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Trials

STUDY PROTOCOL

Open Access

INTENSIFY—a randomized, controlled trial to investigate the effect of an early intensified pharmacological treatment for major psychiatric disorders after treatment failure in the current episode: a study protocol

Cynthia Okhuijsen-Pfeifer[1], Alessandro Serretti[2,3], Eduard Vieta[4], Lidia Ilzarbe[4], Chiara Fabbri[5], Oliver Howes[6], K. Oliver Schubert[7,8,9], Scott R. Clark[7,10], Dennis Liu[7,10], Alex Hofer[11], Simon Gasser[11], Alkomiet Hasan[12,13], Wolfgang Strube[12], Martin Driessen[14], Elilarasi Ratnalingam[14], Andreas Reif[15], Carmen Schiweck[15], Jan Engelmann[16], Susanne Englisch[16], Sarah E. Fromme[17], Rena S. Birner[17], Vivien J. Zobel[17], Mark Weiser[18,19], Revital Amiaz[18,19], Alessandra Minelli[20,21], Antonio Vita[22,23], Mirko Manchia[24,25,26], Pasquale Paribello[24,25], Armida Mucci[27], Paola Bucci[27], Paola Rocca[28], Claudio Brasso[28], Michael Craggs[6], Nikos Stefanis[29], Nikolaos Kokras[29], Ulrich Ebner-Priemer[30,31], Phillippe Fossati[32], Bianca Ueberberg[33], Hans-Jörg Assion[33], Hendrika H. van Hell[1], Peter M. van de Ven[34], Rutger M. van den Bor[34], Ruben P. van Boxel[1], Psych-STRATA consortium group, Inge Winter-van Rossum[1*†] and Bernhard T. Baune[17,35,36*†]

Abstract

Background Schizophrenia, bipolar depression and major depressive disorders collectively affect over 10 million people across the European Union and are associated with annual healthcare and societal costs of more than 600 billion euros. When diagnosed, patients are usually prescribed psychotropic medication. A substantial proportion of patients insufficiently responds to first- and second-line treatments, which is termed as treatment resistance. While third-line treatments are relatively effective in TR conditions, it remains unclear whether providing these treatments in an earlier phase provides benefits.

Methods INTENSIFY consists of three international, multicenter, controlled, randomized, open-label trials, with a treatment duration of 6 weeks. After failure of a first-line treatment in the current episode, 1254 participants will be recruited by at least 16 sites and randomized to either a third-line treatment (early intensified pharmacological treatment) or treatment as usual (standard second-line treatment). Adult participants (age ≥ 18yrs) with a diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder, major depressive disorder, or bipolar

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depression are eligible after a treatment failure in the current episode due to lack of efficacy. The primary objective is to compare change in symptom severity after 6 weeks. The secondary objective is to compare the two treatment arms on changes of severity symptoms, cognitive function, quality of life, functional measures, digital mental health markers, side effects and concomitant medication. ANCOVA analyses will be performed.

Discussion Should the current study show clinical evidence that the use of third-line treatment is efficacious and safe earlier to treat severe mental illness, the results could impact treatment guidelines in due course. In addition, the study will contribute to the identification of clinical, digital and blood-based markers that are associated with treatment response to early and intensified treatments.

Trial registration The trials are registered in www.clinicaltrials.gov under numbers NCT05603104 (merged study protocol; study center in Israel) and under the numbers for the split protocols NCT05958875 (SZ), NCT05973786 (BD) and NCT05973851 (MDD) for the EU and UK sites. The study is registered in the Australian and New Zealand Clinical Trials Registry under Registration number ACTRN12625000327482 (SZ), ACTRN12625000328471 (BD) and ACTRN12625000329460 (MDD). Registered on April 17, 2025.

Keywords Schizophrenia, Depressive disorder, major, Depression, bipolar, Treatment-resistance, Treatment outcome, Treatment failure

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	INTENSIFY—a randomized, controlled trial to investigate the effect of an early intensified pharmacological treatment for major psychiatric disorders after treatment failure in the current episode: a study protocol
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Protocol version {3}	SZ: Protocol V1.1, 15 November 2023 (EU) SZ: Protocol V1.0, 1 July 2023 (UK) BD: Protocol V1.1, 30 November 2023 (EU) BD: Protocol V1.1, 30 November 2023 (pending UK) MDD: Protocol V1.1, 1 December 2023 (EU) MDD: Protocol V1.1, 1 December 2023 (pending UK) Merged Protocol V1.5, 04 March 2023 (Israel) Merged Protocol V3.1, 19 December 2024 (Australia) And potential future amendments.
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Role of sponsor {5c}	The study sponsor has implemented the study design, data collection procedures and conducts clinical trial management, analysis and interpretation of data. Preparation of the manuscript and the decision to submit was made by the sponsor. The funder (European Commission, Horizon 2021; see above) had no role or authority in study design, data collection, management, analysis or interpretation of data. They will have no role in the writing of associated publications and the decision to submit papers for publication.

Introduction

Background and rationale {6a}

Schizophrenia (SZ), bipolar depression (BD) and major depressive disorder (MDD) collectively affect over 10 million people across the European Union (EU) and contribute significantly to the total of 600 billion euro of annual healthcare and societal costs [1]. When diagnosed, patients are commonly prescribed psychotropic medication according to the diagnosis, such as antipsychotics, mood stabilisers, or antidepressants. Following international guidelines for each of these disorders, a failure of a first-line treatment is usually followed by the initiation of a second-line treatment. If a second-line treatment fails as well, third-line treatments are recommended. Failure of two pharmacological treatments, used in adequate doses and duration during a current episode, is commonly defined as treatment resistance (TR) [2–4]. Given the lack of reliable clinical and biological predictors of treatment response, the choice of treatment follows a "trial and error" approach; however, third-line treatments have demonstrated particular efficacy and safety in treatment resistant stages of the illness. Examples are clozapine in treatment-resistant schizophrenia [2] and esketamine in treatment-resistant depression [5–7]. Although these mentioned medications are registered for the treatment of TR schizophrenia and major depression (respectively) and the definition of TR includes two previously failed medication trials, in current clinical practice these medications are underutilized [8]. The burden of not receiving an effective treatment and progressing to a treatment resistant stage is associated with more severe psychopathology, higher rates of unemployment, more relapses and hospitalisations, lower quality of life, poorer cognitive functioning, increased prevalence of smoking and substance use, poorer social and occupational functioning and higher caregiver burden as compared to people responding to first- or second-line treatments [9, 10]. In addition, receiving an effective treatment also reduces suicidal ideation. Hence, the primary objective of this clinical trial is to investigate whether currently recommended third-line treatments would be more effective when prescribed earlier in the disease course (compared to current clinical practice where these medications are underutilized). For SZ, the treatment under investigation is clozapine, while for MDD this is (es)ketamine. For BD, this is the augmentation of antidepressants. These treatments are referred to as early-intensified treatments (EIPT) and are compared to the treatment as usual (TAU).

The current trials will contribute to the larger, overarching Horizon 2021 Psych-STRATA project, aiming to establish evidence-based criteria to make decisions on early intense treatment in individuals at risk for treatment resistance across the three major psychiatric disorders under study in the INTENSIFY trials [11].

Objectives {7}

In summary, current third-line pharmacological interventions include clozapine for SZ, augmentation with antidepressants for patients with BD and (es)ketamine intranasal/infusion for MDD. The overall aim of this study is to investigate whether it would be beneficial to patients to receive third-line treatments earlier in the illness, such as second-line treatment following a treatment failure in the current episode due to lack of efficacy.

The primary objective of the study is to compare the change in symptom severity at end of treatment relative to baseline. Symptom change is measured with the Positive and Negative Syndrome Scale (PANSS; SZ sample) and the Montgomery-Åsberg Depression Rating Scale (MADRS; MDD and BD samples). Secondary objectives compare the two treatment arms on changes in severity and sub-scores of symptoms, remission, cognition, quality of life and functioning measures, adverse events, concomitant medication, suicidal ideation and timing and reasons for treatment discontinuation over the 6-week treatment period. Exploratory objectives will focus on comparing information collected through digital applications and environmental parameters, as well as the identification of transdiagnostic predictors for treatment response and resistance across the three study samples, based on sociodemographic and clinical data, blood biomarkers, cognitive profiles and data obtained from digital applications. A full list of all study objectives can be found in Appendix 1.

