

The efficacy and safety of Anyu Peibo Capsule in the treatment of patients with major depressive disorder in China: study protocol for a randomized placebo-controlled trial

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Study protocol

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Abstract

Background: Major depressive disorder is the second leading cause of year lost to disability worldwide. Anyu Peibo Capsule was shown to have certain effective and favorable safety in phase II trials.

Methods: The clinical study is a multi-center, randomized, double-blinded, placebo-controlled, parallel groups phase II trial of Anyu Peibo Capsule in China, to aim whether the administration of Anyu Peibo Capsule compared to placebo improves clinical outcome in adults (18 years to 65 years) with MDD. The subjects will receive 8-week treatment with Anyu Peibo Capsule 1.6 g per day or placebo. The primary outcome will be the change of total score from baseline to the end of week 8 in Montgomery Asberg Depression Rating Scale.

Discussion: The trial aims to provide pivotal evidence on the efficacy and safety of Anyu Peibo Capsule in patients with major depressive disorder.

Trial registration: ClinicalTrials.gov, NCT04210973. Registered on December 26, 2019.

<https://www.clinicaltrials.gov/ct2/show/NCT04210973>

Protocol version 1.2 from 29 August 2019.

Background

Major depressive disorder (MDD), a recurrent, disabling and serious mental disorder, is the second leading cause of year lost to disability worldwide (World Health Organization, 2017) [1]. In the past two decades, China has experienced rapid changes which had a huge impact on individual's lifestyles and mental health, the current epidemiologic investigations showed that the lifetime prevalence of MDD in China have reached 3.4% [2], about 50 million people in China with MDD should be treated in an appropriate approach.

Antidepressants play a prominent role in the treatment for MDD [3]. The Chinese second guidelines for depressive disorders made antidepressants as a first-line recommendations for MDD treatment [4], however there are about 30% of patients fail to achieve remission despite treatment with multiple antidepressants [5]. Treatment continuity is one of the main challenges in treating patients with MDD [6]. A national survey in China has shown that the top reason (36.1%) why the patients with MDD discontinued their medication was *concern about long-term side effects* [7]. There is a need to develop novel treatments for the relief of symptoms of depression and tolerance for long-term treatment.

Anyu Peibo Capsule is a new antidepressant, extracted from Piper Laetispicum C.D C. (Piperaceae) which is a climbing glabrous plant grows in the south of China and has been used for invigorating circulation and reducing detumescence, stasis, and analgesic [8,9,10,11]. The pharmacodynamics of Anyu Peibo Capsule were assessed in health volunteers. A favorable safety profile, certain efficiency and remission

rate in MDD have been demonstrated in the Anyu Peibo Capsule randomized, blinded and placebo-controlled phase IIa and IIb trials.

The ongoing clinical study is a Chinese multi-center, randomized, double-blinded, placebo -controlled, parallel groups phase III trial of Anyu Peibo Capsule administration in adults (18 years to 65 years) with MDD (AYPB-MDD-III). Based on the results of Phase II study, this trial is designed to detect clinically relevant differences in clinical outcome (at 8 weeks after enrollment) as the primary endpoint.

Methods

Trial design

AYPB-MDD-III is a multi-center, randomized, double-blinded, placebo-controlled, parallel groups phase III clinical trial of Anyu Peibo Capsule to treat adults with MDD, sponsored by Su Zhou YiHua Biotechnology Co. LTD, conducted in Shanghai Mental Health Center and other 13 sites in China (Appendix 1).

Study objectives

The primary objective is to investigate the efficacy and safety of Anyu Peibo Capsule in comparison to placebo in adults with MDD. To identify potential predictive biomarkers for efficacy variables is the exploratory objective.

Participants and eligibility

Patients diagnosed with MDD at the time of screening will be enrolled in 14 sites in China. The trial period will be from July 2019 to December 2020. Inclusion, exclusion and withdraw criteria of AYPB-MDD-III (Table 1) have been chosen to exclude patients at risk of suicide.

Any of the following medications and treatments will be prohibited:

1. Other psychoactive drugs (except the drugs allowed to be used in protocol), at least including antipsychotics, antidepressants, mood stabilizers, anti-anxiety drugs, nootropics, etc.
2. Traditional Chinese medicine (including Chinese patent medicine and traditional Chinese medicine decoction) which maybe have the effect of relieving depression.
3. Modified electroconvulsive therapy (MECT), transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS), light therapy, laser therapy, acupuncture and other traditional Chinese medicine treatment, biofeedback therapy and other treatment methods.
4. Systematic psychotherapy, such as psychoanalysis, cognitive behavior therapy, etc.
5. Other medications and treatments that may significantly affect the efficacy and safety of antidepressants.

