A randomized, double-blind, placebo-controlled trial of extended release quetiapine fumarate augmentation for primary anxiety disorder or mood disorders with comorbid anxiety symptoms

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Key words: Quetiapine, anxiety disorders, mood disorders with comorbid anxiety symptoms
Abstract

Background: Comorbid anxiety symptoms in primary anxiety disorders or mood disorders create a burden on the health care system and lead to poor outcome. The aim of this study was to evaluate the efficacy and safety of extended-release quetiapine fumarate (quetiapine XR) in the treatment of patients with either primary anxiety disorders or mood disorders with comorbid anxiety symptoms when compared to placebo as an adjunct to antidepressant therapy.

Results: A total of 35 patients were included in intention-to treat (ITT) population for efficacy analysis (quetiapine XR: 22 patients; placebo: 13 patients). At week 4, statistically significant differences were observed in both Hamilton Anxiety Rating Scale (HAM-A) score (p=0.003) and Clinical Global Impression of severity (CGI-S) score (p=0.025) in favor of quetiapine XR (-13.00 ± 4.14) compared to placebo (-6.63 ± 5.42). However, no statistically significant difference was observed between the 2 groups in change from baseline to week 8 HAM-A score (p=0.332) or CGI-S score (p=0.833).

Throughout the treatment period, no effect on Abnormal Involuntary Movement Scale global severity scores was observed for quetiapine XR or placebo. Moreover, there were no statistical significant differences between these two groups assessed by Barnes-Akathisia Rating Scale and Simpson-Angus Scale ratings. Quetiapine XR was generally safe and well-tolerated as adjunctive treatment in patients with primary or comorbid anxiety.

Conclusions: Augmentation of antidepressant treatment with quetiapine XR did not result in clinical improvement in outcome measures of anxiety using HAM-A and CGI-S scores at week 8 in patients with either primary anxiety disorders or mood disorders with
comorbid anxiety symptoms. However treatment with quetiapine XR as an adjunct to antidepressant therapy appears to provide short-term benefit over 4 weeks. Further studies are necessary to clarify the longer term efficacy and safety of quetiapine XR in this setting.

**Trial Registration**: Clinicaltrials.gov identifier: NCT00912535
Background

Anxiety disorder can manifest as a primary disorder or as a comorbidity with other psychiatric disorders such as major depressive disorder, bipolar disorder, schizophrenia, or substance use disorder. Major depressive disorder with comorbid anxiety is highly prevalent: ~85% of adults with major depression exhibit significant symptoms of anxiety [1]. Comorbid anxiety leads to more severe symptoms, decreased psychosocial functioning, a higher risk of suicide, and a more chronic course compared with major depressive disorder alone [2,3]. It is also associated with poorer and slower treatment response [1,4]. The treatment options for primary anxiety and comorbid anxiety symptoms included selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants, and other antidepressants. However, not all patients would benefit equally well from the anxiolytic effects of antidepressants.

Treatment strategies for patients with anxiety disorders and comorbid anxiety symptoms who have not responded to therapy with an antidepressant include: switching to another antidepressant monotherapy; augmentation with another agent; or combination therapy with another antidepressant agent [5,6]. Although augmentation or combination therapy is commonly employed in clinical practice, evidence supporting these strategies are limited [5-7]. The benzodiazepines are frequently used to treat sleep and anxiety in addition to SSRI therapy in major depressive disorder and comorbid anxiety; however, cognitive impairment and concerns over the potential for abuse and dependency with these agents has limited their use. In clinical practice, the atypical antipsychotics are commonly used as augmentation therapy in patients presenting mood disorder (typically...
major depressive disorder) with comorbid anxiety symptoms [8-14].

Support for investigation of atypical antipsychotics in patients presenting mood disorder with comorbid anxiety comes partly from preclinical studies suggesting that several atypical antipsychotics are potent 5-HT2A antagonists at low doses [15-17] and may facilitate the action of serotonin at the 5-HT1A receptor, thereby augmenting the efficacy of antidepressants [13]. In addition, certain atypical antipsychotics have other pharmacologic properties that may contribute to antidepressant effects, including α2 antagonism (risperidone), 5-HT1A agonism (aripiprazole and ziprasidone), and monoamine reuptake blockade (ziprasidone). Furthermore, there is some indication that atypical antipsychotics have efficacy in the treatment of anxiety symptoms, suggesting their possible clinical utility in major depression and comorbid anxiety [12,18-22].

