These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi **Drug substance(s):** Amisulpride (Solian®)	**Study Identifiers:** NCT01795183, UTN U1111-1131-0692 **Study code:** AMISUL06155
Title of the study: The Effectiveness and Safety of Amisulpride in Chinese Patients with Schizophrenia-A Prospective Open-Label Multicenter Study	
Study center(s): A total of 13 study sites in Mainland China	
Study period: Date first patient enrolled: 02/Nov/2012 Date last patient completed: 03/Dec/2013	
Phase of development: Phase 4	
Objectives: • Primary objective: To evaluate the efficacy of amisulpride in Chinese patients with schizophrenia. • Secondary objective: To evaluate the safety of amisulpride in Chinese patients with schizophrenia.	
Methodology: A prospective, open-label, national multicenter, single-arm Phase 4 study	
Number of patients**:**	Planned number of enrollment: 300 Actual number of enrollment: 316 Number of treated: 316
Evaluated:	Efficacy evaluation: Based on 295 subjects in intent-to-treat (ITT) set; 221 subjects in per-protocol (PP) set. Safety evaluation: Based on 316 subjects in safety set.
Diagnosis and criteria for inclusion/exclusion: **Inclusion Criteria:** • Male or female, aged 18-65 years, with a documented diagnosis of schizophrenia in accordance with the International Classification of Disease and Related Health Problems (10th edition) (ICD-10) criteria. • Newly diagnosed schizophrenic patients who were not previously treated or newly or previously diagnosed schizophrenic patients who were previously treated and required a switch to other treatments. • Positive and negative syndrome scale (PANSS) total score ≥60. • Informed consent form signed. **Exclusion criteria:** • Patients with refractory schizophrenia or failed to respond to a full-dose full-duration treatment with clozapine. • Patients with contradictions as described in the Chinese Package Insert of Solian®. • Participation in other drug clinical trials within the recent 1 month. • Women who are pregnant or breastfeeding, or childbearing potential without using contraceptive measures.	

- Patients previously received or currently receiving treatment with amisulpride.
- Received treatment with clozapine in the recent 1 month or with long-acting antipsychotic agents in the recent 2 months.
- Received electric convulsion therapy or modified electric convulsion therapy in the recent 1 month.
- Patients with drug or alcohol abuse.
- Patients with severe or uncontrollable concomitant diseases and not suitable for participating in clinical trials due to follow-up compliance or safety issues judged by physicians.

STUDY TREATMENTS

Investigational medicinal product(s): Amisulpride (Solian®)

Formulation: Tablets

Route(s) of administration: Oral

Dose regimen: The recommended dosage regimen was based on the Chinese Package Insert of Solian. Please refer to the package insert for details.

Duration of treatment: 8 weeks

Duration of observation: About 9 weeks (including a 3-day 3 screening period and 8-week treatment period)

Criteria for evaluation:

Efficacy/therapeutic measurements:

Primary variables:

- Proportion of patients achieving significant improvement of clinical symptoms (≥50% decrease in PANSS total score from baseline) after 8 weeks of treatment.

Secondary variables:

- Changes from baseline in PANSS total score, PANSS positive syndrome scale score, PANSS negative syndrome scale score, and clinical global impression (CGI) score after treatment for 8 weeks.
- Proportion of patients achieving early treatment response (≥20％ improvement in PANSS total score after 2 weeks of treatment).
- Among newly diagnosed patients who were naive to treatment and will start on amisulpride and patients who have a history of treatment but will be switched to amisulpride, the proportion of those who achieve significant improvement of clinical symptoms after receiving treatment for 8 weeks.
- Proportion of positive symptom-dominant or negative symptom-dominant patients achieving significant improvement of clinical symptoms after 8 weeks of treatment and the mean dosage of amisulpride.

Safety measurements:

- Evaluation of adverse reactions, by using Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale and Simpson-Angus Rating Scale (SAS).
- Collection of adverse reactions and serious adverse event (SAE) reports, laboratory tests and auxiliary examination data.

Statistical methods:

- **Demographics and baseline data:** For demographics and subject baseline data, descriptive statistical analysis was provided following general principles per categories of the observed value. For continuous variables, number of subjects, mean value, standard deviation, minimum and maximum values were calculated; for categorical variables, frequency and percentage were calculated with 95% confidence interval (CI) if necessary.
- **Primary efficacy variables:** In addition to descriptive statistical analysis for primary efficacy outcomes as categorical variables (calculating frequency, percentage, and 95% CI), subgroup analysis was performed per subset classified based on baseline values. If necessary, a bar graph will be used to illustrate center effect for analysis of variations among study sites.
- **Secondary efficacy variables:** Analyzed as continuous variables using descriptive statistics, and for pre- and post-treatment comparison, use matched-pairs t test (for non-normal data, matched-pairs signed-ranks test was used). A two-sided p value of ≤0.05 is used to denote statistical significance, unless otherwise specified.
- **Safety data:** All adverse reactions and SAEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 14.0 and their overall occurrences and incidence rate were described. Frequency table tabulation was used to describe the frequency rate, severity and relationship with study treatment of each adverse reaction and SAE. Clinically significant laboratory changes were analyzed as adverse events (AEs).
- **Other safety variables** (UKU Side Effect Rating Scale and SAS total score): Analyzed as continuous variables using descriptive statistics, and for pre- and post-treatment comparison, use matched-pairs t test (for non-normal data, matched-pairs signed-ranks test was used). P value of ≤0.05 was used to denote statistical significance.
- **Handling of missing data:** For primary efficacy endpoints, missing data was addressed using last observation carried forward method. Other outcomes were not carried forward.

