**Effectiveness of mirtazapine as add-on to paroxetine versus paroxetine or mirtazapine monotherapy in patients with major depressive disorders with early non-response to paroxetine: a 2-phase, multicenter, randomized, double-blind clinical trial**

**Appendix**

**The Study Statistical Analysis Plan**

1. **Primary outcome**

The Primary outcome is to determine the efficacy of mirtazapine (30 mg/d) combined with paroxetine in MDD patients who have not achieved early improvement to paroxetine mono-therapy for 2 weeks, by the mean change of the 17-item Hamilton Depression Rating Scale (HAMD-17) total score from randomization (week 2) to endpoint (week 8).

2. **Secondary outcome**

1. Remission rate: the proportion of patients with HAMD-17≤7 at endpoint.
2. The time to remission and response from randomization by survive analysis.
3. The change of the total scores of CGI-S, CGI-I and QIDS-SR16 from randomization to endpoint (Week 8).
4. The proportion of patients with “much improved” or “very much improved” of CGI-I at endpoint.
5. Response rate: the proportion of patients with at least 50% reduction of HAMD-17 total score at endpoint;
6. Reduction rate of HAMD-17, CGI-S, CGI-I and QIDS-SR16 from randomization to endpoint.
7. Incidence of side effects, incidence of drug-related side effects, withdraw rate due to side effects

**Study design:**

The study is designed as a multi-site, randomized, double-blind, active-controlled and fixed–dose trial. It consists of 2 phases: 1) An open-label preliminary phase lasts for 2 weeks, during which paroxetine is titrated up to 20mg/day (Day 5). The patients who have not achieved early improvement (the decrease of HAMD-17 total score<20% at Week 2), entered a double-blind treatment phase. The patients who have achieved early improvement (the decrease of HAMD-17 total score ≥ 20% at Week 2) will be discontinued from the study. 2) Randomised and double-blind phase lasts for 6 weeks. The patients were randomised into three treatment arms of mirtazapine alone (30mg/d), paroxetine (20mg/d) and mirtazapine (30mg/d) plus paroxetine (20mg/d).

***Study drug information***

1. mirtazapine (Remeron）or placebo：30mg/tablet
2. paroxetine (Seroxat) or placebo：30mg/tablet

The placebo is identical by appearance to the test drugs. Test drugs are kept by drug administration manager in each site.

*Treatment Regimens*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study Period** | **Group** | **Treatment** | **Number and Type of Tablet** | **Duration** |
| Open-label Phase |  | 10 mg QD paroxetine | 1/2 paroxetine 20mg tablet | 4 days |
|  |  | 20 mg QD paroxetine | 1 paroxetine 20mg tablet | 10 days |
| Double-blind Phase | Mirtazapine | 30 mg QD mirtazapine | 1 mirtazapine 30mg tablet  1 paroxetine placebo | 6weeks |
|  | Paroxetine | 20 mg QD paroxetine | 1 paroxetine 20mg tablet  1 mirtazapine placebo | 6weeks |
|  | Mirtazapine+ Paroxetine | 30 mg QD mirtazapine+  20 mg QD paroxetine | 1 mirtazapine 30mg tablet  1 paroxetine 20mg tablet | 6weeks |

***Sample size***

This study is estimated to have approximately 80% power to detect a treatment difference between mirtazapine + paroxetine group and mono-paroxetine group in mean change from randomization to 6 weeks in HAMD-17 total score using a two-sided test at an alpha level of 0.05. The ratio of the standard deviation to the treatment difference is 1.95. The sample size for one arm is 63 by calculation. With a ratio 1:1:1 randomization, the required sample size will be 189 prior to adjusting for dropouts. Given that approximately 5% of patients will not have a post-randomization measure of HAMD-17, approximately 200 patients will be required in Randomization Phase. According to a meta-analyses 1, the proportion of early improvers in SSRI group (N=1378) was 63% at Week 2, and non-improvers 37%. The total sample size of 540 patients will be required in Open-label Phase.

***Study population***

The following 4 items should be fulfilled before entering the study, including 1) outpatients, aged at least 18 years and not more than 60 years; 2) Having a diagnosis of major depressive disorder by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM–IV) criteria; 3) HAMD-17 ≥ 20 and HAMD-17 Item 1(depressed mood) score ≥2 at enrolment in open-label preliminary phase; 4) Provide written informed consent.

***CONSORT diagram***

The flow of patients through the study will be described with the aid of a CONSORT diagram.

*Characteristics of groups at baseline*

The baseline characteristics of the study population will be summarised for each study group.