Quetiapine was known as an atypical antipsychotic with a moderate affinity for 5-HT2A serotonergic, α1-adrenergic, muscarinic, and histaminergic receptors, a minor affinity for dopamine D2 and 5-HT1A receptor, and a low affinity for 5-HT2C, α2-adrenergic, and D1 receptors [23]. While atypical antipsychotics had been successfully applied in mood disorders with comorbid anxiety, comprehensive data on the clinical usefulness and effectiveness of adjunctive antidepressant therapy with quetiapine in primary anxiety disorder or mood disorders with comorbid anxiety was still lacking. The present study intended to evidence, in a randomized, placebo-controlled fashion, the clinical usefulness and safety of extended-release quetiapine fumarate (quetiapine XR) vs. placebo as adjunctive therapy to antidepressants for the treatment of patients presenting primary anxiety disorder or mood disorders with comorbid anxiety.
Methods

This was a randomized double-blind placebo-controlled study to evaluate the efficacy and safety of quetiapine XR versus placebo as adjunct to an antidepressant in the treatment of patient with primary anxiety disorders or mood disorders with comorbid anxiety symptoms. The study was conducted at a single site and was approved by institutional review board at Chang Gung Memorial Hospital, Keelung and written informed consent was obtained from all subjects before participation. The investigation was recorded in the clinical registry as NCT00912535.

Patient Population

For the present study, patients were randomized with 2:1 probability of receiving either quetiapine XR, or placebo for 8 weeks in order to minimize exposure to antidepressant monotherapy (placebo-controlled group).

For inclusion in the study patients fulfilled all of the following criteria: (1) provision of written informed consent; (2) a diagnosis of primary anxiety disorder or mood disorder with comorbid anxiety symptoms by Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV)[24]; (3) a 14-item Hamilton Anxiety Scale (HAM-A) ≥14 [25]; (4) subject had received single antidepressant at a therapeutic dose for at least 6 weeks; (5) male or female aged 18-65 years; (6) female patients of childbearing potential were using a reliable method of contraception and had a negative urine human chorionic gonadotropin (HCG) test at enrolment; (7) able to understand and comply with the requirements of the study and sign informed consent.

Any of the following was regarded as a criterion for exclusion from the study: (1)
pregnancy or lactation; (2) any DSM-IV Axis I disorder not defined in the inclusion
criteria; (3) receiving any antipsychotic 7 days prior to entering the study; (4) patients
who, in the opinion of the investigator, posed an imminent risk of suicide or a danger to
self or others; (5) administration of a depot antipsychotic injection within one dosing
interval (for the depot) before randomization; (6) substance dependence or substance
abuse within 4 weeks prior to enrolment (except for caffeine or nicotine), as defined by
DSM-IV criteria; (7) unstable or inadequately treated medical illness (e.g. congestive
heart failure, angina pectoris, hypertension) as judged by the investigator; (8) previous
enrolment or randomization of treatment in the present study.

Randomization
Subjects were randomized strictly sequentially. The randomization code that was
generated according to the randomization table was sealed in envelopes and subsequently
distributed to the study site prior to study initiation.

Blinding
Patients received one of the two treatment packages according to a treatment allocated
randomization number. Quetiapine and its matching placebo were indistinguishable in
terms of appearance, smell, taste, and dose regimen. Neither the investigator nor the
subject knew the treatment package received by the patient is the study drug or placebo.
These were provided by AstraZeneca Ltd

Study Medication
Quetiapine XR was given orally at a flexible dose of 50-300mg/day according to the judgment by the investigator for 8 weeks, as adjunct to the same antidepressant at the same dose. Placebo was given orally, as adjunct to the same antidepressant at the same dose.

**Concomitant Medication**

Patients already receiving hypnotics or anxiolytic benzodiazepines were permitted to continue taking them at the same dose, but long-acting benzodiazepines such as diazepam and clonazepam (except \( \leq 4\)mg/day lorazepam or equivalent) were disallowed.

**Efficacy Evaluations**

The primary endpoint was the mean change from baseline to Week 8 in the Hamilton Anxiety Scale (HAM-A) total score [25]. Additional efficacy evaluations included the change from baseline to all time points in Clinical Global Impression–severity of illness (CGI-S) score [26].

**Safety and Tolerability Evaluations**

Safety was evaluated by clinically significant changes occurring from baseline to the end of the study. The following parameters were observed: (1) Abnormal Involuntary Movement Scale [27]; (2) Barnes-Akathisia Rating scale [28]; (3) Simpson-Angus Scale [29]; (4) physical examination; (5) body weight; (6) vital signs; (7) adverse events (AEs).