Some of the combination therapy will be allowed in the trial:

1. For serious insomnia subjects, zolpidem, zopiclone, right zopiclone and zaleplon can be used before sleep, the dose does not exceed the upper limit specified in drug labels, the cumulative dose during the trial duration does not exceed 2 weeks.
2. The medications used to treat physical diseases and try to keep the type and dosage of the drugs unchanged during the trial.

Randomisation

Patients enrolled in AYPB-MDD- \square trial treatment are allocated to treatment with Auyu Peibo Capsule or placebo in a ratio of 1:1, via the clinical trial electronic central stochastic system (DAS) for interactive web response system (IWRS).

Trial interventions

Auyu Peibo is a capsule containing 20mg of extracts (main ingredient: amide alkaloids), the placebo is an identically shaped capsule containing no effective materials. Study drug or placebo will be administered orally, with water, 30 minutes after breakfast and supper, 4 tablets once, twice per day for 8 weeks.

The participant flow was displayed in Fig. 1 according to Consolidated Standards of Reporting Trials (CONSORT) ^[12] diagram, and the SPRIT ^[13] scheme of study procedures is shown in Fig 2.

Blinding

AYPB-MDD- \square is double-blinded. Participant, care provider, investigator, outcomes assessor will not know the treatment allocation. The investigated drug is prepared by the central pharmacy, the ready-to-use drug or placebo, labelled with a random number and a patient number. Emergency unblinding can be done via DAS for IWRS.

Recruitment

The participants will be recruited from 14 sites (psychiatric hospitals) in China, research psychiatrists and clinical staff from each site will invite potential participants to the study.

Data management and quality assurance

Trained research psychiatrists from each site will record the collected data on source document and a web-based eCRF (DAS for EDC V6.0, in Chinese). Verification and cross-check of the eCRF will be conducted by the study monitor, who will be provided by the site clinical research organization as well as the sponsor. Omissions, errors, and values requiring further clarifications will be reviewed. Corrections should be made only by authorized personnel and be documented by audit trail.

Strategies to improve adherence to interventions

Reminder texts will send to the participants before each visit. Public transportation fee will be reimbursed for the participants' attendance to visits.

Provisions for post-trial care

There will be no special post-trial care for the participants. They will continue their usual health care at their centers when the trial has been finished.

Data collection methods

Study instruments

Chinese version of Montgomery Asberg Depression Rating Scale (MADRS)

Chinese version of MADRS^[14,15] is translated from the original English version, consists of 10 items rated on a 0–6 continuum (0=no abnormality, 6=severe) to assess core symptoms of depression. Inter-rater reliability on the Chinese MADRS with different pairs of raters has been reported to be 0.954, reliability, validity and sensitivity has been demonstrated to be good.^[16]

17-items Hamilton Depression Scale (HAMD17) Chinese version

Chinese version of HAMD17 is translated from the original English version, consists of 17 items rated assessing symptoms of depression. Chinese HAMD17 Cronbach's alpha coefficients were calculated to be over 0.70, interior consistence and validity has been demonstrated to be good.^[17]

Chinese version of the Sheehan Disability Scale (SDS)

The Chinese SDS measures the impairment in work/school, social life and family life responsibilities. The Chinese version of SDS has been reported with good validity and reliability.^[18]

Primary outcome

The primary outcome is the changes in the MADRS score, comparing the baseline score and the last observed score after eight weeks of treatment.

Secondary outcomes

Secondary efficacy endpoints are evaluated as following:

1. Clinical Remission Rate according to total score of MADRS at the end of study. Remission=at the end of study, total score of MADRS ≤ 10
2. Clinical Remission Rate according to 1HAMD17 total score at the end of study. Remission=at the end of study, total score of HAMD17 ≤ 7