*Compliance with medication and withdrawal from study medication*

Unused pills and empty pill bottles were returned to the study centres and counted to measure compliance with medication.

***Completeness of data***

Last observation carried forward (LOCF) is used for missing primary efficacy outcome. Date missing: if there is no specific description, fill in the missing date as follows:

1. If the year, month, and day are missing, the date is missing;
2. If only the year is a non-missing value, use July 1 to fill in the missing month and day;
3. If only the day is missing, fill in the missing day as 15.

***General Analysis Considerations***

Unless otherwise stated, all analyses will use two-tailed tests where appropriate with significance level set at 0.05. Statistical packages used is SAS9.4 (SAS Institute Inc., Cary, North Carolina, USA).

***Data Sets for Analysis***

**Intention-to-treat, ITT:** For all randomized subgroups, all cases that received at least one treatment after randomization, the data of the cases in which the entire course of treatment could not be observed, the main indicators were transferred to the final results using the last observation data.

**Per-Protocol, PP:** All those who meet the test plan, have good compliance, have not taken banned drugs during the trial, have used the treatment more than 80% (for paroxetine + mirtazapine group, mirtazapine, paroxetine). The adherence was more than 80%. All cases completed according to the protocol is included in PP analysis.

**Safety, SS：**All randomized subgroups of patients who received at least one treatment after randomization and had data for safety evaluation after treatment constituted the safety population for this study. The safety population is the main population for the safety evaluation of this study.

***Primary outcome***

The primary outcome will be assessed using an intention to treat analysis (patients allocated to the group to which they were randomised regardless of whether they received the treatment).

Primary analysis

The primary outcome is the reduction score for HAMD-17 from baseline to endpoint. HAMD-17 total scores at randomisation is used as a covariate, and the site factor was taken into account. The covariance analysis (ANCOVA) is performed on the change of HAMD-17 at endpoint of each treatment group. Treatment and center interaction was also analysed based on this model. The least squares mean (LSMEAN) 95% confidence interval (CI) and P value of the score of each group and between the two groups at the end of treatment are calculated.

**Secondary analyses**

* The intention to treat analyses above is repeated in a “per protocol analysis” excluding patients who took medication lower than 80%.

***Secondary outcome***

* Remission rate is defined as the proportion of the patients with HAMD-17≤7 at endpoint. Response rate is defined as the proportion of the patients with reduction of HAMD-17 over 50% at the endpoint. Response (defined as 50% reduction in HAMD-17) and remission (defined as HAMD-17 ≤ 7) rates at endpoint is analysed using CMH Chi-Square Test with considering site factor.
* Survival analysis is performed to calculate the time to remission or response from randomization. Kaplan-Meier (KM) is used to plot the survival curve of remission within 6 weeks and the median time is calculated. Comparisons between groups is performed using the log-rank test.
* The overall assessment of CGI-S, CGI-I, and QIDS-SR16 scores and their relative baseline changes at various time points after randomization is described. One-way ANOVA or Kruskal-Wallis rank sum test is used for comparison between groups. Intra-group comparison of each visit relative to randomization using paired T test or pairwise rank sum tests.
* The overall ratings of CGI-S, CGI-I, and QIDS-SR16 scores and their change at each visit after randomization are described. One-way ANOVA or Kruskal-Wallis rank sum test is used to compare each group.

***Statistical Analysis of Safety***

* Adverse effects: Summarize adverse events / severe adverse events / drug-related adverse events / drop-off cases due to adverse events and incidence. The list is used to describe various adverse events.