This study was a national multicenter, prospective, open-label, single-arm phase 4 clinical trial designed to observe and discuss the efficacy and safety of amisulpride in Chinese patients with schizophrenia by selecting 316 subjects from a total of 13 study sites throughout China. This study included a total of 295 schizophrenic patients into the intent-to-treat (ITT) analysis set, 221 subjects into the per-protocol (PP) analysis set, and a total of 316 subjects into the safety set (SS).

The study drug was administered following the package insert approved in China. Therapeutic dose range recommendations were given by physicians based on the Chinese Solian® package insert, and dose adjustment was made based on the patient's individual response.

Summary:

Demographic and baseline characteristics: 316 subjects were included in this study, 295 subject in intention-to-treat (ITT) set and 221 subjects in per-protocol (PP) set. Based on the statistical analysis in safety set. Among the 316 subjects participating in the trial, there were 148 (46.8%) males and 168 (53.2%) females. The mean age of subjects was 32.6±11.84 years, mean height 166.1±7.55 cm, mean body weight was 63.94±13.120 kg, and the mean body mass index (BMI) was 23.126±3.9960 kg/m^2. Seventy-six (24.1%) subjects had a family history of schizophrenia and 237 (75.0%) subjects had a history of medical treatment for schizophrenia.

Primary efficacy analysis result (last observation carried forward method was used for missing primary efficacy data): ITT analysis showed: Proportion of patients achieving significant improvement of clinical symptoms (≥50% decrease in PANSS total score from baseline) after 8 weeks of treatment is 66.8% (197/295), with a 95% CI of (61.1%, 72.1%);

PP analysis showed: Proportion of patients achieving significant improvement of clinical symptoms after 8 weeks of treatment is 73.3% (162/221), with a 95% CI of (67.0%, 79.0%).

Analyses of secondary efficacy endpoints:

1. **Changes from baseline in PANSS total score, PANSS positive syndrome scale score, PANSS negative syndrome scale score, and CGI score after treatment for 8 weeks.**

   - **Change in PANSS total score from baseline:** Intent-to-treat analysis showed: The mean (± SD) baseline PANSS total score of 295 subjects was 89.1±13.70, while as the study proceeded, the PANSS total score gradually decreased to (73.0±17.74), (60.7±17.62) and (51.0±14.58) at Week 2, 4, and 8 visits respectively. Differences between PANSS total scores at each visit had statistical significances ($P<10^{-4}$).
   - **Changes from baseline in PANSS positive syndrome scale score:** similarly, the mean (± SD) positive syndrome scale total score also gradually decreased from (23.8±5.69) at baseline to (18.1±6.18) at Week 2, and (14.1±5.46) at Week 4, and (11.1±4.05) at Week 8, and differences between positive syndrome scale total scores at any 2 visits had statistical significances ($P<10^{-4}$).
   - **Changes from baseline in PANSS negative syndrome scale score**: PANSS negative syndrome scale total score also demonstrated a declining trend over time, its mean (± SD) value decreased from (23.7±7.91) at baseline to (20.7±7.98) at Week 2, (17.8±7.79) at Week 4, and (15.2±6.96) at Week 8, and differences between negative syndrome scale total scores at each visit had statistical significances ($P<10^{-4}$).
   - **Changes from baseline in CGI score:** the trend of changes in CGI-S score: Mean (± SD) value at baseline visit was (5.3±0.77), at Week 2 (4.41±1.077), at Week 4 (3.54±1.194), and at Week 8 (2.75±1.213); differences between each visit had statistical significances ($P<10^{-4}$); the mean (± SD) CGI-G score at Week 2 visit was (2.59±0.893), at Week 4 visit (1.96±0.882), at Week 8 visit (1.58±0.821).

2. **The percentages of patients with early treatment response (≥20％ improvement in PANSS total score after 2 weeks of treatment).**

   Early response is defined as ≥20％ improvement in PANSS total score after 2 weeks of treatment. In ITT analysis set, 56.6% (167/295) of subjects achieved early clinical response, with a 95% CI of (50.7%, 62.3%).

3. **Among newly diagnosed patients who were naive to treatment and will start on amisulpride and patients who have prior history of treatment but will be switched to amisulpride, proportion of those who achieve significant improvement of clinical symptoms after receiving treatment for 8 weeks.**

   ITT analysis showed a total of 70 subjects are newly diagnosed treatment-naive patients, and among them 68.6% (48/70) achieved significant improvement of clinical symptoms; among other 225 subjects who were previously treated but switching to amisulpride, 66.2% (149/225) of them achieved significant improvement of clinical symptoms.