3. Clinical Response Rate according to HAMD17 total score at the end of study. Response=at the end of study, decreased rate (from baseline) of MADRS total score or HAMD17 total score $\geq 50\%$
4. The change of total score of MADRS by time
5. The change of total score from baseline in HAMD17
6. The change of total score from baseline in Hamilton Anxiety Scale (HAMA) ^[19]
7. The change of score from baseline in Clinical Global Impression-Severity of Illness (CGI-S) ^[20]
8. Clinical Global Impression of improvement (CGI-I) ^[21] score in different visits
9. The change of total score from baseline in Discriminative Scale Space Tracker (DSST) ^[22]
10. The change of total score from baseline in Trail Making Test (TMT) A&B ^[23]
11. The change of total score from baseline in Sheehan Disability Scale (SDS) ^[24,25]
12. Proportion of subjects who withdrew from clinical trial due to poor efficacy; investigator will assess subject's efficacy according to his/her clinical status with rating scales, including MADRS, HAMD17, HAMA and CGI, which already listed in outcome
13. Proportion of subjects who combined medication to treat insomnia

Safety evaluation

Every patient enrolled in the trial will be assessed for occurrence of adverse events (AE), the incidence rate of AE will be measured as the main safety outcome. The following measures will be applied when evaluating the study drug safety:

1. Breath Rate per minutes, Pulse Rate per minutes, Heartbeat Rate per minutes, Diastolic and Systolic blood pressure, Sitting position (mmHg)
2. Electrocardiogram (ECG), the number of subjects with abnormal ECG report by 12-lead electrocardiogram
3. Assessment of C-SSRS
4. Assessment of Arizona Sexual Experience Scale (ASES)
5. Number of Participants with AE result in early withdrawal from clinical trials
6. Number of Participants with Serious Adverse Event (SAE) result in early withdrawal from clinical trials
7. Number of Emerging AE during drug withdrawal period

Statistical Analysis

The statistical analysis software shall be SAS statistical analysis software version 9.4 or above. All statistical tests are double sided, P value less than or equal to 0.05 will be considered statistically significant. The statistical analysis shall be carried out according to the statistical analysis plan.

Statistical description case of counting data Number (%); statistics of measurement data describes the number of use cases, mean, standard deviation, median, minimum and maximum.

Sample size determination

For the sample size estimation in the current phase III study, it is based on results of covariance (ANCOVA) comparing changes in the MADRS score from baseline to the last observed one during the 8 weeks of treatment between the study drug group and the placebo group. Referencing the results from trial Phase IIb, the decrease of the MADRS score in study drug group is 16.04 with 12.75 in placebo group. Considering a significance level of 5%, a power of 80%, and a dropout rate of 20%, the sample size should be 133 for each group.

Primary efficacy analysis

The treatment effect will be evaluated using analysis of ANCOVA with the study drug group, the site, depressive episode and baseline MADRS score as the explanatory variables. The 95% confidence interval, and the P-value will be presented. Missing data will be handled with Last Observation Carried Forward (LOCF).

Secondary efficacy analysis

Clinical remission rate of MADRS and HAMD17 at the end of study will be analyzed using ordinal logistic regression as the (proportional) odds ratio of Anyu Peibo versus placebo with a two-sided Wald 95% confidence interval. Treatment, baseline MADRS total score under beyond or under 30 or HAMD17 (beyond or under Median), site, and depressive episode (single episode or relapse) will be included in the model.

The t-test with a two-sided alpha level of 0.05 will be used to analyze the following variables: total scores of MADRS, score of MADRS by time, CGI-I score in different visits, the change of total score from baseline in HAMD17, HAMA, CGI-S, DSST, TMT A&B and SDS. The mean difference in the scores and the 95% confidence interval under Anyu Peibo and placebo will be used as the treatment effect estimate.

The estimate of the difference in proportions of subjects who withdrew from clinical trial due to poor efficacy and in proportions of patients who combined medication to treat insomnia (Anyu Peibo versus Placebo), 95% confidence interval and Chi-square p value will be calculated. In the case of lower cell frequencies (< 5), the Fisher exact test will be used instead.

Trial management, monitoring and auditing

An independent Data and Safety Monitoring Board (DSMB) monitors the quality of the trial and has access to trial outcome and accumulated safety data, including serious adverse events (SAEs), suspected unexpected serious adverse reactions (SUSARs) and mortality. In addition, the DSMB will review the safety data from a clinical and safety point of view on an on-going basis.

The sponsor will perform monitoring visits as frequently as necessary. Representatives of the sponsor's quality assurance department will visit the trial site at any time during the study to conduct an audit of the study in compliance with regulatory guidance.

Discussion

Antidepressants are the priority recommended treatment for MDD, which is a serious mental disorder with high disease burden in adults^[26,27]. However, the long-lasting concern about the balance of the benefit and harm using the current marketed antidepressants raises the need for new antidepressants with improved efficacy and safety.

