investigator:	42. Address of investigator:
43. Notification date: __/__/____ (dd/mm/yyyy)	44. Signature of the investigator completing report:

VIII. TO BE COMPLETED BY THE SPONSOR		
45. Name of reviewer:	46. First date reviewed: __/__/____ (dd/mm/yyyy) Final date reviewed: __/__/____ (dd/mm/yyyy)	47. Signature of person received the report:
48. Event categorised as: <input type="checkbox"/> Serious Adverse Event <input type="checkbox"/> Serious Adverse Reaction <input type="checkbox"/> Suspected Unexpected Serious Adverse Reaction → MUST BE REPORTED TO COMPETENT AUTHORITIES		
49. Expedited safety reported: <input type="checkbox"/> Yes → Date __/__/____ (fulfill 48) (dd/mm/yyyy) <input type="checkbox"/> No <input type="checkbox"/> NA	50. Reported on Eudravigilance: <input type="checkbox"/> Yes → Date __/__/____ (dd/mm/yyyy) <input type="checkbox"/> NA	

**THIS SAE NOTIFICATION FORM MUST SEND COMPLETED IMMEDIATELY AND WITHIN 24 HOURS
OF THE SITE BECOMING AWARE OF THE EVENT BY MAIL**

e-mail: joyera@recerca.clinic.cat;