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The Impact of Baseline Anxiety on Drug Placebo Separation and Drug/Placebo Response in an Acute Schizophrenia Clinical Trial—A Post-hoc Analysis

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Objectives: We sought to evaluate the impact of baseline anxiety levels on drug placebo separation and drug and placebo response in acutely psychotic schizophrenic subjects.Methods: In this post-hoc analysis, modified intent-to-treat Positive and Negative Syndrome Scale data were obtained from a phase 2, multi-center, 5 week, randomized, double-blind, placebo-controlled trial of KarXT in hospitalized adults with DSM-5 schizophrenia experiencing an acute exacerbation or relapse of symptoms. We investigated the impact of anxiety on drug placebo separation and drug and placebo response in 2 ways. In the first set of analyses, we dichotomized the data based on the absence or presence of anxiety symptoms. In the second set of analyses, we categorized subjects by levels of anxiety. All analyses were conducted using generalized linear models with normal distribution and identity link function.Results: On average, subjects entering the trial were suffering from a moderate level of anxiety. Subjects with no baseline anxiety had a significant increase in placebo response, a decrease in drug response and did not separate drugs from placebo. With increasing levels of baseline anxiety, a larger drug placebo difference was observed.Discussion: Our analyses identified that absence of anxiety at baseline was associated with a loss of signal at end of treatment between drug and placebo driven by a differential effect on placebo and treatment response. The effect observed was not related to the overall baseline symptom severity and was not mediated by improvement in anxiety itself. Interpretation of the results is caveated by the retrospective nature of the analyses.

Key words: placebo response/drug response/drug-placebo separation/acute exacerbation/subject selection/trial eligibility

Introduction

Schizophrenic patients do not infrequently display anxiety symptoms. Anxiety may be multifactorial in schizophrenia, potentially a feature of the disease itself, a reaction to psychotic symptoms, a response to cognitive and social impairment, a medication side effect, or due to a comorbid anxiety disorder. Comorbid anxiety disorder is diagnosed in over 40% of schizophrenic inpatients.[1] The severity of psychotic symptoms in acutely decompensated schizophrenic patients is significantly correlated with the severity of concurrent anxiety symptoms, as evidenced by a positive relationship between the adjusted Positive and Negative Syndrome Scale (PANSS-A) total score (total PANSS score minus the anxiety item) and the Hamilton Anxiety Scale (HAM-A) and Staden Schizophrenia Anxiety Rating Scale (S-SARS) total scores.[2]

Subsyndromal-level anxiety symptoms may affect as many as 65% of schizophrenic subjects.[3] Even in an outpatient setting, Lysaker reported a positive correlation between levels of anxiety and severity of hallucinations, social withdrawal, depression, and negative correlation with levels of hope and overall quality of life.[4] While it is generally recognized that comorbid anxiety disorders increase the impairment and burden of schizophrenia,[5–7] it is unclear whether and how the presence of anxiety symptoms affects drug placebo separation and response to either drug or placebo in acute schizophrenia clinical trials.

Clinical trials in schizophrenia suffer from decreasing effect sizes.[8] This is driven by increasing response to placebo while response to drug remains the same.[8] More recently, Leucht et al identified that predictors of placebo response are not necessarily identical to predictors of drug response[9] and therefore suggest assessing the impact of tested predictors on both placebo and drug response separately.

In the current retrospective analysis, we investigated the effect of baseline severity of anxiety symptoms on placebo and drug response and drug-placebo separation in a phase IIb clinical trial of the effect of KarXT in acutely psychotic hospitalized schizophrenic subjects. We hypothesized that severity of anxiety symptoms at baseline would correlate with the overall severity of schizophrenic symptoms, and that absence of anxiety at baseline would decrease the drug placebo separation in the affected subjects. If confirmed, baseline severity of anxiety symptoms could be used as a criterion for study entry.

Methods

Modified intent-to-treat data (all patients who were randomized received at least 1 dose of the study drug or placebo and had a PANSS rating at baseline and at least one PANSS ratings after baseline) was obtained from a phase 2, multi-center, 5-week, randomized, double-blind, placebo-controlled trial of KarXT in hospitalized adults with DSM-5 schizophrenia in the United States experiencing an acute exacerbation or relapse of symptoms. (NCT03697252)[10] The sponsor of the study employed an extensive set of procedures to address the reliability and accuracy of symptom measurement and modulation of placebo response described previously.[10,11] Briefly, these procedures included: (1) site selection based on previous performance; (2) pre-study calibration of interview and symptom severity measurement technique; (3) placebo response mitigation training; (4) operationalization and monitoring of acuity criteria; (5) enhanced instructions and data quality checks embedded in electronic Clinical Outcome Assessment (eCOA); (6) recording and independent expert review of audio-recorded PANSS interviews; (7) blinded analytic review of endpoint data for concerning patterns; (8) rapid remediation of rating and interview errors; and (9) site enrolment continually tied to data quality.