**Supplementary Table 1:** Flow chart of the study

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Screening | | | Open-label | | | | Randomized, double-blind | | | |
| **Visit** | **Visit 1** | | | **Visit 2**  enrollment | | **Visit 3**  withdraw/Randomization | | **Visit 4** | **Visit 5** | **Visit 6** | **Visit 7** |
| **Week** | — | | | 0 | | 2 | | 3 | 4 | 6 | 8 |
| **Day** | Day-7~0 | | | Day 1 | | Day 14 | | Day 21 | Day 28 | Day 42 | Day 56 |
| **Visit window** | （-7~0） | | | （1） | | （12-16） | | （20-22） | （26-30） | （40-44） | （54-58） |
| **Procedure** | | | | | | | | | | | |
| Informed Consent | x |  | | |  | |  | |  |  |  |
| Inclusion/ Exclusion criteria | x | x | | |  | |  | |  |  |  |
| Demography | x |  | | |  | |  | |  |  |  |
| Medical history | x |  | | |  | |  | |  |  |  |
| Physical examination | x |  | | | x | |  | |  |  | x |
| Height | x |  | | |  | |  | |  |  |  |
| Weight | x |  | | | x | |  | |  |  | x |
| Blood pressure, heart rate | x | x | | | x | | x | | x | x | x |
| Combined treatment | x | x | | | x | | x | | x | x | x |
| **Efficacy/ Safety Assessment** | | | | | | | | | | | |
| HAMD-17 | x | x | | | x | | x | | x | x | x |
| QIDS-SR |  |  | | | x | | x | | x |  | x |
| CGI-S |  |  | | | x | |  | | x | x | x |
| CGI-I |  |  | | |  | | x | | x | x | x |
| Side effects report |  | x | | | x | | x | | x | x | x |
| **Laboratory Test** | | | | | | | | | | | |
| Blood routine | x | |  | | x | |  | |  |  | x |
| Biochemical test |  | |  | | x | |  | |  |  | x |
| Urine routine | x | |  | | x | |  | |  |  | x |
| Urine Pregnancy Test (women only) | x | |  | |  | |  | |  |  |  |
| **ECG** | x | |  | | x | |  | |  |  | x |
| **Study drug distribution and/or recycling** |  | |  | | x | | x | | x | x | x |

HAMD-17, 17-item Hamilton Depression Scale

QIDS-SR, Quick Inventory of Depressive Symptomatology-self report

CGI-S, Clinical Global Impression- severity;

CGI-I, Clinical Global Impression- improvement

**Supplementary Table 2.** Description of Rating Scales at Baseline

|  | **ITT** | | |  | **PP** | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Mirtazapine** | **Paroxetine +Mirtazapine** | **Paroxetine** |  | **Mirtazapine** | **Paroxetine +Mirtazapine** | **Paroxetine** |
| HAMD17 |  |  |  |  |  |  |  |
| N (Missing) | 68(0) | 68(0) | 68(0) |  | 56(0) | 59(0) | 56(0) |
| Mean (SD) | 22.69(4.42) | 20.79(2.93) | 21.10(3.40) |  | 23.29(4.60) | 20.92(2.98) | 21.64(3.41) |
| Min, Max | 17,41 | 17,27 | 17,35 |  | 17,41 | 17,27 | 17,35 |
| Md (Q3-Q1) | 22.00(5.00) | 21.00(5.00) | 21.00(5.00) |  | 22.50(6.00) | 21.00(6.00) | 21.00(4.50) |
| QIDS-SR |  |  |  |  |  |  |  |
| N (Missing) | 68(0) | 68(0) | 68(0) |  | 56(0) | 59(0) | 56(0) |
| Mean (SD) | 14.82(4.01) | 14.09(3.50) | 12.87(3.10) |  | 15.38(4.02) | 14.27(3.53) | 13.14(3.15) |
| Min, Max | 6,24 | 5,22 | 8,21 |  | 6,24 | 5,22 | 9,21 |
| Md (Q3-Q1) | 14.50(4.00) | 14.00(4.00) | 12.50(5.00) |  | 15.00(5.00) | 14.00(5.00) | 13.00(5.00) |