Trial design {8}

INTENSIFY consists of three international, multi-center, controlled, randomized, open label trials, with a treatment duration of 6 weeks. In all countries, except Australia and Israel, these are considered as three separate trials. However, the trials are designed as equally as possible with highly overlapping study procedures and could therefore be considered as one trial with three parts (split out by diagnoses). Due to the naturalistic setting, the studies will be conducted in an open-label fashion. To minimize any experimenter bias caused by the open-label character, the raters of the primary outcome measures will be blinded concerning treatment allocation. The participants are randomized 1:1 to either the early

intensified pharmacological treatment (EIPT) group or the treatment as usual (TAU) group.

Methods: participants, interventions and outcomes

Study setting {9}

Recruitment will occur at 16 sites and more may be added; University Medical Center Utrecht (UMCU) serves as the sponsor for all sites, except for Adelaide (Australia). The site in Adelaide (Australia) obtained its own grant and will function as a sponsor for its part of the study; all study procedures will be similar between these sites. The EU authorities requested the study to be split per study sample, which was implemented, also for the UK. The authorities in Australia and Israel approved the protocol in which all three diagnostic groups are included. The sites are (academic) hospitals located in Australia (1), Austria (1), Germany (6), Greece (1), Israel (1), Italy (4), Spain (1) and the UK (1). If needed, more sites will be added in countries with current regulatory approval. For the full list of sites, please refer to www.clinicaltrials.gov (reference numbers can be found in the Administrative Details table).

Eligibility criteria {10}

The study samples include the diagnostic groups of schizophrenia (people with diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder), major depressive disorder (without psychotic features) and bipolar depression (bipolar disorder type I and II, currently in a depressive episode). General inclusion criteria for all study samples are the following: (1) being at least 18 years old, with an age limit of 70 for SZ, 65 for MDD and no age limit for BD; (2) being able and willing to provide written informed consent; (3) females of childbearing potential must use effective contraception throughout the trial and have a negative pregnancy test at visit 1. For males, there are no mandatory contraceptive measures, except for males on valproate acid; they must be willing to use contraception during the trial until 3 months after the trial; (4) participants must experience a treatment failure in the current episode (according to the clinical opinion, during screening confirmed by PANSS/MADRS); and (5) at least a moderate level of symptom severity and functional impairment needs to be present in the current episode. General exclusion criteria for all study samples are as follows: (1) females being pregnant or breastfeeding; (2) failures or intolerances to specific study drugs, or meeting contraindications on (part of) the study drugs; (3) participation in another interventional clinical trial within the last 30 days; (4) meeting substance use disorder criteria (nicotine, mild or moderate alcohol and/or cannabis disorder are allowed); (5) meeting criteria for high suicidal ideation where the clinician deems the risk for the potential participant is too high; 6) being admitted to an institution by virtue of an order issued by the judicial or administrative authorities. A full list of eligibility criteria and their operationalisation per study sample can be found in Appendix 2.

Who will take informed consent? {26a}

The informed consent process is as follows: the potential participant is orally informed by an authorized trained study team member, and the informed consent document is provided. In the written informed consent and in the oral informed consent discussions, it is ensured that potential participants understand that they may not benefit from their new treatment and that certain risks are associated with the new treatment, specifically for EIPT, and that there are specific procedures (such as laboratory tests) in place to limit the risks as much as possible. Potential participants are allowed time to consider their participation. Once all questions are answered and the decision to participate is made, informed consent is signed in line with International Conference on Harmonisation–Good Clinical Practice (ICH-GCP) requirements [12, 13].

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Specific components in the informed consent are optional, such as participation in central laboratory analyses, providing stool samples, storing blood samples for 10 years, providing digital biomarker data and sharing data within and beyond the consortium. Not consenting to these components still allows the patient to participate in the clinical trial.

Interventions

Explanation for the choice of comparators {6b}

The participants are randomized to either the early intensified pharmacological treatment (EIPT) group or the treatment as usual (TAU) group. The TAU group serves as the control arm/comparator to reflect routine daily practice and enables us to compare the intensified treatment with the treatment as per therapeutic guidelines. The reason for providing choices between various medication combinations in both TAU and EIPT (as described below) is to enable the clinician and patient to tailor the medication to the patient's needs and preferences (as in clinical practice). It is important to note that for the SZ and MDD TAU group, the clinician is free to choose any antipsychotic or antidepressant (respectively), except the EIPT arm medications. This ensures that it is possible to prescribe the medication that is best suitable for a participant and that this mimics daily clinical practice as that is our comparator

arm. No direct medication to medication are compared head-to-head (for example risperidone vs. olanzapine), but the arms are compared (EIPT vs. TAU).

Intervention description {11a}

Study medication will be prescribed between visit 2 and visit 4. Most medication will be oral medication that needs to be taken daily (in line with the applicable Summary of Product Characteristics (SmPC)). Doses can be modified at any time according to clinical needs by the treating physician/psychiatrist. The need for a dose adjustment is reviewed during every medication administration point (for the BD study sample and SZ TAU during the visits; for MDD during every (es)ketamine administration or TAU check-up visit). Dose adjustments can be done as long as they balance the potential side effects against improvements in symptoms and follow the local SmPC. Commercial medication is used. For all medication, dosing is in line with local daily practice and the latest applicable version of the SmPC. The only exception is (es)ketamine IV, as there is limited information available on dosing in MDD patients. The choices per study sample can be found in Table 1.

The EIPT MDD group will receive esketamine nasal spray or (es)ketamine IV two times per week for the first 4 weeks and weekly for the last 2 weeks. If participants use the esketamine nasal spray, they stay in the hospital for a minimum of 2 h to be monitored. If participants use (es) ketamine IV, the duration of the infusion is 40 min with a maximum of 60 min and after the infusion, participants stay in the hospital for a minimum of 2 h to be monitored. In the current study, the dosage will be at least 0.5 mg/kg body weight and can be increased up to 1.0 mg/kg body weight according to clinical needs as deemed appropriate by the treating physician/psychiatrist [13]. The infusion rate could range from 0.5 mg/kg/hour (0.5 mg/kg body weight for a 60 min infusion) to 1.5 mg/kg/hour (1.0 mg/kg body weight with a 40 min infusion). All site staff is trained on (es)ketamine administration before they start to administer it to participants during the study. A monitor is performing monitoring visits to ensure all interventions are performed in line with the most recently approved research protocol/SmPC.

Criteria for discontinuing or modifying allocated interventions {11b}

Reasons for discontinuing treatment can be diverse and include insufficient clinical effect, side effects, meeting contraindications, becoming intolerant, becoming pregnant, developing high suicidal ideation where the clinician deems the risk too high to continue participation, meeting criteria for current substance use disorder, need to use prohibited medication (refer to 11 d). Participants can discontinue the treatment, while continuing the other study procedures.

Strategies to improve adherence to interventions {11c}

Since this is a real-world study, medication adherence is thoroughly not assessed unless this is mandatory according to the SmPC (e.g. for the participants on lithium in the BD group, clozapine in the SZ group). Medication adherence is measured by a short self-report questionnaire between visit 2 and 4.

Relevant concomitant care permitted or prohibited during the trial {11d}

All additionally required concomitant medication is allowed when entering the study, as long as it is used stable and in line with the SmPC of the study medication. The doses for psychotropic concomitant medication can be decreased but not increased during the study. If new psychotropic concomitant medication needs to be added during the study for other indications than the primary diagnosis, one (additional) antipsychotic can be used for other indications than the primary diagnosis, if the maximum dose is $\leq$ 50% of the minimal effective dosage according to the SmPC. In addition, for the BD/MDD study sample, one new benzodiazepine can be used, if the maximum dose per day is less than 3 mg lorazepam equivalent, and 50% of the effective dosage for trazodone and amitriptyline is allowed. All other concomitant medication or psychotherapy is allowed; for SZ there is no restriction on benzodiazepines or antidepressants. Lifestyle restrictions are limited to what is included in the SmPC to mirror the real world as much as possible.