**Statistical Analyses**
Sample sizes were determined to provide 85% power to detect a difference of 5 points on HAM-A total score between quetiapine group and placebo group. A minimum of 36 patients were needed in order to yield sufficient power. Data analyses and summaries of efficacy and safety assessment were performed on the intention-to-treat (ITT) population: patients who had taken at least one dose of the study medication and had at least one evaluation for primary efficacy endpoint, regardless of their compliance with the protocol. A last-observation-carried-forward (LOCF) analysis was applied if data were unavailable at the analysis time point. Two sample t-test was applied for continuous variable and chi-square test was applied for categorical variable. An analysis of covariance (ANCOVA) was applied to test superiority of treatment group over the placebo for the change from baseline in HAM-A total scores and CGI-S scores. All statistical tests were two-tailed, and the level of significance was set at p<0.05.

**Results**

**Disposition of Patients**

Patient flow is depicted in Figure 1. A total of 35 eligible patients who received study medication and had at least one follow-up evaluation were included in intention-to-treat (ITT) population (quetiapine XR: 22 patients; placebo: 13 patients). Pre-existing antidepressants included escitalopram, paroxetine, venlafaxine, duloxetine and mirtazapine. A total of 21 eligible patients (quetiapine XR: 13 patients; placebo: 8 patients) completed the study. Table 1 shows the demographic data of ITT population. All demographic data were comparable between quetiapine XR group and placebo group with no statistically significant difference (p>0.05). At baseline, HAM-A total score in
ITT population with LOCF was 24.73 ± 4.45 and 27.15 ± 3.95 in quetiapine XR and placebo groups respectively.

**Change from baseline to Week 8 in HAM-A total scores**

At Week 8, the mean HAM-A score was 13.15 ± 5.30 and 18.13 ± 5.69 for quetiapine XR and placebo group respectively, however, no statistically significant difference was observed between the 2 groups in change from baseline to Week 8 In a subgroup analysis, there was no statistically significant difference in this measure between patients primary anxiety disorder treated with quetiapine XR (N=10) or placebo (N=7). A similar nonsignificant difference was observed in the patients with mood disorders treated with quetiapine XR (N=12) or placebo (N=6).

At Week 4, however, an approximate 2-fold change from baseline to Week 4 was observed in HAM-A score for patients receiving quetiapine XR (-13.00 ± 4.14) compared to those receiving placebo (-6.63 ± 5.42) \[p=0.003\] (Figure 2).

**Change from baseline to Week 8 in CGI-S scores**

At Week 8, the mean CGI-S score was 3.50 ± 0.86 and 3.62 ± 0.51 for quetiapine XR and placebo group respectively, however, no statistically significant difference was observed between the 2 groups in change from baseline to Week 8 CGI-S score.

At Week 4, however, as many as 2.3-fold change from baseline to Week 4 CGI-S score was observed in patients receiving quetiapine XR (-1.05 ± 0.95) compared to placebo (-0.46 ± 0.52). Statistically significant difference was observed between the 2 groups in change from base line to Week 4 CGI-S score (p=0.025) (Figure 3).
Safety and Tolerability

A total of 36 patients (quetiapine XR: 23 patients; placebo: 13 patients) were included in the safety population for analysis. The rate of discontinuation due to adverse events was 22% (N=5) in the quetiapine XR group and 23% (N=3) in the placebo group. Throughout the treatment period, 27 patients were reported 60 adverse events. Among these, 35 adverse events were reported by 17 patients in the quetiapine XR group, and 25 adverse events were reported by 10 patients in the placebo group (Table 2). Furthermore, 17 patients in the quetiapine XR group and 10 patients in the placebo group were reported to experience treatment-related adverse events. However, all treatment-related adverse events were judged by investigator as “Mild” or “Moderate” in severity. None of patients in both quetiapine XR and placebo group experienced any serious adverse event during the treatment period. During the treatment period, the most common adverse events reported by patients were dry mouth, dizziness, somnolence, constipation, and sedation. However, all adverse events were judged by investigator as “Mild” or “Moderate” in severity.

Throughout the study, a total of one patient for quetiapine XR group had a weight gain ≥7% until Week 8, while a total of 2 patients for placebo group had a weight gain ≥7% at Week 1, Week 4, and Week 8 respectively. Findings of laboratory measurements, vital signs, physical examinations, weight changes and body mass index were clinically comparable between both groups. Throughout the treatment period, no effect on AIMS global severity scores was observed for quetiapine XR or placebo. Moreover, there were no statistical significant differences between both groups as assessed by BARS and SAS rating scales.
Discussion

The primary outcome measures (HAM-A and CGI-S) did not show significant differences between quetiapine XR and placebo. However, treatment with quetiapine XR as an adjunct to antidepressant therapy appears to provide short-term benefit over 4 weeks in difficult-to-treatment patients with primary or comorbid anxiety despite existing antidepressant treatment.