   In the PP analysis set, a total of 50 subjects are newly diagnosed treatment-naive patients, and 80.0% (40/50) of them achieved significant improvement of clinical symptoms; the rest of 171 subjects were previously treated but switching to amisulpride, and among them 71.3% (122/171) of patients achieved significant improvement of clinical symptoms.

4. **Proportion of positive symptom-dominant or negative symptom-dominant patients achieving significant improvement of clinical symptoms after 8 weeks of treatment and the mean dosage of amisulpride.**

   In this study, patients predominantly with negative symptoms were defined as: PANSS negative symptoms score >20, and PANSS negative symptoms score > PANSS positive symptom score; patients were considered as predominantly with positive symptoms if 2 out of 7 items listed in the PANSS positive symptoms had a score of ≥4, irrespective of negative symptoms score.

In ITT analysis set, the proportions of positive symptoms-dominant subjects achieving significant clinical symptoms improvement at Week 2, Week 4, and Week 8 visits were 16.5% (44/266), 47.0% (125/266), and 68.4% (182/266), respectively; the mean value of their mean (± SD) daily administrated dose at Week 2 was 547.3±209.89 mg, and increased to 724.4±229.30 mg at Week 2-4, then 756.8±234.02 mg at Weeks 4-8.

In the 26 negative symptoms-dominant patients, proportions of subjects achieving significant clinical symptoms improvement at Week 2, Week 4, and Week 8 visits were respectively 3.8% (1/26), 30.8% (8/26), and 50.0% (13/26). At Week 2 visit, only 1 subject achieved significant clinical symptoms improvement at the average daily dose of 543.0 mg; the mean value of average daily dose at Week 2-4 was 517.0±237.03 mg; the value of mean (± SD) daily dose at Weeks 4-8 reached 572.7±225.74 mg.

In PP analysis set, the proportions of positive symptoms-dominant patients achieving significant clinical symptoms improvement at Week 2, 4, and 8 visits were respectively 17.7% (35/198), 49.5% (98/198) and 75.3% (149/198); the proportions of negative symptoms-dominant patients achieving significant clinical symptoms improvement at Week 2, 4, and 8 visits were 4.5% (1/22), 36.4%(8/22) and 59.1% (13/22), respectively.

Safety analysis:

1. **Extent of exposure:** With the exception of 11 subjects who had no record of drug use duration, the value of the mean (± SD) daily dose throughout 8 weeks in all other 305 subjects was 678.0±224.56 mg, the minimum value was 100 mg, median value was 717.2 mg, and the maximum value was 1200 mg.
2. **Adverse Events (AEs):** In this study, the overall incidence rate of AEs was 61.1% (193/316), and the proportion of patients who reported at least one TEAE was 59.2% (187/316). The incidence rate of drug-related treatment-emergent adverse events (TEAEs) was 58.9% (186/316), with 10.1% (32/316) of them required measures being taken to the investigational medicinal product (IMP). Per system organ class (SOC), the most common TEAEs were nervous system disorders with an incidence rate of 33.9% (107/316). Per preferred term classification, the most frequently reported AEs included extrapyramidal disorder (with an incidence rate of 25.9% [82/316]), blood prolactin increased (25.9% [82/316]), Hyperprolactinemia (8.2% [26/316]), akathisia (4.7% [15/316]), and weight increased (4.4% [14/316]). Reports of such adverse events were basically the same as those recorded in the amisulpride package insert. In this study, there were a total of 9 (3.1%) patients who withdrew from the study due to adverse reactions.
3. **Severity of Adverse Events:** Within the same SOC or preferred term classification, the incidence rate of mild AE was prevalently high, followed by that of moderate AEs, and the rate of severe AEs is the lowest. In this study, the severe AE of extrapyramidal disorders (SOC: Nervous system disorders) had the highest incidence rate of 2.5% (8/316), followed by weight increased (SOC: Investigations) with an incidence rate of 1.3% (4/316). As presented by the data, incidence rates of severe AEs were all lower than 3%.
4. **Serious Adverse Events (SAEs) and Death Event**: No death case was reported in the study. Only 1 subject experienced an SAE of Suicide attempt which is not related to study drug per Investigator's judgment.
5. **Clinically Laboratory Tests:** Among various significant clinically laboratory tests, blood prolactin increase had the highest incidence rate of 28.2 (89/316); it was followed by weight increase with an incidence rate of 5.1% (16/216).
6. **UKU Side Effect Rating Scale Score**: The mean (± SD) value of UKU score was 4.41±5.164 at baseline visit and 2.72±3.135 at Week 8 visit. The mean (± SD) UKU total score at Week 8 visit decreased by 1.43±4.905 from baseline, the difference of UKU scores between baseline and 8 week had statistical significance ($P<10^{-4}$); the decrease of UKU total scores was observed in more than half of the subjects in this study.
7. **SAS total score**: The mean (± SD) of SAS total score was 10.4±1.86 at baseline and 10.61±1.606 at Week 8. The difference between them has statistical significance (p=0.0119). The mean (± SD) of SAS total score slightly increased by 0.25±1.841 compared with that of baseline.

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