Provisions for post-trial care {30}

Participants who discontinue the allocated treatment and/or the study are treated as per usual treatment options. In some countries, this might mean that the medication used as intervention during the study might not be available after the study; this is to be resolved by the treating physician/psychiatrist in line with local healthcare insurance policies.

All participants are insured during the study: should they suffer from substantial harm during the trial or because of the trial, they get compensated according to the criteria of the insurance policy.

Table 1 Overview of treatment randomization per study sample

	SZ study sample	MDD study sample	BD study sample
Treatment as usual (TAU)	Switch to any second-line antipsychotic	Switch to any second-line antidepressant	Switch to quetiapine plus lithium or valproate acid
Early-intensified pharmacological treatment (EIPT)	Switch to clozapine	Second-line oral antidepressant plus esketamine nasal spray or esketamine IV or ketamine IV	Switch to 1. one of the following: escitalopram, sertraline, bupropion or venlafaxine plus 2. two of the following: lithium, valproate acid or quetiapine

Outcomes {12}

The primary outcome is the mean change in symptom severity from baseline (visit 2) compared to 6 weeks (visit 4) between the two treatment arms (EIPT vs. TAU). Symptom severity is measured with the Positive and Negative Syndrome Scale (PANSS) [14] in the SZ sample and the Montgomery-Åsberg Depression Rating Scale (MADRS) [15] in the MDD and BD samples. The mean change in PANSS and MADRS is measured as a continuous variable.

Secondary outcomes

1a. Change from baseline (visit 2) in the severity sub-score of the Clinical Global Impression Scale (CGI [16]) at visit 4: EIPT vs TAU.
1b. Improvement sub-score of the Clinical Global Impression Scale (CGI [16]) at visit 4; EIPT vs TAU.
2. Changes from baseline (visit 2) in total Hospital Anxiety and Depression Scale (HADS [17]) total score and anxiety and depression subscales at visit 4; EIPT vs TAU.
3. Change from baseline (visit 2) in quality of life and functioning measures (Q-LES-Q-SF [18], LAPS [19, 20], QLS-100 [52] and SDS [21]) at visit 4; EIPT vs TAU.
4. Changes from baseline (visit 2) on Trail Making Test (TMT [22]), Digit Symbol Substitution Test (DSST [22]), Rey Auditory Verbal Learning Test (RAVLT [22]) as well as the Perceived Deficits Questionnaire [23] at visit 4; EIPT vs TAU.
5. Presence of symptomatic remission at visit 4; EIPT vs TAU. Remission is defined as a MADRS score ≤ 12 (BD and MDD study samples) and presence of symptomatic remission at visit 4; EIPT vs TAU. For the SZ study sample, remission is defined as meeting the PANSS modified Andreasen criteria (Low scores (≤3) P1. Delusions; P3. Hallucinatory behaviour; P2. Conceptual disorganization; N1. Blunted affect; N4. Passive/apathetic social withdrawal; N6. Lack of spontaneity and flow of conversation; G5. Mannerisms/posturing; G9. Unusual thought content).
6. Presence of reported adverse events (related and unrelated to treatment) as measured through General Assessment of Side Effects Scale (GASE [24]) and reported spontaneously throughout the study; EIPT vs TAU.
7. Concomitant medication use throughout the study; EIPT vs TAU.
8. Premature treatment discontinuation before visit 4 and time to treatment discontinuation and reported reason of treatment discontinuation; EIPT vs TAU.
9. Changes on the Columbia-Suicide Severity Rating Scale (C-SSRS [25]) throughout the study; EIPT vs TAU.
10a. BD study sample only: Occurrence of (hypo) manic episodes throughout the study (including V5); EIPT vs TAU. Scores of 12 or higher on the YMRS [26] mean that a participant is in a (hypo)manic episode of bipolar disorder.
10b. SZ study sample only: Change from baseline (visit 2) in PANSS subscale scores (positive, negative and general) at visit 4; EIPT vs TAU.

Exploratory outcomes

The trials contain two innovative exploratory outcomes: first, information on digital biomarkers collected through digital applications will be compared between the two treatment arms (EIPT/TAU) over the 6-week treatment period within each diagnostic sample. This includes everyday life affect (valence, affective instability, inertia); stress (stress reactivity, reward experience); social context (being alone, enjoying social contact, belongingness)

and environmental parameters. Second, we will explore transdiagnostic predictors for treatment resistance and treatment response across the three diagnostic samples (SZ, BD, MDD). This will be based on sociodemographic, clinical and psychological data, blood biomarkers, stool samples, cognitive profiles and digital biomarkers.

Participant timeline {13}

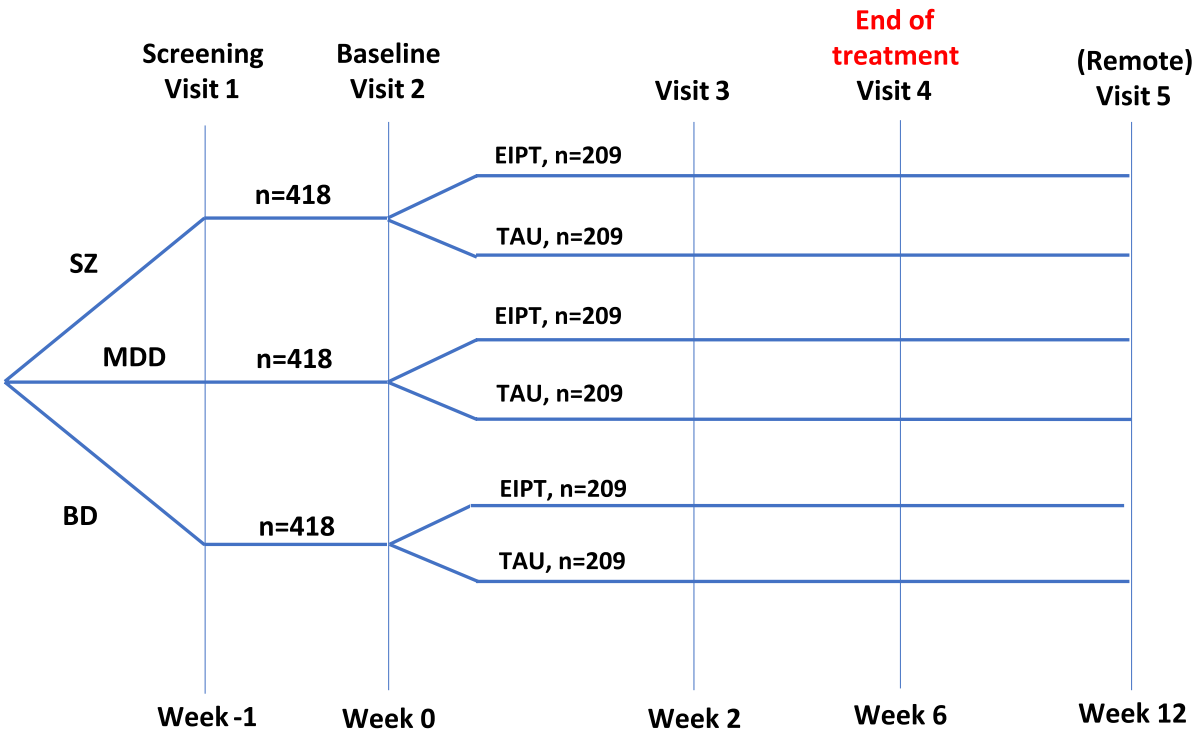
Participants will be in the trial for 12 weeks; the treatment duration is 6 weeks. The timing of visits is depicted in Fig. 1. In summary, there are 5 visits. At visit 1, screening is performed to determine eligibility for the study. Examples of checks are a confirmation of the diagnosis, treatment history and failure, safety tests, symptom severity, not meeting any of the contraindications, not having a severe substance and/or alcohol use disorder or being suicidal. The full list of eligibility criteria and assessments can be checked in Appendices 2 and 3 respectively. At visit 2, randomization takes place, the change of treatment is initiated, and baseline assessments are performed. At visit 3, early changes in symptomatology and development of side effects are assessed. From visit 4 on, medication is tapered off and at visit 4 post-treatment assessments are performed. Visit 5 is a follow-up visit. For the MDD study sample specifically, there are additional visits between visit 2 and 3 and between visit 3 and 4, due to the timing of (es)ketamine administration in the EIPT arm. The first 4 weeks of treatment, these additional visits occur twice weekly; in the last 2 weeks of treatment, these additional visits occur weekly. For the EIPT MDD group, (es)ketamine is administered, while for the TAU MDD group general well-being and treatment adherence is assessed (subjectively). The number of the additional visits is identical, independent of the randomized arm to avoid a bias.