While this is the first local study to investigate the short-term efficacy of adjunctive quetiapine XR in patients with primary or comorbid anxiety, the results at week 4 are in agreement with a recently published report demonstrating the efficacy of adjunctive quetiapine XR in patients with treatment-resistant or non-remitted GAD [30].

In clinical practice, the atypical antipsychotics are commonly used as augmentation therapy in patients presenting mood disorder (typically major depressive disorder) with comorbid anxiety symptoms [8-14].

The mechanism of action that results in anxiolytic effects in presenting mood disorder with comorbid anxiety has yet to be established, but there is an increasing speculation that it is linked to the ability of atypical antipsychotics to block 5-HT2A receptors [31,32]. Blocking these receptors is thought to contribute to the efficacy of atypical antipsychotics in treating anxiety symptoms, suggesting their potential clinical utility in major depression with comorbid anxiety.

Quetiapine XR was generally safe and well-tolerated as adjunctive treatment in patients with primary or comorbid anxiety. The pattern of common AEs, incidence of AEs of special interest, and changes in clinical laboratory results and vital signs for quetiapine XR treatment group were generally consistent with the known
pharmacological profile [33,34].

EPS-related AEs were not observed with quetiapine XR during the study period. These results were confirmed by the assessment of parkinsonian and akathisia symptoms using AIMS, SAS and BARS scores, which indicated minimal changes in both treatment groups. While atypical antipsychotics are associated with lower risk for EPS than conventional antipsychotics, it is important that patients are monitored for the emergence of events potentially related to EPS [35].

Laboratory data revealed no clinically relevant changes in glucose in patients receiving quetiapine XR. Modest increases in body weight were seen in this trial; however, long-term studies are needed to evaluate these metabolic effects.

The limitations of the present study must be noted and included the fact that this was a single center, short-term pilot study with small patient population and may be underpowered to detect differences between quetiapine XR and placebo at week 8. Moreover, the statistical analysis was not adjusted for potential co-variables such as disease or baseline scores. Although atypical antipsychotics are generally well tolerated, weight gain, extrapyramidal symptoms, prolactin elevations and somnolence have been reported with these agents to variable degrees [36]. Therefore, as the present trial did not investigate the long-term safety profile of adjunctive quetiapine XR, further clinical trials are necessary to verify the long-term safety and efficacy of adjunctive quetiapine XR.

**Conclusion**

Augmentation of antidepressant treatment with quetiapine XR did not result in clinical improvement in outcome measures of anxiety using HAM-A and CGI-S scores at week 8.
in patients with either primary anxiety disorders or mood disorders with comorbid anxiety symptoms. However treatment with quetiapine XR as an adjunct to antidepressant therapy appears to provide short-term benefit over 4 weeks. Further studies are necessary to clarify the longer term efficacy and safety of quetiapine XR in this setting.

**Competing Interests**

In the past 3 years, YCC received lecture fees from Astra-Zeneca Ltd. CKC received research support from AstraZeneca Ltd, Lundbeck Ltd and Otsuka Taiwan Ltd. LJW has no additional disclosure to make. This study is funded by AstraZeneca Ltd.

**Author’s contributions**

YCC and CKC contributed equally to this study and manuscript. LJW involved in the clinical work. All authors read and approved the final manuscript.

**Acknowledgments**

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Figure 1 legend:

For the present study, patients were randomized with 2:1 probability of receiving either quetiapine (N=26), or placebo (N=13) for 8 weeks in order to minimize exposure to single SSRI/SNRI alone (placebo-controlled group). A total of 35 eligible patients who applied study medication and had at least one follow-up evaluation were included in intention-to treat (ITT) population. A total of 21 patients completed the study.
**Figure 2 legend:**

During 8 weeks of quetiapine XR augmentation to antidepressant treatment among patients with primary anxiety disorders or mood disorders with comorbid anxiety symptoms, statistically significant difference was observed between quetiapine XR group and placebo group in change from baseline to Week 4 HAM-A total scores (p=0.003). However, no statistically significant difference was observed between the 2 groups in change from baseline to Week 8 HAM-A total scores.

HAM-A: Hamilton Anxiety Scale
Figure 3 legend:

During 8 weeks of quetiapine XR augmentation to antidepressant treatment among patients with primary anxiety disorders or mood disorders with comorbid anxiety symptoms, statistically significant difference was observed between quetiapine XR group and placebo group in change from baseline to Week 4 CGI-S score (p=0.025). However, no statistically significant difference was observed between the 2 groups in change from baseline to Week 8 CGI-S score.

