Conclusions

“Paired” ratings is a quality assurance (QA) surveillance strategy that has been used to conduct concordance analyses of site-based PANSS interviews that were paired with blinded, site-independent scores derived from the audio-digital recordings of the site-based interviewers. The results of our comparative analyses suggest an excellent test-retest reliability and high agreement between the site-based and blinded, site-independent scores in order to:

1. Confirm the primary site-based ratings
2. Help identify and remediate any potential rater inconsistencies
3. Evaluate possible effects of functional unblinding. As with any treatment associated with site-based raters, we performed paired site-based and site-independent scores.

The primary objective of the trial was to assess the efficacy of KarXT versus placebo in reducing PANSS total scores in adult inpatients with schizophrenia. The study was conducted between September 2015 and September 2019 at 21 study centers in the United States. All subjects consented to study participation and to audio recording of PANSS interviews.

Trial Eligibility and Design

Eligible subjects were men or women between the ages of 16 and 60 (inclusive) who met DSM5 criteria for schizophrenia and presented with an acute exacerbation of psychosis and at least one key symptom from Table 1 using least 2 of 4 key symptom items.

Audio-digital recording method of site-independent PANSS assessment

The site-independent PANSS ratings were derived from audio recordings of site-based PANSS interviews with accompanying digital notes that provided corroborative informant information. The paired PANSS scoring data was used for quality assurance to independently confirm the site-based PANSS ratings. The study plan anticipated a review of all site-based interviews for completeness and independent scoring of 10% of interviews conducted at the baseline and end visit and 20% of the other visits.

We conducted concordance analyses of the paired site-based and site-independent PANSS interviews that were positive correlations with the PANSS total score (Spearman’s rho = 0.35, p < 0.001). There were 142 subjects with paired site-based and site-independent PANSS data available from both the baseline and end of study (week 5) visits.

There were 553 pairs of paired PANSS scores available for analysis from the full study data. We conducted concordance analyses of the paired site-based and site-independent PANSS interviews and compared the PANSS treatment outcome at the study endpoint by these two methods of assessment.

Results

We calculated the proportion of site-based and site-independent PANSS available from both the baseline and end of study visits (5 visits).

Concordance analyses of the paired site-based and site-independent PANSS ratings revealed a high correlation (κ = 0.746; p < 0.001) with minimal scoring discordance. Paired scoring differences were positively correlated with the PANSS total score (Spearman’s rho = 0.35, p < 0.001).

The site-based PANSS total scores revealed a significantly greater improvement from baseline to week 5 than the site-independent PANSS total scores derived from listening to and scoring the recorded site-based PANSS interviews (p = 0.0003).

Conclusions

Blind site-based scoring of audio-digital recordings of site-based PANSS interviews continues to be a primary PANSS Post hoc analysis. Following efforts at rater remediation, 2 raters were dismissed for site-independent ratings that required remediation during the study.

Table 1. Site-based and Site-independent PANSS Treatment Outcome

As shown in Table 2:

- The intraclass correlation between site-based and paired independent total PANSS scores was 0.769 (p < 0.001).
- 306 of the paired ratings differed by 5 points (53.5%), and 444 pairs differed by 10 points (80.3%). 14 pairs with > 20 points scoring difference (2.5%)
- The higher paired discordances were due to either an effort to administer accurate drug or placebo data, and the other raters demonstrated improvement during the remainder of the study.

Comparison of site-based and site-independent PANSS outcomes

As shown in Table 2:

- There were 30 KarXT responders (43.5%) in contrast to 8 placebo responders (11.0%) based on the site-based PANSS total score (p = 0.001) and site-independent PANSS total scores (p = 0.0005).
- There were 21 KarXT responders (30.4%) and 10 placebo responders (17.3%) based on the site-independent PANSS scores (p = 0.48; F = 1.0; p = 0.31). The use of PANSS total score improvement from baseline as the criterion for treatment response.

While the primary endpoint analysis used MMRM-based analysis, this comparative analysis used ANOVA analysis on the mean changes from baseline to week 5 and week 5 (endpoint) visits.

We used a 30% PANSS total score improvement from baseline as the criterion for treatment response.

SUMMARY AND CONCLUSIONS

As shown in Figure 2:

- The subjects assigned to the KarXT treatment group in this analysis revealed significantly greater improvement from baseline to endpoint on the site-based PANSS total scores than the 7% subjects assigned to placebo (F = 27.0; p < 0.0001).
- Similarly, the blinded site-independent PANSS total scores also revealed significantly greater improvement favoring KarXT over placebo as assessed by both the site-based PANSS total score (F = 30.1; p < 0.0001) and the mean paired site-independent PANSS total scores (F = 12.0; p < 0.001).