Measures

The PANSS[12] was used to measure the severity of the psychotic symptomatology throughout the study. The scale consists of 30 items, each of which is rated from 1 (absent) to 7 (extreme), with explored symptoms being at the upper extreme of normal limits receiving a score of 2 (minimal) and symptoms being clearly present if the item score is at least 3 (mild). The total score can thus range between 30 and 210 points, with higher scores indicating higher severity. Item G2 measures the severity of anxiety; we excluded this item from the PANSS total score calculation, creating an anxiety-adjusted PANSS total score (PANSS-A) with a possible score range between 29 and 203 points.

Statistical Analyses

Mean and standard deviation on the anxiety-adjusted PANSS total score (PANSS-A) and item G2 (Anxiety) were calculated at baseline. The relationship between the baseline severity of PANSS-A and item G2 was tested by means of linear regression.

The impact of anxiety on drug placebo separation, drug response, and placebo response was investigated in 2 alternative ways. In the first set of analyses, we dichotomized the data based on the absence or presence of anxiety symptoms. All baseline assessments with an item G2 score of 2 or less were classified as anxiety absent. A linear model was fitted with fixed effect of subgroup (anxiety present/missing), treatment (KarXT/placebo), baseline anxiety-adjusted PANSS total score (PANSS-A), both linear and quadratic terms, and subgroup treatment two-way interaction as covariates. In the conventional approach, baseline PANSS total score is adjusted for by including a linear term in the model; however, the linearity assumption might not be valid. Kahan et al[13] found that misspecification of the covariate for linear model might have negative impact on the power in detecting treatment effect. A semiparametric generalized additive model (GAM) that was fitted to check the linearity of the baseline score (here the adjusted baseline PANSS total score) indicated a quadratic term should be included in the model.

In the second set of analyses, we wanted to assess the impact of baseline anxiety levels on drug placebo separation and drug and placebo response. Given the small number of cases in the extremes of the anxiety item scoring range, we have mapped the G2 anxiety item on a new three (3) point categorical anxiety score as follows: original G2 item score of 1 and 2 as a G2-A group I, scores of 3 and 4 as group II, and the remaining scores 5 and 6 as group III. There was no instance of a score of 7 in the dataset. We then assessed the impact of G2-A on the end of treatment anxiety-adjusted PANSS total score change from baseline by first fitting a semiparametric GAM where linearity of G2-A and baseline PANSS total score were checked, and then a linear model was fitted with fixed effect of treatment (KarXT/placebo), baseline anxiety-adjusted PANSS total score (PANSS-A) and its quadratic term, G2-A treated as categorical variable and treatment G2-A interaction as covariates. The analysis was carried out in SAS 9.4 (TS1M2). Given the exploratory nature and the small number of planned analyses, no correction for multiple testing was applied.

Results

Baseline Characteristics

The mITT dataset consisted of 170 subjects with evaluable data, 83 randomized to KarXT and 87 randomized to placebo. The overall anxiety-adjusted total PANSS score at baseline was 92.9(±8.7). In the placebo and the KarXT arms the anxiety-adjusted total PANSS score at baseline was 92.6(±8.3) and 93.1(±9.2), respectively. The difference between the study arms was not significant; $t(168) =$