CGI-S: Clinical Global Impression–severity of illness
Table 1 Demographic and Other Baseline Characteristics of ITT Population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Quetiapine XR N=22</th>
<th>Placebo N=13</th>
<th>p-value</th>
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<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td>0.057</td>
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<tr>
<td>Mean (S.D.)</td>
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<td>48.57 (9.17)</td>
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<tr>
<td>Median</td>
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<td>47.95</td>
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<tr>
<td><strong>Height, cm</strong></td>
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<tr>
<td>Mean (S.D.)</td>
<td>159.77 (5.70)</td>
<td>160.62 (6.91)</td>
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<tr>
<td>Median</td>
<td>158.50</td>
<td>160.00</td>
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<tr>
<td><strong>Gender</strong></td>
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<tr>
<td>Male</td>
<td>4 (18%)</td>
<td>2 (15%)</td>
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<tr>
<td>Female</td>
<td>18 (82%)</td>
<td>11 (85%)</td>
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<tr>
<td><strong>HAM-A (LOCF)</strong></td>
<td></td>
<td></td>
<td>--</td>
</tr>
<tr>
<td>Mean (S.D.)</td>
<td>24.73 (4.45)</td>
<td>27.15 (3.95)</td>
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<tr>
<td>Median</td>
<td>24.00</td>
<td>28.00</td>
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ITT population: Intention-to-treat population
HAM-A: Hamilton Anxiety Scale
LOCF: Lost Observation Carried Forward
<table>
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<tr>
<th>System Organ Class /Preferred Term</th>
<th>Quetiapine XR N=23</th>
<th>Placebo N=13</th>
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<td>Subjects with at least 1 related adverse event</td>
<td>17 (47%)</td>
<td>10 (28%)</td>
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<tr>
<td>Eye disorders</td>
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<td>Vision blurred</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
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<tr>
<td>Gastrointestinal disorders</td>
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<tr>
<td>Constipation</td>
<td>3 (8%)</td>
<td>2 (6%)</td>
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<td>Dry mouth</td>
<td>7 (19%)</td>
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<td>Nausea</td>
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<tr>
<td>Vomiting</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
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<td>Investigations</td>
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<tr>
<td>Blood pressure increased</td>
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<tr>
<td>Glycosylated haemoglobin increased</td>
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<td>Weight increased</td>
<td>3 (8%)</td>
<td>3 (8%)</td>
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<td>Increased appetite</td>
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<td>Nervous system disorders</td>
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<td>Dizziness</td>
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<tr>
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<td>Restless legs syndrome</td>
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<td>Sedation</td>
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<tr>
<td>Somnolence</td>
<td>4 (11%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Tremor</td>
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<td>Renal and urinary disorders</td>
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<td>1 (3%)</td>
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<tr>
<td>Oligomenorrhoea</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
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<td>1 (3%)</td>
</tr>
<tr>
<td>Rash papular</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>
Figure 1 Patient flow

Enrollment

Assessed for eligibility (N=39)

Randomized (N=39)

Allocation

Allocated to quetiapine group (N=26)
• Received allocated intervention (N=23)
• Did not receive allocated intervention (withdrew informed consent) (N=3)

Allocated to placebo group (N=13)
• Received allocated intervention (N=13)

Follow-Up

Discontinued intervention (N=10)
• Lost to follow-up (N=1)
• Adverse event (N=4)
• Protocol noncompliance (N=2)
• Lack of efficacy (N=3)

Discontinued intervention (N=5)
• Adverse event (N=3)
• Lack of efficacy (N=2)

Analysis

Completed study (N=13)
Intention-to-treat population (N=22)

Completed study (N=8)
Intention-to-treat population (N=13)
Figure 2 Change in Mean HAM-A total Score to Week 8

[Graph showing the change in mean HAM-A total score from baseline to Week 8 for Quetiapine and Placebo treatments.]

- Quetiapine shows a decrease in HAM-A score from baseline, with a significant improvement by Week 8.
- Placebo treatment shows a more gradual decrease in HAM-A score, with no significant improvement by Week 8.

* Significant difference compared to baseline.
Figure 3 Change from Baseline in Mean CGI-S Score to Week 8

Study Period (Week)

CGI-S total score change from baseline

-2 -1 0 1 2 3 4 5 6 7 8 9

-1.2 -1 -0.8 -0.6 -0.4 -0.2 0

Quetiapine  Placebo

*
Additional files provided with this submission:

Additional file 1: CONSORT+2010+checklist_Chen.pdf, 49K