HAMD-17, 17-item Hamilton Depression Scale

QIDS-SR, Quick Inventory of Depressive Symptomatology-self report

**Supplementary Table 3.** ANCOVA Analysis of Change of HAMD-17 from randomization to endpoint

|  | **Mirtazapine** | **Paroxetine +Mirtazapine** | **Paroxetine** | **F** | **P** |
| --- | --- | --- | --- | --- | --- |
| Randomization (Week 2) |  |  |  | 5.32 | 0.0056 |
| N (Missing) | 68(0) | 68(0) | 68(0) |  |  |
| Mean (SD) | 22.69(4.42) | 20.79(2.93) | 21.10(3.40) |  |  |
| Min, Max | 17,41 | 17,27 | 17,35 |  |  |
| Md (Q3-Q1) | 22.00(5.00) | 21.00(5.00) | 21.00(5.00) |  |  |
| Week 3 |  |  |  | 3.06 | 0.0489 |
| N (Missing) | 68(0) | 68(0) | 68(0) |  |  |
| Mean (SD) | 17.18(6.86) | 14.88(4.90) | 16.54(4.74) |  |  |
| Min, Max | 1,41 | 5,26 | 3,28 |  |  |
| Md (Q3-Q1) | 17.50(10.00) | 15.00(8.00) | 17.00(6.00) |  |  |
| Randomization - Week 3 |  |  |  | 1.60 | 0.2038 |
| N (Missing) | 68(0) | 68(0) | 68(0) |  |  |
| Mean (SD) | 5.51(4.87) | 5.91(4.58) | 4.56(4.10) |  |  |
| Min, Max | -3,16 | -3,17 | -2,17 |  |  |
| Md (Q3-Q1) | 4.50(8.00) | 5.50(6.50) | 4.00(5.00) |  |  |
| Week 4 |  |  |  | 1.80 | 0.1677 |
| N (Missing) | 68(0) | 68(0) | 68(0) |  |  |
| Mean (SD) | 13.69(7.33) | 11.66(5.83) | 13.12(6.02) |  |  |
| Min, Max | 1,41 | 2,24 | 1,26 |  |  |
| Md (Q3-Q1) | 12.50(11.50) | 11.00(9.50) | 13.00(9.50) |  |  |
| Randomization - Week 4 |  |  |  | 0.76 | 0.4676 |
| N (Missing) | 68(0) | 68(0) | 68(0) |  |  |
| Mean (SD) | 9.00(5.90) | 9.13(5.97) | 7.99(5.90) |  |  |
| Min, Max | -2,25 | -3,21 | -3,30 |  |  |
| Md (Q3-Q1) | 10.00(9.00) | 9.00(9.50) | 8.00(7.50) |  |  |
| Week 6 |  |  |  | 0.92 | 0.3999 |
| N (Missing) | 68(0) | 68(0) | 68(0) |  |  |
| Mean (SD) | 10.87(8.10) | 9.41(5.90) | 10.74(6.57) |  |  |
| Min, Max | 0,41 | 1,23 | 1,25 |  |  |
| Md (Q3-Q1) | 9.00(12.00) | 9.00(8.50) | 10.00(10.00) |  |  |
| Randomization - Week 6 |  |  |  | 0.82 | 0.4435 |
| N (Missing) | 68(0) | 68(0) | 68(0) |  |  |
| Mean (SD) | 11.82(6.94) | 11.38(6.43) | 10.37(7.05) |  |  |
| Min, Max | -2,30 | -3,23 | -5,34 |  |  |
| Md (Q3-Q1) | 12.50(8.00) | 13.00(9.00) | 11.00(8.00) |  |  |
| Week 8 |  |  |  | 0.97 | 0.3821 |
| N (Missing) | 55(13) | 60(8) | 59(9) |  |  |
| Mean (SD) | 5.75(4.51) | 5.87(4.67) | 6.00(4.21) |  |  |
| Min, Max | 0,22 | 0,18 | 0,16 |  |  |
| Md (Q3-Q1) | 5.00(3.00) | 5.00(5.00) | 6.00(7.00) |  |  |
| Randomization - Week 8 |  |  |  | 2.64 | 0.0745 |
| N (Missing) | 55(13) | 60(8) | 59(9) |  |  |
| Mean (SD) | 8.85(4.39) | 8.23(4.79) | 6.90(4.91) |  |  |
| Min, Max | -1,19 | -6,16 | -5,21 |  |  |
| Md (Q3-Q1) | 9.00(5.00) | 9.00(5.50) | 7.00(9.00) |  |  |