Piper Laetispicum C.D C. have been used in Chinese traditional medicine as sedatives, to alleviate pain, for the treatment of toothaches and snake bites.^[28] The n-hexane extracts from Laetispicum C.D C. were tested for their anti-inflammatory activity against cyclooxygenase-1 (COX-1) and 5-lipoxygenase (5-LOX), showing evidence that extracts of these species act as in vitro inhibitors of both enzymes^[29,30,31]. Piper alkaloids have been reported to possess various activities, like antidepressants. Its anxiolytic and antidepressant activity have been explained by its capability to inhibit monoamine oxidase activity and increase the levels of serotonin and noradrenaline in some regions of the mouse brain.^[32,33]

Anyu Peibo Capsule included the extracted piper alkaloids (amide alkaloids), the administration of Anyu Peibo Capsule has been estimated to improve the MDD clinical outcome with favorable safety in phase I and II trials. This phase II trial aims to demonstrate a beneficial effect of Anyu Peibo Capsule on patients with MDD, while minimizing the side effects, in particular for sexual dysfunction and gastrointestinal discomforts.

Trial Status

The trial is currently recruiting and enrolling participants according to version 1.2 of the protocol in August 2019. Recruitment began on January 23, 2020, and the approximate date for completion of recruitment will be December 2020.

Appendix 1

AYPB-MDD-II-Trial centers location and investigators:

China, Shanghai, Shanghai Mental Health Center, Principal Investigator: Huafang Li

China, Beijing, Peking University Sixth Hospital, Deputy Investigator: Yi FU

China, Beijing, Beijing Anding Hospital, Capital Medical University, Deputy Investigator: Yazhou LU

China, Beijing, HuiLongGuan Hospital, Deputy Investigator: Yajuan NIU

China, Jilin, Brain Hospital of Jilin Province, Deputy Investigator: Yeping TAO

China, Shanxi, XI'AN Mental Health Center Xi'an, Deputy Investigator: Bin WU

China, Chongqing, Chongqing Mental Health Center, Deputy Investigator: Xueqin YU

China, Guangdong, Guangzhou Brain Hospital, Deputy Investigator: Xingbing HUANG

China, Hebei, The Sixth People's Hospital of Hebei Province Deputy Investigator: Keqing LI

China, Henan, The Second Affiliated Hospital of Xinxiang Medical University Deputy Investigator: Ruiling ZHANG

China, Henan, Zhumadian mental Hospital , Deputy Investigator: Hongjun CAO

China, Hubei, Renmin Hospital of Wuhan University Deputy Investigator: Jing CHENG

China, Jiangxi, Jiangxi Mental Hospital, Deputy Investigator: Kan LI

China, Zhejiang, Ningbo Kangning Hospital, Deputy Investigator: Zezhong FANG

Abbreviations

AE: Adverse event; ALP: Alkaline phosphatase; ALT: Alanine Transaminase; ASES: Arizona Sexual Experience Scale; AST: Aspartate Transaminase; BUN: Blood Urea Nitrogen; CGI-I: Clinical Global Impression- Improvement; CGI-S: Clinical Global Impression-Severity of Illness; CK: Creatine Kinase; CK_MB: Creatine Kinase MB; Cr: Creatinine; CFDA: China Food and Drug Administration; CRO: Contract Research Organization; C-SSRS: Columbia-Suicide Severity Rating Scale; DBIL: Direct Bilirubin; DSM: The Diagnostic and Statistical Manual of Mental Disorders; DSMB: Data and Safety Monitoring Board; DSST: Discriminative Scale Space Tracker; ECG: Electrocardiogram; ECT: Electroconvulsive therapy; eCRF: electronic Case Report Form; EMA: European Medicines Agency; FAS: Full Analysis Set; FDA: Food and Drug Administration; FT3: Free Three iodine thyroid original acid T3; FT4: Free Thyroid hormone T4; GCP: Good Clinical Practice; HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Scale; Hb: Hemoglobin; HCAs: Heterocyclic Antidepressants; HCG: Human Chorionic Gonadotropin; ITT: Intention-to-treat; MADRS: Montgomery-Asberg depression rating scale; MDD: Major depressive disorder; NaSSAs: Noradrenergic and Specific Serotonergic Antidepressant; NDRIs: Norepinephrine-dopamine Reuptake Inhibitor; NE: Norepinephrine; NMPA: National Medical Products Administration; NRIs: Selective Norepinephrine Reuptake Inhibitor; PLT: Platelet; PT: Prothrombin Time; PPS: Per-Protocol Set; RBC: Red Blood Cell; rMAOIs: Reversible Monoamine Oxidase Inhibitors; SAE: Serious Adverse Event; SARIs: Serotonin Antagonist and Reuptake Inhibitor; SAS: Safety Analysis System; SDS: Sheehan Disability Scale; SSRAs: Selective Serotonin Reuptake Agonist; SNRIs: Serotonin and Norepinephrine Reuptake Inhibitors; SS: Safety Set; SSRIs: Selective Serotonin Reuptake Inhibitors; STP: Serum Total Protein; T3: Tri-iodothyronine Total; T4: Thyroxine; TBIL: Total Bilirubin; TCAs: Tricyclic Antidepressants; TMS:

Transcranial Magnetic Stimulation; TMT-A&B: Trail Making Test A&B; TSH: Thyroid Stimulating Hormone; VNS: Vagus Nerve Stimulation; WBC: White Blood Cell; WHO: World Health Organization; 5-HT: 5-Hydroxytryptamine

Declarations

Acknowledgments

The authors would like to thank all the members who have involved in the protocol design and the members of DSMB. Each author contributed substantially to this work.

Availability of data and materials

Not Applicable.

Consent for publication

Participants will be asked for consent to use their anonymized data in scientific publications. Informed consent form template has provided, which has approved by Shanghai Mental Health Center Institutional Review Board.

Authors' contributions

JJH, YMY and HFL participate in study concept and design, planned the analyses and manuscript preparation. HFL is the lead investigator of this study. YJ and WC coordinated the funding, regulatory permission. QSZ developed the statistical part of the protocol. JJH and HFL assisted in further development of the protocol and manuscript preparation. All authors read and approved the final manuscript.

Ethics and dissemination

The trial was approved by the Shanghai Mental Health Center Institutional Review Board (central IRB, Approval No. 2019-39, No. 2019-39R1, IORG No. IORG0002202; FWA No. FWA00003065). All protocol amendments must be issued by the sponsor and signed by the investigator. Protocol amendments must not be implemented without IRB approval.

The procedures are in compliance with local ethical regulations, the institutional regulations, and the Declaration of Helsinki (2013) and its amendments. It is also in compliance with the currently approved international codes and norms regarding Good Clinical Practice in Clinical Investigation.

Prior to enrollment informed consent forms will be signed by each patient, as well as the investigator who informed the patient. The patients will be invited personally when they attend their regular visits to the outpatient clinic and should be informed about the freedom to withdraw consent at any time during the trial. The collection and processing of personal data from participants in this study will be limited to

those data that are necessary to fulfill the objectives of the study. These data should be collected with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

All information supplied by the sponsor to the investigator and the data generated as a result of this trial are considered confidential and remain property of the sponsor. The investigators agree to maintain the data in confidence and will not use it for other purpose only to accomplish this study without the sponsor's consent.

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Competing interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Tables