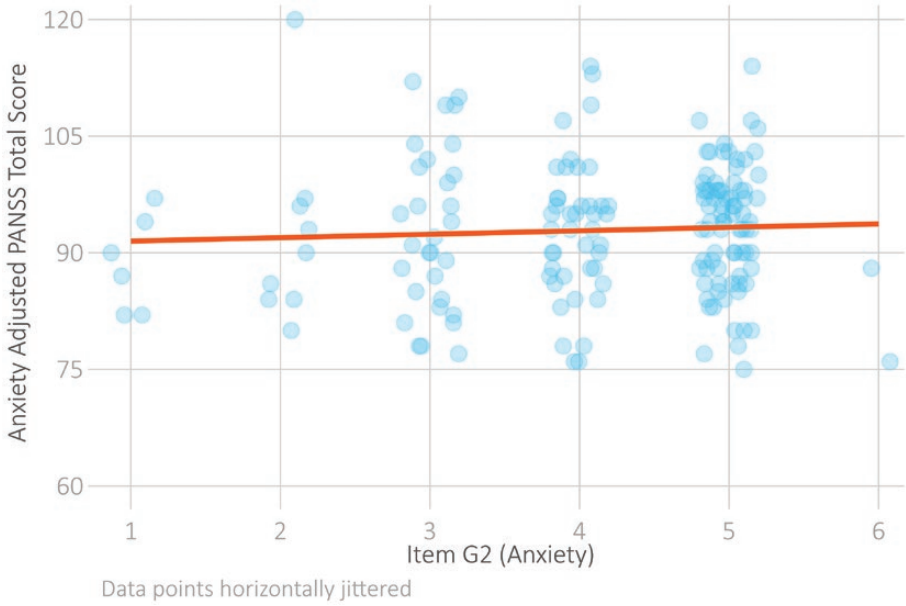

Fig. 1. Baseline relationship between anxiety adjusted PANSS total score (total PANSS with item G2 subtracted) and PANSS item G2 (Anxiety). PANSS-A = 91.06 + G2*0.44; R2 = 0.003, *P* = NS.

0.4, *P* = .697. Similarly, the overall severity of item G2 at baseline was 4.1(±1.1), with 4.0(±1.3) in the placebo arm and 4.2(±1.0) in the KarXT arm, the difference again not being significant; $t(168) = 1$, *P* = .318.

Anxiety at baseline was absent or questionable in 11 subjects randomized to placebo and 4 subjects randomized to KarXT, the difference between the treatment arms approaching but not reaching statistical significance, $Chi^2(1) = 3.2$, *P* = .072.

No relationship between the baseline severity of the anxiety-adjusted PANSS total score and the severity of anxiety as measured by PANSS item G2 was observed (rho = 0.0561, *P* = .4677) (figure 1).

Results I

The objective of the first set of analyses was to assess whether the absence of anxiety symptoms at baseline impacted signal detection by comparing drug placebo separation for the subjects with anxiety versus those without anxiety. Additionally, we performed separate analyses for the placebo response and the drug response to assess whether the absence of anxiety had a differential effect on subjects in the treatment or the placebo arm. Figure 2 shows the drug placebo difference at end of treatment in subjects with and without baseline anxiety. While KarXT clearly separated from placebo in the group of subjects who had anxiety symptoms present (drug placebo difference was estimated to −12.46 points favoring KarXT (95% CI: −16.57 to −8.34; *P* < .001), the drug did not separate from placebo when symptoms of anxiety were questionable or absent at baseline: the drug placebo difference was estimated to 4.51 points favoring placebo (95% CI: −10.45 to 19.46; *P* = NS). The effect size in the group of subjects with baseline anxiety present was 0.87 favoring KarXT, and 0.13 in the group of subjects without baseline anxiety, favoring placebo. The impact of absent or questionable anxiety was an increase in placebo response by 8.4 points (*P* = .0473), while the response to drug decreased by 8.5 points, the difference not reaching statistical significance though (*P* = .2004). The difference in drug placebo separation between the group of subjects with anxiety and the group of subjects without anxiety was estimated to 16.96 points (95% CI: 1.40 to 32.52; *P* = .0326).

Results II

The objective of the second set of analyses was to assess whether there is any relationship between the baseline severity of anxiety as measured by PANSS item G2 and the change from baseline in the anxiety-adjusted PANSS score (PANSS-A). While subjects in the group with lowest anxiety scores as shown already in the prior analysis did not separate from placebo, subjects in either of the 2 remaining groups (scored as mild to moderate or moderate to moderate-severe with respect to their anxiety) significantly separated from placebo. The drug placebo difference was estimated to 4.16 points favoring placebo (NS) in the group with lowest anxiety scores, to –11.66 points favoring KarXT (*P* = .001) in the middle group with G2 scores of 3 and 4, and to –13.51 points favoring KarXT (*P* < .001) in the group with the highest anxiety scores of 5 and 6 (figure 3). The estimated changes from baseline for each group and treatment arm are summarized in table 1.