**Supplementary Table 4.** ANCOVA Analysis of Change of QIDS-SR16 from randomization to endpoint

|  | **Mirtazapine** | **Paroxetine +Mirtazapine** | **Paroxetine** | **F** | **P** |
| --- | --- | --- | --- | --- | --- |
| Randomization (Week 2) |  |  |  | 5.25 | 0.0060 |
| N (Missing) | 68(0) | 68(0) | 68(0) |  |  |
| Mean (SD) | 14.82(4.01) | 14.09(3.50) | 12.87(3.10) |  |  |
| Min, Max | 6,24 | 5,22 | 8,21 |  |  |
| Md (Q3-Q1) | 14.50(4.00) | 14.00(4.00) | 12.50(5.00) |  |  |
| Week 3 |  |  |  | 0.60 | 0.5505 |
| N (Missing) | 61(7) | 63(5) | 65(3) |  |  |
| Mean (SD) | 11.10(4.00) | 10.60(4.21) | 10.34(3.60) |  |  |
| Min, Max | 2,20 | 4,21 | 1,20 |  |  |
| Md (Q3-Q1) | 11.00(6.00) | 10.00(5.00) | 10.00(4.00) |  |  |
| Randomization - Week 3 |  |  |  | 2.05 | 0.1316 |
| N (Missing) | 61(7) | 63(5) | 65(3) |  |  |
| Mean (SD) | 3.54(2.91) | 3.60(3.95) | 2.49(3.51) |  |  |
| Min, Max | -5,10 | -16,16 | -4,15 |  |  |
| Md (Q3-Q1) | 3.00(4.00) | 3.00(4.00) | 2.00(3.00) |  |  |
| Week 4 |  |  |  | 0.44 | 0.6416 |
| N (Missing) | 58(10) | 59(9) | 60(8) |  |  |
| Mean (SD) | 8.64(4.00) | 7.95(4.00) | 8.23(3.91) |  |  |
| Min, Max | 1,20 | 2,18 | 0,21 |  |  |
| Md (Q3-Q1) | 8.00(5.00) | 8.00(5.00) | 8.00(4.50) |  |  |
| Randomization - Week 4 |  |  |  | 2.95 | 0.0549 |
| N (Missing) | 58(10) | 59(9) | 60(8) |  |  |
| Mean (SD) | 5.90(3.42) | 6.24(4.58) | 4.53(4.07) |  |  |
| Min, Max | -1,16 | -12,19 | -4,19 |  |  |
| Md (Q3-Q1) | 6.00(4.00) | 7.00(6.00) | 4.00(5.00) |  |  |
| Week 8 |  |  |  | 0.05 | 0.9547 |
| N (Missing) | 55(13) | 60(8) | 59(9) |  |  |
| Mean (SD) | 5.75(4.51) | 5.87(4.67) | 6.00(4.21) |  |  |
| Min, Max | 0,22 | 0,18 | 0,16 |  |  |
| Md (Q3-Q1) | 5.00(3.00) | 5.00(5.00) | 6.00(7.00) |  |  |
| Randomization - Week 8 |  |  |  | 2.59 | 0.0779 |
| N (Missing) | 55(13) | 60(8) | 59(9) |  |  |
| Mean (SD) | 8.85(4.39) | 8.23(4.79) | 6.90(4.91) |  |  |
| Min, Max | -1,19 | -6,16 | -5,21 |  |  |
| Md (Q3-Q1) | 9.00(5.00) | 9.00(5.50) | 7.00(9.00) |  |  |

**Supplementary Table 5.** Response at endpoint determined by the reduction of HAMD-17 total score ≥50%

|  | **ITT** | | |  | **PP** | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Mirtazapine** | **Paroxetine +Mirtazapine** | **Paroxetine** |  | **Mirtazapine** | **Paroxetine +Mirtazapine** | **Paroxetine** |
| Response |  |  |  |  |  |  |  |
| No | 18(26.47%) | 20(29.41%) | 25(36.76%) |  | 8(17.39%) | 14(25.45%) | 16(30.19%) |
| Yes  Total | 50(73.53%)  68 | 48(70.59%)  68 | 43(63.24%)  68 |  | 38(82.61%)  46 | 41(74.55%)  55 | 37(69.81%)  53 |
| CMH (P)： ITT:1.81(0.4051)    PP:2.50(0.2871) | | | | | | | |

**Supplementary Table 6.** Time to response rate (standard error)

|  | **ITT** | | | | | | | | | | |  | **PP** | | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Mirtazapine** | | |  | **Paroxetine +Mirtazapine** | | |  | **Paroxetine** | | |  | **Mirtazapine** | | |  | **Paroxetine +Mirtazapine** | | |  | **Paroxetine** | | |
|  | **Remission** | **Left** | **Rate (SE)** |  | **Remission** | **Left** | **Rate (SE)** |  | **Remission** | **Left** | **Rate (SE)** |  | **Remission** | **Left** | **Rate (SE)** |  | **Remission** | **Left** | **Rate (SE)** |  | **Remission** | **Left** | **Rate (SE)** |
| Week 1 | 8 | 53 | 88.10(3.95) |  | 8 | 58 | 88.24(3.91) |  | 4 | 61 | 94.12(2.85) |  | 5 | 46 | 91.07(3.81) |  | 8 | 49 | 86.44(4.46) |  | 3 | 52 | 94.64(3.01) |
| Week 2 | 28 | 31 | 53.77(6.47) |  | 29 | 34 | 55.18(6.21) |  | 20 | 42 | 68.20(5.89) |  | 20 | 30 | 60.84(6.87) |  | 25 | 30 | 55.22(6.69) |  | 17 | 36 | 68.20(6.38) |
| Week 3 | 30 | 29 | 50.30(6.50) |  | 33 | 27 | 48.58(6.28) |  | 23 | 37 | 63.24(6.12) |  | 22 | 28 | 56.79(6.99) |  | 26 | 27 | 53.38(6.72) |  | 19 | 32 | 64.41(6.57) |
| Week 4 | 43 | 16 | 27.75(5.87) |  | 39 | 19 | 37.79(6.24) |  | 36 | 24 | 41.02(6.36) |  | 35 | 15 | 30.42(6.53) |  | 32 | 19 | 41.52(6.75) |  | 32 | 19 | 38.24(6.82) |
| Week 5 | 46 | 12 | 22.55(5.48) |  | 46 | 12 | 23.87(5.75) |  | 39 | 21 | 35.89(6.21) |  | 38 | 11 | 24.34(6.10) |  | 39 | 12 | 26.22(6.27) |  | 34 | 17 | 34.22(6.67) |
| Week 6 | 47 | 7 | 20.50(5.36) |  | 48 | 5 | 19.69(5.45) |  | 43 | 9 | 28.49(5.94) |  | 39 | 6 | 21.90(5.95) |  | 41 | 5 | 21.63(5.96) |  | 38 | 6 | 25.30(6.26) |
| Week 7 | 50 | 1 | 7.32(5.79) |  | 50 | 0 |  |  | 46 | 1 | 15.19(6.63) |  | 41 | 1 | 14.60(5.79) |  | 43 | 0 |  |  | 41 | 0 |  |