Sample size {14}

For each study sample (SZ, BD, MDD), the study is powered to have 80% power to detect an effect size corresponding to a Cohen's D of 0.3. This estimate of Cohen's D is conservatively assumed to be at least 0.3, based on literature in SZ, BD and MDD [27–29]. Assuming two-sided testing at a 5% significance level, a total number of 350 (175 per arm) would be required for each study sample in case the means at follow-up would be compared using the independent-samples t-test. As ANCOVA has more power, this number can be reduced to 318 participants per study sample under a conservative estimate of 0.3 for the within-subject correlation [30]. The sample size is set at 418 participants per study sample, accounting for an expected drop-out rate of 24% (based on our previous international trials with this study population). The effect size of 0.3 can be considered as moderate, which is not uncommon in psychiatry (especially since two treatment regimens are compared). For SZ, this can be considered a small to moderate effect and is expected to translate to a mean difference of roughly 4 to 5.5 points on the PANSS total score based on the standard deviations presented in Cramer et al. (2001) [31], Hermes et al. (2013, Table 1, baseline scores) [32] and Volavka et al. (2002, Table 1, baseline scores) [33]. For BD, this can be considered a small to moderate effect and is expected to translate to a mean difference of approximately 1.5 to 3 points on the MADRS total score based on published studies, where SDs ranged from 4.5 to 10 [34–36]. For MDD, this can be considered a small to moderate effect and is expected to translate to a mean difference of approximately 1.4 to 2.3 points on the MADRS total score based on published studies, where SDs ranged from 4.5 to 7.5.

Recruitment {15}

Recruitment sources will differ between sites but will include in- and outpatients and referrals from nearby hospitals, clinics and/or primary care facilities. When a potential participant is identified, (s)he will be informed about the study by a delegated study team member. Oral explanation as well as written information will be provided. During conversations with the potential participants it is ensured that they understand that there are certain potential risks associated with the new treatment, specifically for EIPT as this is a more intense treatment that they would otherwise receive. It is explained that there are specific procedures (such as laboratory tests) in place to limit the risks throughout the study as much as possible. It is emphasized that we currently are unsure whether EIPT is superior to TAU, that they can experience side effects during the study and that they can stop at any time. This conversation is performed by study personnel, trained and authorized to perform this task. During the conversation, they will ensure that the participant is aware of all relevant information and is mentally competent to make an informed consent decision. All questions of a potential participant will be addressed. Participants have time to consider their participation where local law is followed for each site individually. When the study team and participant interact during the next appointment and it turns out the participant fully understands the trial, has no more questions and is willing and able to participate, informed consent will be signed. After that, screening procedures will take place to assess eligibility (see Participant timeline {13} and Appendices 2 and 3).



EIPT=Early Intense Pharmacological Treatment; TAU=Treatment AsUsual

Fig. 1 Flowchart of the trial design

Patient involvement

Representatives of the Global Alliance of Mental Illness Advocacy Networks–Europe (GAMIAN-Europe), a European patient and carer organisation representing individuals affected by SZ, BD and MDD, were involved during the grant preparation and protocol development phases of the study. Engagement occurred through consortium and study-level meetings, as well as written feedback on draft study documents, including the protocol and participant-facing materials such as informed consent forms.

Input from GAMIAN-Europe was obtained through iterative discussions and document-based comments, focusing on study procedures, participant burden and the clarity and tone of communication materials. This feedback informed several aspects of the study design, including refinement of participant-facing language to reduce potentially stigmatizing terminology and strengthening the representation of patient perspectives through the inclusion of multiple self-report measures. In addition, a patient satisfaction questionnaire was added at Visit 4 to capture participants' experiences of study participation.

The involvement of GAMIAN-Europe was primarily consultative, and formal metrics to evaluate the impact of patient and public involvement were not prospectively defined. GAMIAN-Europe will also contribute to dissemination activities, supporting communication of study findings to patients, carers, healthcare providers, policymakers and the broader public, aiming to (1) empower patients and family members to evaluate the development, methodology and output of treatment decision-making processes, (2) engage all relevant stakeholders throughout the project, (3) communicate the need for personalised approaches in mental health to stakeholders and inform about the goals and results of the current trial and (4) disseminate project results to the main target groups: researchers, healthcare providers, policymakers, authorities and patients.

Assignment of interventions: allocation

Sequence generation {16a}

The randomization process (1:1 allocation to treatment) is carried out with (a) study center and (b) in- or outpatient status as stratification parameters, and it is implemented separately for each of the diagnostic samples. This randomization process with stratification will reduce selection bias and control for confounders. To reduce the predictability of the sequences, minimum (size 2) and maximum block sizes (size 4) are used. The allocation sequence is computer-generated via the Castor EDC.

Concealment mechanism {16b}

After informed consent, the participants perform the screening visit. If participants fulfill all eligibility criteria, they will perform visit 2 that includes randomization. Randomization is performed through the online module available in the Castor EDC. The full randomization list (incl. unassigned participants) is hidden for all investigators and the central study team. The central study team can see the allocation of all participants of all sites that are already randomised. Delegated study team members who perform randomization for their study site have access to the participants (incl. the allocation) for their site only.

Implementation {16c}

Randomization is conducted by a site team member trained and authorized for this activity, through the online module available in the Castor EDC. The allocation sequence is created by the Castor EDC that includes the stratification factors and the block sizes (refer to 16a). The study team member performing the randomization in the Castor EDC is not allowed to rate the primary outcome throughout the study. Participants are enrolled by an authorized study team member and the intervention will be prescribed by the investigator/physician.

Assignment of interventions: blinding

Who will be blinded {17a}

This study has an open label character. Therefore, participants, physicians and raters of the non-primary outcomes will be aware of the treatment allocation. To minimize any experimenter bias, the raters of the primary outcome measures (PANSS/MADRS) will be blinded towards treatment allocation and will not have access to any participant data, including the CentraXX electronic data capture (EDC) system or the Castor EDC, where the randomization takes place. These blinded raters are all trained via the same training procedure: a PANSS/MADRS trainer teaches the use of the instrument after which the raters and trainer jointly discuss their rating of a (video recording of a) participant. This is followed by an exam where the blinded raters watch another video of an interview with a patient and complete the scoring individually. The exam scores are evaluated and only when they have passed the exam, they are certified for the study and allowed to perform the rating. If a blinded rater becomes unblinded during the study, (s)he is replaced by a new unblinded rater.

Procedure for unblinding if needed {17b}

The blinded raters will only assess the primary outcome; all other measures including safety measures are overseen by unblinded site team members, hence unblinding is not needed.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Trained and authorized site team members will assess the participant following the procedures in the study protocol on the visits as depicted in Fig. 1. For central lab procedures, digital biomarkers, PANSS and MADRS, there is a mandatory training. For PANSS and MADRS there is also a formal assessment that assessors need to formally pass before they are certified to perform PANSS/MADRS for the trial. Participants will complete the self-report measures themselves, on paper source or directly in the CentraXX Patient Application. In Appendix 3, an overview can be found of all assessments per visit.