Table 1 Inclusion criteria, Exclusion criteria and Withdraw criteria

| Inclusion criteria | Exclusion criteria | Withdraw criteria |
|---|---|--|
| <p>1 Adult (18~65 years old), outpatients or inpatients, male or female.</p> <p>2 patients with primary diagnosis of major depressive disorder (MDD) based on the criteria of DSM-5, single episode or recurrent episode.</p> <p>3 the total score of MADRS is ≥ 26 in both screening visit and baseline visit.</p> <p>4 the first item of MADRS is ≥ 3 in both screening visit and baseline visit.</p> <p>5 CGI-S is ≥ 4 in both screening visit and baseline visit.</p> <p>6 the subject understands and consents to takes part in this clinical trial. The subjects should sign informed consent form.</p> | <p>1 the subject has a current psychiatric diagnosis other than depression according to DSM-5, including schizophrenia spectrum disorders, bipolar and related disorders, anxiety disorders, obsessive compulsive and related disorders, physical disorders and related disorders and other mental disorders.</p> <p>2 the subject has a suicide attempt within recent 1 year, or has a currently significant risk of suicide, or has a score ≥ 3 on item 10 (suicidal ideation) of MADRS.</p> <p>3 the subject has a current depressive episode due to somatic general disease or a neurological disease, such as hypothyroidism.</p> <p>4 when the MADRS total score of baseline visit compares with the screening visit, the decreasing rate is $\geq 25\%$.</p> <p>5 any unstable cardiovascular, hepatic, renal, blood, endocrine, or other medical disease.</p> <p>6 any neurological disease (such as Parkinson's Disease, cerebrovascular accident and epilepsy) or cerebral injury (traumatic or disease related). Had a history or a high-risk related disease or medication of seizure disorder, except infantile febrile convulsion.</p> <p>7 known hypersensitivity to Piper Laetispicum C.D C., or at least to two kinds of drugs.</p> <p>8 within 6 months before screening, there were addiction of alcohol and other substances (except nicotine).</p> <p>9 the subject could not take medication or has a disease affecting drug absorption, distribution, metabolism and excretion.</p> <p>10 clinically significant abnormal laboratory values (eg. ALT or AST value above 2 times of clinical top-limit; Cr value above normal top-limit; thyroid gland function index (≥ 2 items in 5 items) above 1.2 times or below 0.8 times of the normal range, or investigator diagnosed with hypothyroidism or hyperthyroidism).</p> <p>11 clinically significant electrocardiographic (ECG) abnormalities in screening visit. Such as QTc ≥ 450 ms in male or ≥ 470 ms in female.</p> <p>12 the subject who used at least two different antidepressants with recommended dose and adequate duration (maximum dosage by at least 4 weeks according to label) treatment still had no respond.</p> <p>13 the subject uses antidepressant drug normally before 2 weeks of screening and stops using psychotropic drug before randomization less than 5 half-life period (monoamine oxidase inhibitor: at least 2 weeks; fluoxetine: at least 1 month).</p> <p>14 the subject received modified ECT, trans-cranial magnetic stimulation (TMS), vagus nerve stimulation (VNS) or systematic psychotherapy within 3 months. the subject received systematic light therapy, laser therapy and acupuncture or other Traditional Chinese Medicine, or systemic biofeedback therapy within 2 weeks.</p> <p>15 women who were pregnant, breast-feeding, or serum-HCG (+) on screening; or planning to become pregnant within 3 months after kick-off of clinical trial.</p> <p>16 education level below junior high school.</p> <p>17 the subject has participated in a drug clinical trial within 1 month before screening.</p> | <p>1 Occurrence of intolerable adverse events or serious adverse events.</p> <p>2 Obvious protocol violation will impact on the efficacy and safety assessment.</p> <p>3 the subjects had symptoms of self injury, suicide, manic episode and with psychopathical feature.</p> <p>4 the efficacy is not good.</p> <p>5 the investigator determines to withdraw.</p> <p>6 the subject will not continue the clinical trial or withdraw his/her informed consent.</p> <p>7 loss of follow-up.</p> <p>8 other circumstances in which the subject withdraw from the trial (such as changes in residence, which made it impossible to continue medication and follow-up).</p> |