**Supplementary Table 7.** Remission at endpoint determined by HAMD-17 total score ≤7

|  | **ITT** | | |  | **PP** | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Mirtazapine** | **Paroxetine +Mirtazapine** | **Paroxetine** |  | **Mirtazapine** | **Paroxetine +Mirtazapine** | **Paroxetine** |
| Remission |  |  |  |  |  |  |  |
| >7 | 30(44.12%) | 34(50.00%) | 36(52.94%) |  | 15(32.61%) | 27(49.09%) | 26(49.06%) |
| ≤7  Total | 38(55.88%)  68 | 34(50.00%)  68 | 32(47.06%)  68 |  | 31(67.39%)  46 | 28(50.911%)  55 | 27(50.94%)  53 |
| CMH (P)： ITT:1.16 (0.5587)    PP:4.81 (0.0904) | | | | | | | |

**Supplementary Table 8.** Time to remission rate (standard error)

|  | **ITT** | | | | | | | | | | |  | **PP** | | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Mirtazapine** | | |  | **Paroxetine +Mirtazapine** | | |  | **Paroxetine** | | |  | **Mirtazapine** | | |  | **Paroxetine +Mirtazapine** | | |  | **Paroxetine** | | |
|  | **Remission** | **Left** | **Rate (SE)** |  | **Remission** | **Left** | **Rate (SE)** |  | **Remission** | **Left** | **Rate (SE)** |  | **Remission** | **Left** | **Rate (SE)** |  | **Remission** | **Left** | **Rate (SE)** |  | **Remission** | **Left** | **Rate (SE)** |
| Week 1 | 4 | 57 | 94.05(2.89) |  | 2 | 64 | 97.06(2.05) |  | 2 | 63 | 97.06(2.05) |  | 3 | 48 | 94.64(3.01) |  | 2 | 55 | 96.61(2.36) |  | 1 | 54 | 98.21(1.77) |
| Week 2 | 11 | 47 | 82.13(4.91) |  | 17 | 46 | 73.61(5.50) |  | 12 | 50 | 80.90(4.97) |  | 8 | 41 | 84.57(5.03) |  | 15 | 40 | 72.96(5.97) |  | 9 | 44 | 83.14(5.13) |
| Week 3 | 13 | 45 | 78.64(5.28) |  | 19 | 40 | 70.41(5.71) |  | 15 | 45 | 75.98(5.42) |  | 9 | 40 | 82.51(5.32) |  | 17 | 36 | 69.32(6.21) |  | 11 | 40 | 79.36(5.55) |
| Week 4 | 23 | 34 | 61.16(6.38) |  | 27 | 30 | 56.33 6.38) |  | 20 | 40 | 67.54(5.99) |  | 17 | 31 | 66.01(6.73) |  | 24 | 27 | 55.84(6.77) |  | 16 | 35 | 69.44(6.39) |
| Week 5 | 26 | 30 | 55.77(6.53) |  | 30 | 27 | 50.70(6.52) |  | 25 | 35 | 59.10(6.32) |  | 20 | 27 | 59.62(7.02) |  | 27 | 24 | 49.63(6.90) |  | 20 | 31 | 61.50(6.78) |
| Week 6 | 32 | 16 | 44.28(6.66) |  | 34 | 14 | 42.76(6.60) |  | 30 | 14 | 49.71(6.57) |  | 26 | 14 | 45.93(7.30) |  | 28 | 14 | 47.38(6.95) |  | 25 | 11 | 50.30(7.17) |
| Week 7 | 38 | 1 | 21.79(8.29) |  | 38 | 0 |  |  | 33 | 1 | 34.19(9.06) |  | 32 | 1 | 18.23(9.18) |  | 32 | 0 |  |  | 28 | 0 | 28.58(10.92) |