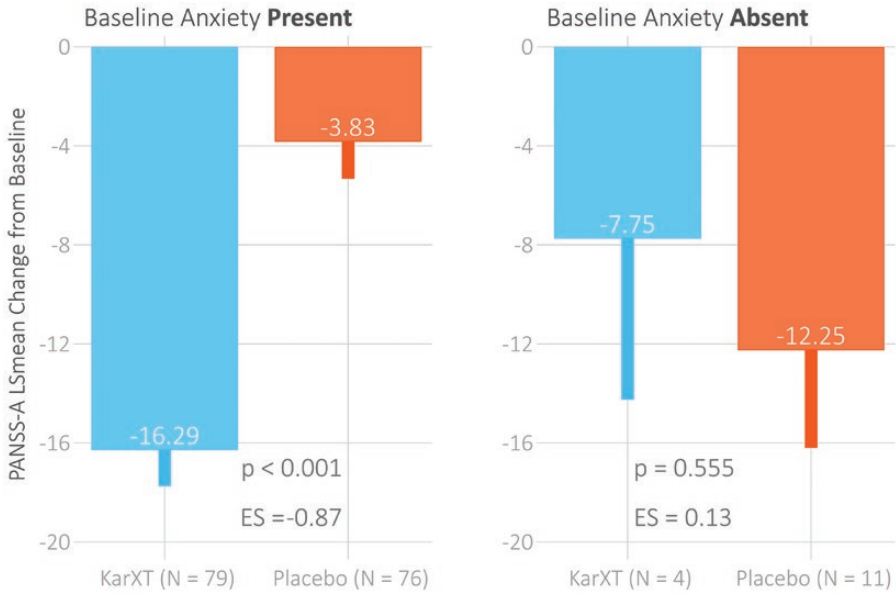

Fig. 2. Last visit drug and placebo response in least square mean change in anxiety adjusted PANSS total score from baseline for subjects with symptoms of anxiety at baseline present (G2 score ≥ 3) vs absent (G2 score ≤ 2). *P* values and effect sizes represent comparison with the placebo group.

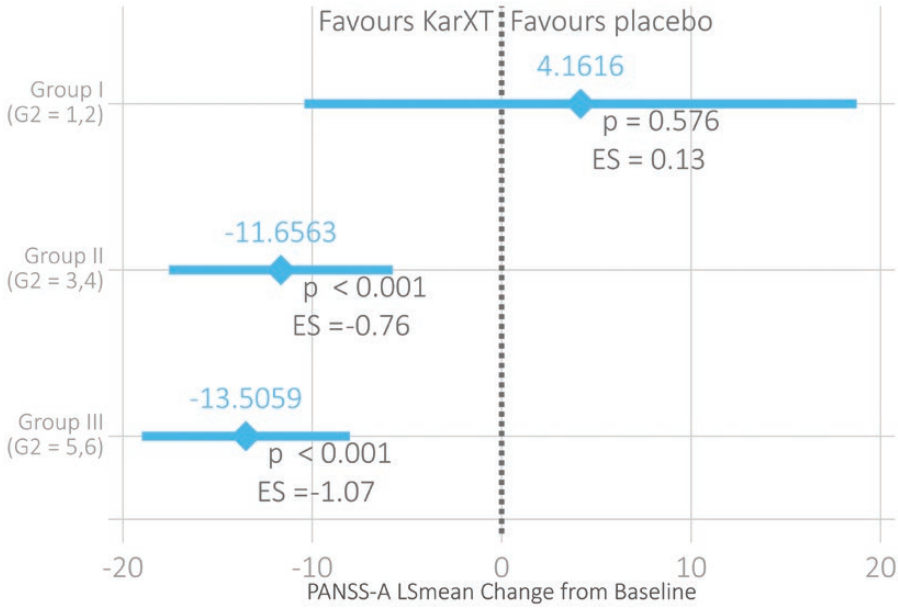

Fig. 3. Last visit drug-placebo difference in least square mean change in anxiety adjusted from baseline by baseline anxiety severity group. *P* values and effect sizes represent comparison with the placebo group.

Discussion

Our analyses confirmed a high prevalence of anxiety symptoms in this sample of acutely psychotic schizophrenic subjects, consistent with appropriate subject selection into the trial. The data are in line with Naidu et al's observations in similar populations.[2] While we failed to replicate the previously reported relationship between severity of anxiety and overall symptom severity, our analyses identified that the absence of anxiety at baseline was associated with a loss of signal at end of treatment between KarXT and placebo driven by a differential effect on placebo and treatment response. The effect observed was not related to the overall baseline symptom severity and was not mediated by improvement in anxiety itself.