Site-independent PANSS and site-based PANSS ratings

Site-based PANSS and site-independent PANSS ratings across all visits were conducted on the audio-recorded interviews with audio and visual transmission. There were 553 pairs of paired PANSS scores available for analysis.

Within the site treatment, there were 182 paired PANSS ratings with baseline and 444 paired PANSS ratings with end point site-based treatment outcome used ANOVA analysis on the mean changes from baseline to week 5 and week 5 (endpoint) visits.

Within the group, 58 subjects completed the study and 14 subjects withdrew but had at least one postbaseline PANSS assessment. The mean site-based PANSS total score (± SD) across all study visits was 93.0 ± 12.7 and the mean paired site-independent PANSS total score was 96.2 ± 12.8 (p = NS).

REFERENCES

1. KarXT is a hallucinatory antipsychotic that is marketed for the treatment of medicated patients and does not cross the blood-brain barrier. It has shown to substantially reduce the side-effects of antipsychotics in previous Phase 3 trials of KarXT.

2. Kavoussi R, Miller AC, Brannan, SK, Breier A. The clinical effectiveness of functional unblinding. As with any treatment associated with site-based raters, we performed paired site-based and site-independent scores.

3. Summarized in Table 1: While the primary endpoint analysis used MMRM-based analysis, this comparative analysis used ANOVA analysis on the mean changes from baseline to week 5 and week 5 (endpoint) visits.

4. As shown in Table 2: While the primary endpoint analysis used MMRM-based analysis, this comparative analysis used ANOVA analysis on the mean changes from baseline to week 5 and week 5 (endpoint) visits.

5. Both site-based and site-independent PANSS scores achieved statistical significance favoring KarXT over placebo on the PANSS total score from baseline to endpoint (F = 12.7; p = 0.0005 respectively) and the 4 key positive symptom items (p = 0.0005 and p = 0.02 respectively).

6. Site-based PANSS and site-independent PANSS ratings across all visits were conducted on the audio-recorded interviews with audio and visual transmission. There were 553 pairs of paired PANSS scores available for analysis.

7. Both site-based and site-independent PANSS scores achieved statistical significance favoring KarXT over placebo on the PANSS total score from baseline to endpoint (F = 12.7; p = 0.0005 respectively) and the 4 key positive symptom items (p = 0.0005 and p = 0.02 respectively).

8. Site-based PANSS and site-independent PANSS ratings across all visits were conducted on the audio-recorded interviews with audio and visual transmission. There were 553 pairs of paired PANSS scores available for analysis.

9. Both site-based and site-independent PANSS scores achieved statistical significance favoring KarXT over placebo on the PANSS total score from baseline to endpoint (F = 12.7; p = 0.0005 respectively) and the 4 key positive symptom items (p = 0.0005 and p = 0.02 respectively).

10. Site-based PANSS and site-independent PANSS ratings across all visits were conducted on the audio-recorded interviews with audio and visual transmission. There were 553 pairs of paired PANSS scores available for analysis.

11. Both site-based and site-independent PANSS scores achieved statistical significance favoring KarXT over placebo on the PANSS total score from baseline to endpoint (F = 12.7; p = 0.0005 respectively) and the 4 key positive symptom items (p = 0.0005 and p = 0.02 respectively).

12. Site-based PANSS and site-independent PANSS ratings across all visits were conducted on the audio-recorded interviews with audio and visual transmission. There were 553 pairs of paired PANSS scores available for analysis.

13. Both site-based and site-independent PANSS scores achieved statistical significance favoring KarXT over placebo on the PANSS total score from baseline to endpoint (F = 12.7; p = 0.0005 respectively) and the 4 key positive symptom items (p = 0.0005 and p = 0.02 respectively).

14. Site-based PANSS and site-independent PANSS ratings across all visits were conducted on the audio-recorded interviews with audio and visual transmission. There were 553 pairs of paired PANSS scores available for analysis.

15. Both site-based and site-independent PANSS scores achieved statistical significance favoring KarXT over placebo on the PANSS total score from baseline to endpoint (F = 12.7; p = 0.0005 respectively) and the 4 key positive symptom items (p = 0.0005 and p = 0.02 respectively).

16. Site-based PANSS and site-independent PANSS ratings across all visits were conducted on the audio-recorded interviews with audio and visual transmission. There were 553 pairs of paired PANSS scores available for analysis.