**Supplementary Table 9.** The proportion of patients with "much improved" or "very much improved " of CGI-I at endpoint

|  | **ITT** | | |  | | **PP** | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Mirtazapine** | **Paroxetine +Mirtazapine** | **Paroxetine** | |  | | **Mirtazapine** | **Paroxetine +Mirtazapine** | **Paroxetine** | |
| "much improved" or "very much improved " | 42(76.36%) | 52(82.54%) | 40(67.80%) | |  | | 37(80.43%) | 47(85.45%) | 36(70.59%) | |
| Others | 13(23.64%) | 11(17.46%) | 19(32.20%) | |  | | 9(19.57%) | 8(14.55%) | 15(29.41%) | |
| Total | 55 | 63 | 59 | |  | | 46 | 55 | 51 | |
| CMH (P)： ITT:3.54(0.1707)    PP:4.03(0.1336) | | | | | | | | | |

Note：others are slight improvement + no improvement + slight deterioration + obvious deterioration + serious deterioration

**Supplementary Table 10.** ANCOVA Analysis of Change of CGI-S from randomization to endpoint

|  | **Mirtazapine** | **Paroxetine +Mirtazapine** | **Paroxetine** |  | **F** | **P** |
| --- | --- | --- | --- | --- | --- | --- |
| Randomization (Week 2) |  |  |  |  | 0.59 | 0.5571 |
| N (Missing) | 60(8) | 64(4) | 65(3) |  |  |  |
| Mean (SD) | 3.75(0.93) | 3.77(0.75) | 3.89(0.75) |  |  |  |
| Min, Max | 1,5 | 2,5 | 2,5 |  |  |  |
| Md (Q3-Q1) | 4.00(1.00) | 4.00(1.00) | 4.00(1.00) |  |  |  |
| Week 4 |  |  |  |  | 0.71 | 0.4928 |
| N (Missing) | 58(10) | 59(9) | 60(8) |  |  |  |
| Mean (SD) | 3.28(0.91) | 3.17(0.81) | 3.37(0.97) |  |  |  |
| Min, Max | 1,5 | 1,5 | 1,6 |  |  |  |
| Md (Q3-Q1) | 3.00(1.00) | 3.00(1.00) | 3.00(1.00) |  |  |  |
| Week 6 |  |  |  |  | 0.65 | 0.5219 |
| N (Missing) | 55(13) | 56(12) | 56(12) |  |  |  |
| Mean (SD) | 2.73(1.04) | 2.63(0.89) | 2.84(1.04) |  |  |  |
| Min, Max | 1,5 | 1,4 | 1,6 |  |  |  |
| Md (Q3-Q1) | 3.00(1.00) | 3.00(1.00) | 3.00(1.00) |  |  |  |
| Week 8  N(Missing)  Mean（SD）  Min，Max  Md（Q3-Q1） | 55(13)  2.44(1.13)  1,5  2.00(1.00) | 63(5)  2.33(1.12)  1,6  2.00(2.00) | 59(9)  2.54(1.24)  1,5  3.00(2.00) |  | 0.49 | 0.6132 |

**Supplementary Table 11.** Adverse events after randomization (SS)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Mirtazapine  (N= 68) | | |  | Paroxetine+Mirtazapine  (N= 68) | | |  | | Paroxetine (N= 68) | | | | |
|  | No. | Cases | Incidence (%) |  | No. | Cases | Incidence (%) | |  | | | No. | Cases | Incidence (%) | |
| All adverse events | 29 | 57 | 42.65 |  | 29 | 47 | 42.65 | |  | | 15 | | 21 | 22.06 | |
| Drug-related adverse events | 22 | 44 | 32.35 |  | 25 | 41 | 36.76 | |  | | 10 | | 15 | 14.71 | |
| Serious adverse events | 1 | 1 | 1.47 |  | 1 | 1 | 1.47 | |  | | 0 | | 0 | 0 | |
| Serious adverse events related to study drugs | 0 | 0 | 0 |  | 0 | 0 | 0 | |  | | 0 | | 0 | 0 | |