Figures

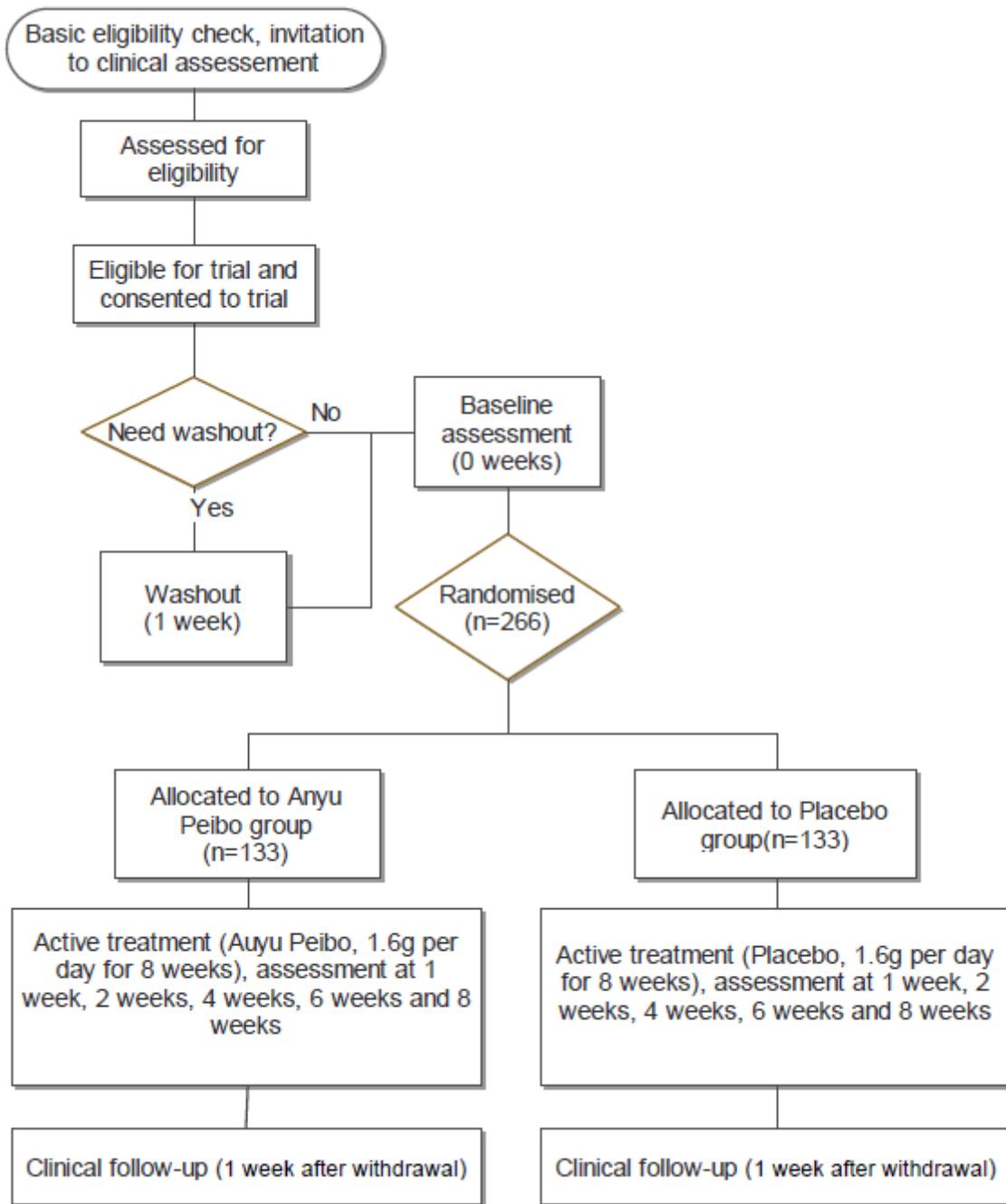


Figure 1

Participant flow through the AYPB-MDD

Fig 2. SPRIT scheme of study procedures

| TIMEPOINT | STUDY PERIOD | | | | | | | |
|------------------------------------|--------------------------|------------|-----------------|--------------|--------------|--------------|---------------|------------------------------|
| | Enrolment | Allocation | Post-allocation | | | | | Close-out |
| | January to December 2020 | 0 | t_{1week} | t_{2weeks} | T_{4weeks} | T_{8weeks} | $T_{12weeks}$ | T_1 week after withdrawing |
| ENROLMENT: | | | | | | | | |
| Eligibility screen | X | | | | | | | |
| Informed consent | X | | | | | | | |
| Demographic investigation | X | | | | | | | |
| Allocation | | X | | | | | | |
| INTERVENTIONS: | | | | | | | | |
| Ayu Peibo capsule | | | ←—————→ | | | | | |
| Placebo | | | ←—————→ | | | | | |
| ASSESSMENTS: | | | | | | | | |
| MADRS | | | | | | | | |
| CGI-S | | | | | | | | |
| SDS | | | | | | | | |
| DSST | X | X | | | | | | |
| TMT-A&B | | | | | | | | |
| C-SSRS | | | | | | | | |
| ASES | | | | | | | | |
| MADRS | | | | | | | | |
| HAMD ₁₇ | | | | | | | | |
| HAMA | | | X | X | X | X | X | |
| CGI-S | | | | | | | | |
| CGI-I | | | | | | | | |
| C-SSRS | | | | | | | | |
| Hematology panel | | | | | | | | |
| Thyroid function tests | X | | | | | | | |
| pregnancy test | | | | | | | | |
| Urinalysis | | | | | | | | |
| Serum Chemistry Panel | X | | | | X | | X | |
| ECG | | | | | | | | |
| Adverse Events Combination Therapy | | | | | | | | X |

Figure 2

SPRIT scheme of study procedures

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SPIRITChecklistforrandomisedstudies.doc](#)