In the current retrospective analysis, 91% of all subjects randomized into the trial suffered from at least mild levels of anxiety as measured by the Anxiety item G2 of the PANSS scale. No anxiety was identified in a

Table 1. Estimated Anxiety Adjusted PANSS Changes From Baseline for Each Group and Treatment Arm

	Placebo			KarXT				
Group	*N*	LS Mean	SEM	*N*	LS Mean	SEM	*P*[a]	Cohen's *d*[a]
I (G2 = 1, 2)	11	−12.048	3.855	4	−7.887	6.342	.5759	0.13
II (G2 = 3, 4)	34	−1.072	2.177	39	−12.729	2.058	.0001	−0.76
III (G2 = 5, 6)	42	−6.181	1.959	40	−19.687	2.010	<.0001	−1.07

[a]KarXT group compared to placebo group.

small subset of 15 subjects (9%), 9 of whom had anxiety symptoms scored as questionable (score of 2) and 6 of whom as absent (score of 1). The proportion of subjects suffering from anxiety in our sample was higher than the figures previously reported.[1,3] One reason for that may be driven by the fact that the prior reports did not focus specifically on acute exacerbation of psychosis and it is conceivable that anxiety symptoms may be more pronounced during an acute exacerbation than during a remission. Indeed, in a study of prospectively included 51 acutely exacerbated subjects,[2] only 3 (5.9%) subjects scored zero on the HAM-A. On average, the HAM-A score was 11.29 (SD = 6.68), corresponding to mild anxiety levels, and the highest score observed was 27 points, corresponding to severe anxiety.[14] In the perspective of this study, our results are comparable, even though the average level of anxiety the subjects suffered from in our dataset corresponds to moderate level of severity. We are, however, not aware of any work that would establish correspondence between the PANSS anxiety item and the HAM-A and thus it is difficult to make any head-to-head comparisons related to the overall anxiety levels.

The key finding of the current retrospective analysis is the impact of the absence of anxiety symptoms at baseline on drug placebo separation at end of treatment. While subjects who suffered from anxiety at baseline clearly separated KarXT from placebo, subjects with questionable and absent levels of anxiety not only failed to separate KarXT from placebo but placebo numerically outperformed KarXT in this group of subjects. The lack of anxiety in a subset of subjects may represent a phenotype that is less distressed by their psychotic symptoms and more responsive to placebo and the supportive aspects of hospitalization. In addition, our data indicate that the largest drug-placebo difference was achieved in the group of subjects with the highest levels of anxiety in the sample. While one possible explanation for this finding could be related to the previously described positive relationship between severity of psychotic symptoms and anxiety[2,4] and the positive relationship between baseline overall symptom severity and end-of-treatment drug placebo separation,[9,15] we were not able to replicate either of those findings during our analyses. Our analyses did not identify any meaningful correlation between severity of anxiety symptoms and the overall anxiety-adjusted PANSS total severity, nor did they identify baseline severity to impact on drug-placebo separation.

The absence of correlation between the levels of anxiety and overall PANSS-A symptom severity is, in light of prior publications, surprising; however, there are a number of reasons that could have obscured the relationship in our data.

First of all, severity of anxiety was measured using the PANSS anxiety item G2 score only. Item G2 may be only a crude approximation of anxiety severity and may be unable to provide a nuanced gradation of subjects' anxiety severity. Indeed, in a non-parametric item response theory analysis of the PANSS scale, item G2 was judged as a weak-performing item suffering from a number of problems, including the inability of the item to clearly separate between all the severities.[16] It is thus feasible to expect that this item may not accurately discern gradual differences in anxiety severity levels to the same level as a dedicated anxiety scale such as the HAM-A[17] used in prior analyses.[2,18]

The second factor that could have contributed to this loss of relationship may be driven by the restricted range of item G2 scores in our dataset. The majority of subjects (153/170) entering the trial had an anxiety score between 3 and 5 points. The most severe score, score of 7, was absent in the data and the remaining scores; that is, scores 1, 2, and 6, were infrequent in the dataset with less than 10 subjects scored with those aforementioned severities. Additionally, even the PANSS total score range and variability was restricted compared to the data presented by Naidu et al[18]; both of these findings impact on the strength of relationship between the PANSS total score and anxiety in the data.

Last but not least, despite extensive training on the PANSS scale, a small subset of raters may have struggled in correctly assessing anxiety levels at baseline, as anxiety symptoms can be confounded with psychotic symptoms and their presentation.[3] While plausible, this explanation seems unlikely as all baseline assessments were

audio-recorded and independently reviewed and the reviews did not indicate problems with the assessment of anxiety.