**Supplementary Table 12.** Combined Medication of hypnotics or anxiolytic drugs

|  | **Mirtazapine** | **Paroxetine +Mirtazapine** | **Paroxetine** | **χ2** | **P** |
| --- | --- | --- | --- | --- | --- |
| Combined medication |  |  |  | 1.90 | 0.3869 |
| No | 46(67.65%) | 53(77.94%) | 48(70.59%) |  |  |
| Yes | 22(32.35%) | 15(22.06%) | 20(29.41%) |  |  |
| Total | 68 | 68 | 68 |  |  |

**Supplementary Table 13. Adverse events after randomization (SS)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Mirtazapine  (N= 68) | Paroxetine+Mirtazapine  (N= 68) | Paroxetine  (N= 68) |
| AEs leading to discontinuation of study medications | 3(4.41) | 2(2.94) | 1(1.47) |
| Any adverse events | 29(42.65) | 29(42.65) | 15(22.06) |
| AEs happens over 2% |  |  |  |
| Investigations | 6(8.82) | 6(8.82) | 10(14.71) |
| Dizziness | 4(6.90) | 4(6.90) | 0 |
| Aspartate aminotransferase increased | 0 | 1(1.47) | 2(2.94) |
| Somnolence | 4(6.90) | 5(7.35) | 0 |
| Constipation | 2(2.94) | 1(1.47) | 3(5.17) |
| Fatigue | 3(5.17) | 4(5.88) | 2(2.94) |
| drowsiness | 3(5.17) | 6(8.82) | 0 |
| Dry mouth | 4(6.90) | 4(5.88) | 2(2.94) |
| Anxiety | 3(5.17) | 0 | 0 |
| Alanine aminotransferase increased | 0 | 3(4.41) | 3(4.41) |
| Any AEs by systems |  |  |  |
| Nervous system disorders | 16(23.52) | 19(27.94) | 2(2.94) |
| Psychiatric disorders | 5(7.35) | 2(2.94) | 0(0.00) |
| Gastrointestinal disorders | 10(14.71) | 5(7.35) | 7(10.29) |
| General disorders and administration site conditions | 6(8.82) | 7(10.29) | 2(2.94) |

**Supplementary Table 14. Post-hoc of primary efficacy outcome of the change in HAMD-17 total score from baseline to endpoint of first episode MDD subgroup**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Subgroup of first episode MDD | Mirtazapine | Mirtazapine and Paroxetine | Paroxetine | F | P |
| ITT |  |  |  |  |  |
| No. | 39 | 32 | 44 | - | - |
| LS mean change (95% CI) | 10.7(8.9-12.6) | 10.4(8.3-12.5) | 9.1(7.3-10.9) | 1.55 | 0.2166 |
| LS mean difference from paroxetine (95% CI) | 1.6(-0.4,-3.6) | 1.3(-0.7-3.3) | - | - | - |

**Supplementary Table 15. Sensitivity analysis of primary efficacy outcome of the change in HAMD-17 total score from baseline to endpoint using MMRM**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Mirtazapine | Mirtazapine and Paroxetine | Paroxetine | F | P |
| ITT |  |  |  |  |  |
| No. | 68 | 68 | 68 | - | - |
| LS mean change (95% CI) | 11.11(9.68,12.55) | 11.24(9.82,12.66) | 9.79(8.37,11.21) | 2.23 | 0.1107 |
| LS mean difference from paroxetine (95% CI) | 1.33(-0.21,2.87) | 1.45(-0.05,2.95) | - | - | - |

**Supplementary Table 16. List of participants who withdraw but still included in PPS**

|  |  |  |
| --- | --- | --- |
| Group | Participant | Defined as withdraw but included in PPS |
| Mirtazapine | Participant 1 | Missing data of assessment at week 6 |
| Participant 2 | Missing data of assessment at week 6 |
| Mirtazapine and Paroxetine | Participant 3 | Missing data of assessment at week 6 |
| Participant 4 | Missing data of assessment at week 4 |
| Participant 5 | Missing data of assessment at week 3 |
| Paroxetine | Participant 6 | Missing data of assessment at week 6 |
| Participant 7 | Missing data of assessment at week 4 |

**Reference**

1. Szegedi A, Jansen WT, van Willigenburg AP, van der Meulen E, Stassen HH, Thase ME. Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder: a meta-analysis including 6562 patients. *The Journal of clinical psychiatry* 2009.