Plans to promote participant retention and complete follow-up {18b}

The participating sites selected for the study have experience in conducting clinical trials in the specific diagnostic areas and will focus on building rapport with participants to maximize retention and follow-up assessments. When participants discontinue the study medication, they are invited to complete the remaining study assessments to facilitate the intent-to-treat analysis approach. Additionally, participants consenting for the DBM part of the study will get a sheet with their individual research results on mood, self-esteem, positive and negative events. This is an incentive to continue the study, but also to provide participants more insight in their symptoms.

Data management {19}

Data is collected on paper worksheets. Direct data entry in the CentraXX EDC is allowed according to the protocol, if pre-specified in the confirmation of source data document. Some sites will use the optional CentraXX Patient Application, which participants can access directly to provide the answers to self-report questionnaires. Authorized and trained site team members will obtain a personal, password-protected user account to CentraXX. All data collected is pseudonymized; a code is used to identify a participant (e.g. 01001) and only the participating site has the key to link the code to the name of the participant. All paper source documentation is filed securely at the site until archival after study closure, ensuring that all documents containing the name of the participant are sealed and all other documents are

pseudonymized. A Data Protection Impact Assessment (DPIA) is in place at the sponsor to ensure confidentiality of the participants. The CentraXX EDC data are stored on secure servers from the Fraunhofer Institute, located in Germany.

Confidentiality {27}

The study will be conducted in accordance with the principles of the Declaration of Helsinki (64th WMA general assembly; October 2013), with the ICH-GCP guidelines, General Data Protection Regulation (GDPR), Clinical Trial Regulation (CTR; No 536/2014) and other applicable (national) laws and regulations. Disclosure of personal data to others than the study team is prohibited. Their names and other sensitive identifying information will be stored only at the participating site to protect participant privacy. The participating site will enter the pseudonymized data in CentraXX, a secured, password-protected electronic data capture system (EDC). For randomization, Castor EDC is used. In Castor, the pseudonymized participant ID and stratification parameters are added. This leads to a randomization outcome, which is added to CentraXX. Castor is a secured, password-protected electronic data capture system (EDC).

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Blood and stool samples are collected for genomic, epigenomic, transcriptomic, iPSC and proteomic analyses. These lab samples are stored at each site and shipped yearly to the Ludwig Maximilians-University (LMU) in Munich, Germany. From there, they are sorted and forwarded to the selected laboratories that will perform the analyses. The data resulting from the raw analyses will be kept securely on the Fraunhofer servers. Only authorized personnel have access to the data. The results will be used for the exploratory objectives of the current study. Consent for providing blood samples and/or stool samples is optional, as well as consent to storage of remaining samples at the LMU for a maximum of 10 years.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Primary analysis

The primary statistical analysis will compare mean changes from baseline (visit 2) in PANSS (SZ) and MADRS (BD/MDD) total scores at week 6 (visit 4) between the treatment arms for each study sample separately, using analysis of covariance (ANCOVA) adjusting for PANSS/MADRS total score at baseline and country and in- or outpatient status (covariates). As sensitivity analyses, the ANCOVA analysis will be repeated (i) without adjustment for country and in- or outpatient status and ii) with additional adjustment for the following prognostic covariates: biological sex [37], age and duration of untreated illness [38, 39]. The primary endpoint will be tested at a significance level of 5% (two-tailed testing) on an intention-to-treat basis, i.e. outcome data will be included irrespective of treatment adherence and the analysis will in principle include all randomized subjects as randomized. Last, as the TAU is to be determined before randomization, subgroup analysis for intended TAU (first-generation, second-generation, or third-generation antipsychotics) is performed as well (total and, if feasible, per country). These sensitivity and subgroup-specific treatment effects will be derived without adjusting for country and inpatient/outpatient status and will be reported with 95% CIs and presented in forest plots. No formal statistical testing will be done within subgroups per sample; therefore, no correction for multiple testing is applied.

Secondary analyses

For the secondary analyses, each study sample will be analyzed separately (in line with the primary analyses). The following secondary endpoints are included in the confirmatory testing strategy, per study sample:

1. Change from baseline (visit 2) in the severity subscore of the CGI at visit 4.
2. Change in total HADS score from baseline (visit 2) to visit 4.
3. Presence of symptomatic remission at visit 4. For SZ, symptomatic remission is defined as meeting the Andreasen criteria. For BD/MDD, symptomatic remission is defined as a MADRS total score ≤ 12.

A hierarchical testing procedure will be used in which change from baseline in CGI severity will only be tested in case the primary endpoint is significant. The following secondary endpoints will only be tested if the previous secondary endpoint is significant. A two-sided significant level of 5% will be used for all tests.

Change from baseline in CGI severity and HADS total score will be tested using analysis of covariance (ANCOVA) with an adjustment for the baseline value and country. Presence of symptomatic remission at visit 4 will be compared using logistic regression analysis adjusted for baseline value and country. In case the adjustment for country causes estimation issues due to (quasi-)separation, an unadjusted analysis will be performed for this endpoint.

All secondary endpoints not included in the hierarchical testing sequence will be considered exploratory. For

these secondary endpoints mean differences with 95% confidence intervals will be calculated for the continuous endpoints. Relative risks and absolute risk differences with 95% confidence intervals will be calculated for the dichotomous endpoints. Therefore, no multiple testing correction is applied.

Interim analyses {21b}

Interim analysis of this trial is not planned.

Methods for additional analyses (e.g. subgroup analyses) {20b}

Subgroup analyses

For the primary endpoint, pre-specified subgroup analyses will be performed for potential prognostic factors (biological sex, in-/outpatient status, age, duration of untreated illness) and by country. Subgroup-specific treatment effects will be reported with 95% CIs and presented in forest plots. All subgroup analyses are considered exploratory.

Transdiagnostic analyses

For transdiagnostic evaluation of EIPT compared to TAU, a pooled summary effect size will be estimated from the effect sizes for the primary endpoint using a fixed effects meta-analysis. As the primary outcome differs between the study samples, standardized effect sizes will be first calculated within for each study sample and then pooled to obtain an average standardized effect size. Mean differences in the change from baseline for EIPT compared to TAU for secondary outcome variables that are collected in all three trials and measured on a continuous scale will be pooled transdiagnostically (across the three trials). Transdiagnostically-pooled effect sizes for dichotomous secondary outcome variables collected in all trials will be obtained using Cochran-Mantel–Haenszel methods with the trials considered as strata. Further, additional exploratory analyses include analyses to transdiagnostically find prognostic factors for the secondary outcomes measured in all three trials. This model is based on sociodemographic, clinical and psychological data, blood biomarkers, stool samples, cognitive profiles, and digital biomarkers, the results from the personalized disease models, the genotype based cellular trait risk scores and the PBMC based transcriptomic, epigenomic and proteomic profiling, sociodemographic, clinical and psychological data, stool samples, cognitive profiles and digital biomarkers will be combined within a machine learning framework to build an integrated, multi-modal predictive model of treatment response across diagnoses.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

All protocol non-adherence will be registered in the protocol violation log. Only in extreme cases of protocol non-adherence (i.e. participant included who did not meet the eligibility criteria), this could lead to exclusion of the database, in line with the ITT approach. Multiple imputation will be used to handle missing data. Per study sample, a dataset (per arm and in wide format) will be constructed containing, among others, data from all primary and key secondary outcome variables from all visits, all variables included as covariates in any of the primary or secondary analysis models, PID-5 domain scores and level of functioning. Missing values will be imputed using the Multiple Imputation by Chained Equations (MICE) algorithm as implemented in the R package mice (version 3.16.0 or higher) [40]. In case of non-convergence, imputation models may be simplified according to the statistical analysis plan. Following imputation, the trial arm indicator and derived scores will be added, and the trial arm-specific imputed datasets will be merged for analysis. Analyses will be performed in each multiply imputed dataset, and effect estimates will be pooled using Rubin's rules. Full details will be provided in the Statistical Analysis Plan.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

The datasets analyzed during the current study and statistical code are available from the corresponding author on reasonable request, as is the full protocol. With the publication of the main manuscript, de-identified participant data will be made available to promote open science.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The sponsor and coordinating center is the University Medical Center Utrecht, where a team of project managers (PM) and monitors/clinical research associates (CRAs) will implement, coordinate and monitor the trials. This team meets at least weekly to discuss progress and ongoing issues and is part of the Study Management Group (SMG), who meets on a regular basis (quarterly or more frequent when needed) to discuss study progress and day-to-day issues. The SMG consists of the sponsor team and expert psychiatrists in MDD, BD and SZ. During bi-annual meetings, study progress and issues concerning the trial will be shared with the Executive Board (EB), functioning as a trial steering committee, consisting of all principal investigators of the participating centers,

the sponsor team as well as other parties involved in the setup and progress of these trials. The EB monitors the progress of the trial towards its interim and overall objectives.