The lack of relationship between baseline symptom severity and end-of-treatment change is equally surprising. A possible explanation requiring further investigation could be that the differential mechanism of action of KarXT could contribute to this finding. The results presented by Furukawa et al[15] were based on a patient-level data meta-analysis of 3 trials of either olanzapine or risperidone, both D2 antagonists; similarly, the meta-regression analysis by Leucht[9] was on molecules that all affected the D2 receptor. The KarXT mechanism of action on the other hand is unrelated to direct dopamine involvement. Whether such explanation is feasible is yet to be seen.

The second key finding coming from our analyses is the differential impact absent or questionable anxiety had on placebo response versus drug response. In the placebo arm, the change from baseline in the PANSS-A was significantly increased in the subjects with absent or questionable anxiety compared to subjects with anxiety symptoms present. In the drug arm, the response was numerically, but not significantly, decreased in the subjects with absent or questionable anxiety compared to subjects with anxiety symptoms present. However, the small sample size of the absent/questionable anxiety subset (n = 4) precludes statistical significance or otherwise drawing conclusions. This differential effect on the placebo and the treatment arms ultimately resulted in the drug-placebo separation to be significantly different between the affected and the non-affected subjects.

Interestingly, the change from baseline in the placebo and drug groups showed differential patterns with increasing levels of anxiety. As the severity of anxiety grew, the response to placebo followed an inverted V shape, with the highest response seen in the group of no anxiety followed by the group with the highest anxiety. The response to KarXT, on the other hand, showed a gradual increase with increasing levels of anxiety. This differential effect is noteworthy and will require further examination.

The key limitations of our analyses are driven by the fact that all analyses were retrospective and therefore exploratory in nature. Additionally, the number of subjects with no anxiety symptoms present at baseline was small and unevenly distributed between the placebo and KarXT treatment arms. Since the study did not utilize any anxiety-specific measuring instrument, our analyses were based on the PANSS anxiety item G2 which has previously shown suboptimal performance. To correct for the possible regression to the mean phenomenon we have based our analyses on an anxiety-corrected PANSS total score removing item G2 from the scale. Additionally, in examining the effect of baseline severity of anxiety symptoms on drug-placebo separation, we compensated for the modest number of subjects with more extreme anxiety scores by collapsing the anxiety rating into three categorical levels. Despite the fact that this analysis was treated as categorical, our findings demonstrated a strong impact on drug-placebo separation with increasing levels of anxiety.

We have previously reported the detrimental effect of aberrant variability such as erratic changes, large post-baseline improvement, (nearly-) identical ratings and low temporal variability identified after randomization on drug placebo differences in this trial.[11] The presence of these markers of aberrant variability could be indicative of expectation bias or measurement error or inappropriate subject selection. However, since these get identified after randomization, it limits the ability to proactively intervene and restrict the impact of these factors on study outcomes. In the current analysis, we have identified a marker that could potentially differentiate placebo and drug change from baseline in an acute schizophrenic population. The putative marker of anxiety is tentative since it has only been identified retrospectively in one clinical trial. It is unknown whether this is peculiar to KarXT's non-dopaminergic mode of action and/or potentially a marker of a subpopulation of acute schizophrenic clinical trial subjects. Analyses of trial data in such a population with therapeutics of a different mode of action need to be conducted to confirm whether this is widespread or related to a particular mode of action specific to KarXT.

To conclude, our analyses confirmed high prevalence of anxiety symptoms in the population of acutely exacerbated schizophrenic subjects consistent with appropriate subject selection into the trial. While we failed to replicate the previously reported relationship between severity of anxiety and overall symptom severity, our analyses identified that absence of anxiety at baseline was associated with a loss of signal at end of treatment between KarXT and placebo driven by a differential effect on placebo and treatment response. The effect observed was not related to the overall baseline symptom severity and was not mediated by improvement in anxiety itself. If replicated in independent samples, our result could lead to a modification of typical inclusionary criteria into acute schizophrenia clinical trials and require the presence of at least mild levels of anxiety at the time of study entry. Anxiety levels at baseline could also be added, in line with recent FDA draft guidance,[19] as a covariate to the study analysis models. Alternatively, the presence of anxiety could be used as a marker of treatment-responsive subject selection in data analytical programs modeling study outcomes.

Conflict of Interest

This post-hoc analysis was funded by Signant Health. Dr Kott, Dr Daniel, and MS Wang are employees of Signant Health. Dr Brannan is an employee of Karuna Therapeutics.

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