Composition of the data monitoring committee, its role and reporting structure {21a}

The Data Safety Monitoring Board (DSMB) meets at least once per year to review trends indicating potential safety concerns and protocol procedures related to Serious Adverse Events (SAEs). The DSMB is allowed to suggest changes to the protocol or provide an altered judgement of feasibility if information from the Development Safety Update Report (DSUR) or new information about the medication included in the study has become available. The DSMB consists of independent experts with no conflicts of interest. The DSMB Charter is available on request.

Adverse event reporting and harms {22}

After participants have provided consent and are enrolled in the study, adverse events will be documented and recorded until visit 5 (end of study). Adverse events can be reported spontaneously, via electrocardiograms, local laboratory assessments, physical examinations or via the General Assessment of Side Effects (GASE [24]) questionnaire. All adverse events that meet the ICH-GCP criteria of being a Serious Adverse Event (SAE) or Suspected Unexpected Serious Adverse Reaction (SUSAR) will be reported according to the Clinical Trial Regulation and any other national or local regulations.

When an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator consult the DSMB and take appropriate urgent safety measures to protect the participants. In addition, the sponsor will notify the applicable authorities without undue delay but no later than 7 days from the date the measures have been taken.

Frequency and plans for auditing trial conduct {23}

Site monitoring will be performed by the Clinical Research Associates (CRAs) hired by the sponsor. In the CentraXX EDC, automatic edit checks are implemented ensuring data quality. The CRA will perform weekly centralized monitoring activities on the EDC data and can raise queries in case of inconsistencies. On-site visits are conducted annually by the CRA. A risk-based monitoring approach is followed; for all participants, all data related to eligibility, informed consent, primary outcomes and safety outcomes are checked. In addition, all data for a sample of 10% of participants are checked; this portion can be increased for individual sites when deemed necessary.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Any amendments to the study documents will be submitted to the applicable authorities for their approval. Once approval is received, a copy of the revised protocol and other amended documents will be provided to the principal investigator for implementation. When needed, the registration on www.clinicaltrials.gov will be updated. If the change has a substantial impact on the participant, the informed consent will be amended, and participants are asked to reconsent.

Dissemination plans {31a}

Results of these trials will be available through scientific publications in peer-reviewed journals and at scientific conferences. Further dissemination might take place via GAMIAN-Europe (see section Patient involvement). The results will be published on www.clinicaltrials.gov and the CTIS database. Psych-STRATA consortium partners can obtain access to all data, including the biological material and/or data, after their publication proposal is approved by the Executive Board and transfer agreements for data and/or materials are in place. For parties external to the consortium, the same procedure applies; however, data and materials can only be shared for those study participants who have consented to this optional component.

Discussion

These will be the first RCTs systematically addressing the question whether third-line treatments are more effective when used earlier in the disease course for SZ, BD and MDD, compared to treatment as usual. One note here is that for SZ this is the second trial: the EARLY trial, where people were offered clozapine or olanzapine as second-line treatment has just finalized the patient recruitment and we are interested to see the results soon [41]. For the current RCTs, the unique study setup will provide the opportunity to explore the effects of EIPT on quality of life, functioning and other patient-centered measures, as well as predictors for treatment resistance. The latter could be utilized as guidance for physicians when prescribing psychotropic medication, moving towards precision medicine instead of a trial-and-error process. In addition, the rich datasets for each of the diagnostic samples will be combined to identify patient and illness characteristics (including biomarkers) associated with treatment resistance in a transdiagnostic approach, across the three diagnostic samples. It is important to note that the EIPT treatment for the BD and MDD sample, as well

as TAU treatment for all study samples, is composed of multiple medication options to be selected for individual patients, probably leading to a variety of medications used during the study [42]. The current study design does not allow us to compare the efficacy of specific medications; however, this is not our study aim; the current setup allows us to determine whether pre-specified third-line treatments (as a group) are more effective compared to current second-line treatments (as a group; treatment as usual).The current trial will contribute to the larger, overarching Horizon 2021 Psych-STRATA project, aiming to establish evidence-based criteria to make decisions on early intense treatment in individuals at risk for treatment resistance across the three major psychiatric disorders under study in the INTENSIFY trials.

Strengths

A major strength of the current study is the pragmatic design, mirroring clinical practice as much as possible. When selecting medication in the TAU group, for SZ and MDD, clinicians can prescribe any psychotropic medication, if they follow the treatment guidelines and Summary of Product Characteristics (SmPC). In the EIPT group, although the choice is limited to third-line treatments, in most study samples there is still a choice between treatments. This is in line with daily clinical practice and facilitates shared decision-making between clinician and participant. A pragmatic design is often lacking in clinical trials, limiting generalization of study results to daily clinical practice. Another strength is the 12-week follow-up visit (visit 5), to measure treatment effects on a longer term and to determine whether participants continued using the study medication. Moreover, the current trials will result in a uniquely rich dataset that will be utilized to identify transdiagnostic predictors for treatment resistance (exploratory objectives). Finally, assessing the subjective impact for patients is often missing in clinical trials; our focus on functioning and quality of life will be an important contribution to the field.

Limitations

First, only the primary outcome raters are blinded. The psychiatrists who prescribe the medication, raters of other outcomes and the participants are unblinded. This is done to ensure this is a real-world trial, but it could lead to performance bias, assessment bias and attrition bias. Investigators are trained to minimize these biases as much as possible and participants are repeatedly instructed not to disclose their treatment allocation to the primary outcome rater. However, these biases will impact the study. Furthermore, the treatment duration is 6 weeks, which is long enough to detect early treatment effects but fails to detect the long-term effects. Last, the advantage of a large consortium such as Psych-STRATA is the number of participating sites. However, at the same time this also results in some limitations such as the differences in TAU in different countries and other variability.

Conclusion

The current study will investigate whether it would be beneficial to prescribe third-line treatments for SZ, BD and MDD earlier in the illness course. If EIPT is proven to be more effective than TAU, this could be one of the first steps to prevent unnecessary trials of ineffective treatments, a substantial reduction of individual suffering (including less hospitalisations and suicide attempts) as well as healthcare and societal costs. Moreover, it could start a new discussion on recommendations for adaptations of treatment guidelines worldwide and will provide a better assessment on what research is still needed in this area. Finally, all measurements from the primary and secondary outcomes could be tested as potential transdiagnostic predictors for treatment resistance to advance personalised treatment in psychiatry for SZ, BD and MDD.

Trial status

Recruitment (screening) started in April 2024. The first participant for the SZ study was included on 01 August 2024; for the BD study on 11 February 2025 and on 29 August for the MDD study.

The latest approved protocol versions (for the EU) are for SZ: Protocol V1.3, 23 January 2026; for BD: Protocol V1.4, 16 December 2025; and for MDD: Protocol V1.3, 30 January 2026. The latest protocol versions for the UK are for SZ: Protocol 1.2, 15 October 2024, BD: Protocol 1.1, 30 November 2023, MDD: Protocol 1.1, 1 December 2023. The current protocol version for Israel is a merged protocol (including SZ/BD/MDD) V1.5, 4 March 2024. The current protocol version for Australia is V3.1, 19 December 2024. The estimated primary completion date is January 2027.

The last amendment was submitted to facilitate recruitment. We are interested in participants that have a current treatment failure, who did not yet try a treatment-resistant medication (i.e. clozapine for the SZ trial). In the previous version, we were only interested in first-line treatment failure in the current episode which turned out to be too restrictive.

Appendix 1

Overview of all objectives and endpoints

Primary objective and endpoint

The primary objective is measure the mean change in symptom severity from baseline (visit 2) compared to 6 weeks (visit 4) between the two treatment arms (EIPT vs. TAU). Symptom severity is measured with the Positive And Negative Syndrome Scale (PANSS) [15] in the SZ sample and the Montgomery-Åsberg Depression Rating Scale (MADRS) [16] in the MDD and BD samples. The mean change in PANSS and MADRS is measured as continuous variable.

Secondary objectives and endpoints

Objective	Endpoint
1. To compare changes in severity and improvement in global functioning assessed by the Clinical Global Impression Scale (CGI) between the two treatment arms	1.a. Change from baseline (visit 2) in the severity sub-score of the Clinical Global Impression Scale (CGI) at visit 4; EIPT vs TAU 1.b. Improvement sub-score of the Clinical Global Impression Scale (CGI) at visit 4; EIPT vs TAU
2. To compare changes in the levels of depression and anxiety between treatment arms	2. Changes from baseline (visit 2) in total Hospital Anxiety and Depression Scale (HADS) total score and anxiety and depression subscales at visit 4; EIPT vs TAU
3. To compare changes in quality of life and functioning measures between treatment arms	3. Change from baseline (visit 2) in quality of life and functioning measures (Q-LES-Q-SF, LAPS, QLS-100 and SDS) at visit 4; EIPT vs TAU
4. To compare changes in cognitive performance between treatment arms	4. Changes from baseline (visit 2) on Trail Making Test, Digit Symbol Substitution Test, Rey Auditory Verbal Learning Test as well as the Perceived Deficits Questionnaire at visit 4; EIPT vs TAU
5. To compare the proportion of participants (EIPT vs. TAU) that is in symptomatic remission at visit 4	5. Presence of symptomatic remission at visit 4; EIPT vs TAU. Remission is defined as a MADRS score ≤ 12
6. To compare presence of adverse events (related and unrelated to treatment) between treatment arms	6. Presence of reported adverse events (related and unrelated to treatment) as measured through General Assessment of Side Effects Scale (GASE) and reported spontaneously throughout the study; EIPT vs TAU
7. To compare use of concomitant medication between treatment arms	7. Concomitant medication use throughout the study; EIPT vs TAU
8. To compare premature treatment discontinuation (timing and reason) between treatment arms	8. Premature treatment discontinuation before visit 4 and time to treatment discontinuation and reported reason of treatment discontinuation; EIPT vs TAU
9. To compare changes in suicidal ideation between treatment arms	9. Changes on the Columbia-Suicide Severity Rating Scale (C-SSRS) throughout the study; EIPT vs TAU
10. BD study sample only: To compare occurrence of (hypo) manic episode during the study between the treatment arms	10. Occurrence of (hypo)manic episodes throughout the study (including V5); EIPT vs TAU. Scores of 12 or higher means that a participant is in a (hypo)manic episode of bipolar disorder
10. SZ study sample only: To compare changes in PANSS subscale scores (positive, negative and general) between the two treatment arms	10. Change from baseline (visit 2) in PANSS subscale scores (positive, negative and general) at visit 4; EIPT vs TAU

Exploratory objectives and endpoints

1. All study samples: To compare information on digital biomarkers collected through digital applications between the two treatment arms (EIPT/TAU) over the 6-week treatment period (visit 2 versus visit 4), such as everyday life affect (valence, affective instability, inertia), stress (stress reactivity, reward experience), social context (being alone, enjoying social contact, belongingness) and environmental parameters.
2. All study samples: To identify transdiagnostic predictors for treatment resistance and treatment response across the three Psych-STRATA study samples (Schizophrenia, Bipolar Depression and Major Depressive Disorder), based on sociodemographic, clinical and psychological data, blood biomarkers, stool samples, cognitive profiles and digital biomarkers.

Appendix 2

Overview of eligibility criteria

A criterion is applicable for all study samples, unless otherwise indicated.

Inclusion criteria

1. For SZ study sample: In- or out patients, at least 18 years of age up until 70.
   For BD study sample: In- or out patients, at least 18 years of age.
   For MDD study sample: In- or out patients, at least 18 years of age up until 65.
2. Being willing and able to provide written informed consent. Having a legal guardian to cosign is allowed. Informed consent will be signed at visit 1, before any study procedure.
3. Female participants of child bearing potential must use effective contraception during the trial as per the

requirements of the applicable SmPCs and should have a negative pregnancy test at visit 1.
For BD study sample in addition: Male participants that will use valproate acid during the trial must use effective contraceptive measures during the trial.

4. For SZ study sample: Meeting diagnostic criteria for a primary diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder, according to DSM-5. The primary diagnosis will be confirmed by the Mini International Neuropsychiatric Interview (MINI v7.0.2).
   For BD study sample: Meeting diagnostic criteria for a primary diagnosis of bipolar depression (bipolar disorder type I and II currently in a depressive episode), according to DSM-5. The primary diagnosis will be confirmed by the Mini International Neuropsychiatric Interview (MINI v7.0.2).
   For MDD study sample: Meeting diagnostic criteria for a primary diagnosis of major depressive disorder (without psychotic features), according to DSM-5. The primary diagnosis will be confirmed by the Mini International Neuropsychiatric Interview (MINI v7.0.2).
5. Participant experiences a treatment failure due to lack of efficacy in the current episode, as confirmed by a CGI-I $\geq$ 3. Preferably, this treatment is a first-line pharmacotherapeutic agent for the primary DSM-5 diagnosis and was prescribed for at least 4 weeks within an effective dose range as specified in the Summary of Product Characteristics (SmPCs). However, other lines of treatments are allowed as well.
6. Participant and clinician intend to change pharmacotherapeutic treatment.
7. A minimum symptom severity threshold needs to be present (moderate level; see below) and participant needs to experience functional impairment.
   - For SZ study sample: The minimum symptom severity threshold is at least 2 PANSS positive or negative items with a score of 4, or at least one PANSS positive or negative item with a score of 5 [43].
   - For BD study sample: The minimum symptom severity threshold is a score of $\geq$ 20 on the Montgomery Åsberg Depression Rating Scale (MADRS [44])
   - For MDD study sample: The minimum symptom severity threshold is a score of $\geq$ 20 on the Montgomery Åsberg Depression Rating Scale (MADRS [45, 46])
   - For all study samples: Functional impairment is defined as a score of 5 or higher on any of the three scales of the Sheehan Disability Scale (SDS).

Exclusion criteria

1. Being pregnant or breastfeeding.
2. For SZ study sample: Participant has used clozapine in the past. For MDD study sample: Participant has used (es)ketamine previously for the treatment of depressive symptoms.
3. For SZ study sample: Participant has a known intolerance to clozapine or to all TAU medication options. For BD study sample: Participant has a known intolerance to quetiapine or to all EIPT medication or to all TAU medication. For MDD study sample: Participant has a known intolerance to (es)ketamine or to all TAU medication.
4. For SZ study sample: Meeting any of the contraindications of clozapine or to all TAU medication options, as specified within the applicable SmPC. For BD study sample: Meeting any of the contraindications for quetiapine, or to all EIPT medication or to all TAU medication options, as specified within the applicable SmPC, supported by clinically significant abnormal values on local laboratory tests, electrocardiogram (ECG) or physical examinations. For MDD study sample: Meeting any of the contraindications for (es)ketamine, or to all TAU medication options, as specified within the applicable SmPC, supported by clinically significant abnormal values on local laboratory tests, electrocardiogram (ECG) or physical examinations.
5. Participant has participated in another clinical trial in which the participant received an experimental or investigational drug or agent within 30 days before visit 1.
6. Participant experiences any other significant disease or disorder which, in the opinion of the investigator, may either put the participant at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.
7. Participants with active suicidal ideation with some intent to act, without specific plan ("Yes" to question 4 of the Columbia-Suicide Severity Rating Scale (C-SSRS)) or active suicidal ideation with specific plan and intent ("Yes" to question 5 of the C-SSRS), followed by an assessment by the treating clinician who determines it is not safe for the participant to participate in the study.
8. Participant meets criteria for current substance use disorder, as confirmed by the Mini International Neuropsychiatric Interview (MINI v7.0.2).

Nicotine dependency is allowed, as well as mild and moderate alcohol and/or cannabis use disorder (as defined by MINI v7.0.2). Severe alcohol and/or cannabis use disorder are not allowed.

9. Participants have not been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.
10. Participants dependent on the sponsor, investigator or trial site must be excluded from participation in advance
11. For SZ study sample only: Participants who meet the modified Andreasen criteria for remission.
12. For SZ study sample only: Participants that have any clinically significant abnormal values on the local laboratory test (especially ANC/WBC and liver values), electrocardiogram (ECG) or physician examinations.
13. For BD study sample only: A score of 12 or higher on the Young Mania Rating Scale (YMRS [44]) in order to exclude participants with predominant manic symptoms or mixed symptoms.
14. For BD study sample only: Participants with pre-existing severe liver damage (as tested within the local laboratory test at visit 1).
15. For BD study sample only: Participants with a history of antidepressant-induced mania or hypomania or recent rapid cycling (based on the medical file of the potential participant or the clinical judgment of the clinician).

Appendix 3

Overview of all measurements per study visit

Trial procedures	Visit 1 screening	Visit 2 baseline	Visit 3	Visit 4	Visit 5 follow-up
	Week -1	Week 0 (maximum of 10 days after visit 1)	Week 2 (11–15 days after visit 2)	Week 6 (39–45 days after visit 2)	Week 12 (81–87 days after visit 2)
Informed consent	X				
Inclusion/exclusion criteria review	X	X			
Mini International Neuropsychiatric Interview v7.0.2 (MINI v7.0.2) [47]	X				
Personality inventory for DSM-5 (PID-5) [48]	X				
Sociodemographic data	X				
Medical/psychiatric history	X				
Medication use past/current	X	X	X	X	X
Clinical global impression (CGI) [49]	X	X	X	X	X
Pregnancy test[1]	X	(X)	(X)	(X)	X
Central laboratory assessment		X	X	X	
Questions microbiome (incl. Bristol Stool Scale)[2]		X		X	
Randomization		X			
Childhood Trauma Questionnaire short form (CTQ short form) [50]		X			
Hospital Anxiety and Depression Scale (HADS) [17]		X		X	
Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) [51]		X		X	
Drug abuse (MINI v7.0.2 module J) [5]	X		X	X	
Columbia–Suicide Severity Rating Scale (C-SSRS)	X		X	X	
Quality of Life Scale 100 (QLS-100; subscale inner tension) [36]		X		X	
Quality of Life Enjoyment and Satisfaction Short Form (Q-LES-Q-SF) [18]		X		X	
Sheehan Disability Scale (SDS) [21, 52]	X	X		X	X

Trial procedures	Visit 1 screening	Visit 2 baseline	Visit 3	Visit 4	Visit 5 follow-up
	Week -1	Week 0 (maximum of 10 days after visit 1)	Week 2 (11–15 days after visit 2)	Week 6 (39–45 days after visit 2)	Week 12 (81–87 days after visit 2)
Leuven Affect and Pleasure Scale (LAPS) [19]		X		X	
Patient Global Impression (PGI)		X	X	X	X
Perceived Deficits Questionnaire 5 (PDQ-5) [24, 53]		X		X	
General Assessment of Side Effects (GASE) [24]		X	X	X	X
Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) [54]		X		X	
Cognitive battery (Digit Symbol Substitution Task, Rey Auditory Verbal Learning Test, Trail Making Test part B) [22]		X		X	
Digital biomarkers		X	X	X	
Medication adherence and opinion			X	X	
Relapse/hospitalisation	X	X	X	X	X
Patient satisfaction questionnaire				X	
Local laboratory results	X	(X)	(X)	X	(X)
ECG	X	(X)	(X)	X	(X)
Physical examination	X	(X)	(X)	X	(X)
Reason discontinuation		If applicable			
In addition, for SZ sample only:					
Positive And Negative Syndrome Scale (PANSS) [14]	X	X	X	X	X
In addition, for MDD sample only:					
Montgomery Åsberg Rating Scale (MADRS) [15]	X	X	X	X	X
EIPT only: medication administrations, incl. blood pressure measurement	Between visit 2 and visit 4; twice per week for 4 weeks and weekly for 2 weeks				
TAU only: check up visits	Between visit 2 and visit 4; twice per week for 4 weeks and weekly for 2 weeks				
In addition, for BD sample only:					
Montgomery Åsberg Rating Scale (MADRS) [15]	X	X	X	X	X
Young Mania Rating Scale (YMRS) [26]	X	X	X	X	X
Alda (only when on lithium treatment) [55]		X		X	

[1] Pregnancy test are performed at least before randomization and at visit 5. During the study, they are performed as part of standard clinical practice procedures (depending on local regulations). If not pregnant in subsequent visits, nothing needs to be reported

[2] Optional, only when sites participate in this part of the study and participants do not opt-out. Consists out of 7 additional demographic questions and the Bristol Stool Scale

Abbreviations

ANCOVA	Analysis of Covariance
BD	Bipolar Depression
CGI	Clinical Global Impression scale
CRA	Clinical Research Associate
C-SSRS	Columbia-Suicide Severity Rating Scale
CTIS	Clinical Trials Information System
CTQ	Childhood Trauma Questionnaire
CTR	Clinical Trial Regulation
DPIA	Data Protection Impact Assessment
DSMB	Data Safety Monitoring Board
DSST	Digit Symbol Substitution Test
DSUR	Development Safety Update Report
EB	Executive Board
EDC	Electronic Data Capture (system)
EIPT	Early-Intensified Pharmacological Treatment
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GAMIAN	Global Alliance of Mental Illness Advocacy Networks
GASE	General Assessment of Side Effects Scale
GDPR	General Data Protection Regulation
HADS	Hospital Anxiety and Depression Scale
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonisation—Good Clinical Practice
IV	Intravenous (administration)
LAPS	Leuven Affect and Pleasure Scale
LMU	Ludwig Maximilians-Universität
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major Depressive Disorder
mg/kg	Milligram per Kilogram (body weight)
MICE	Multiple Imputation by Chained Equations
MINI	Mini International Neuropsychiatric Interview
PANSS	Positive And Negative Syndrome Scale

PBMC	Peripheral Blood Mononuclear Cells
PDQ-5	Perceived Deficits Question 5 item version
PID-5	Personality Inventory for DSM-5
PM	Project Manager
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire Short Form
QLS-100	Quality of Life Scale 100
RAVLT	Rey Auditory Verbal Learning Test
RCT	Randomized Clinical Trial
SAE	Serious Adverse Event
SDS	Sheehan Disability Scale
SDV	Source Data Verification
SMG	Study Management Group
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SZ	Schizophrenia
TAU	Treatment As Usual
TMT	Trail-Making Test (part B)
TRBD	Treatment-Resistant Bipolar Depression
TRD	Treatment-Resistant Depression
UK	United Kingdom
UMCU	University Medical Center Utrecht

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To describe the author contributions, we used the ICJME guidelines on authorship conditions: IW, BB, CO, AS provided substantial contributions to conception, design, or data; IW, BB, CO, AS, EV, AH, EV, LI, CF, KOS, SRC, MM, HA, PB, AM, SFF, CS, RB, PV drafting the work or revising it critically for intellectual content; All authors provided final approval of the version to be published and agreement to be accountable for all aspects of the work. No professional writing services were used.

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Data availability {29}
To promote study transparency, datasets and statistical analysis of this trial will be available from the corresponding author on reasonable request following completion of the trial.

Declarations

Ethics approval and consent to participate {24}
This study protocol has been approved by the local ethics committees.
Australia: 2023/HRE00041, merged protocol, approved by the Central Adelaide Local Health Network Human Research Ethics Committee, Adelaide.
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Consent for publication {32}
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