DO PATTERNS OF INSTABILITY OR SEVERITY OF PSYCHOPATHOLOGY DURING SCREENING PREDICT RELAPSE IN SCHIZOPHRENIC OUTPATIENT SUBJECTS WITH MODERATE TO SEVERE NEGATIVE SYMPTOMS ASSIGNED TO PLACEBO?

David G Daniel, MD (1), Alan Kott, MD (2), Jay Saoud (3), Remy Luthringer, PhD (3), Vadym Rud, MD, PhD (4), Andrii Skyrpnikov, MD, PhD (4), Rodica Stan, MD, PhD (5) Veselin Palazov,M.D (6), Xingmei Wang(7) Michael Davidson, MD (3)

(1) Signant Health, Mclean, VA, USA, (2) Signant Health, Prague, Czech Republic, (3) Minerva Neurosciences, USA, (4) Department of Psychiatry, Ukranian Medical Academy, Ukraine, (5) County Hospital, Piatra Neamt, Romania, (6) Clinic of Psychiatry Mental Health, Burgas, Bulgaria, (7) Signant Health, Wayne, PA, USA

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Corresponding Author: David Daniel, PO Box 7137, McLean, VA 22106; dgdanielmd@gmail.com; Phone: 703-638-2500; Fax: 703-759-4619

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Abstract

Objective: In order to ensure the safety of schizophrenia patients who participate in placebo-controlled trials, investigators seek to identify patients at higher risk of symptomatic worsening or exacerbation upon withdrawal of antipsychotic medication. This is particularly relevant for trials in which relatively stable patients are treated for moderate to severe negative symptoms. It is hypothesized that those patients who prior to the trial experience the most severe and/or unstable symptoms are more likely to manifest symptomatic worsening upon antipsychotic discontinuation.

Design: This retrospective analysis included all randomized patients assigned to placebo (n=83) in the 12-week, double-blind, placebo-controlled outpatient trial of MIN-101 (roluperidone) for the treatment of negative symptoms in schizophrenia. For purposes of this

retrospective analysis, we defined the following risk factors for exacerbation: instability between screening and baseline defined operationally as patients with the highest 10% of absolute change from the screening visit to baseline in the PANSS total or one of the 5 PANSS Marder factors; Screening or Baseline severity in PANSS total or one of the 5 PANSS Marder factors; Gender and Age . We used 2 operational criteria of relapse: 1) 20% worsening from baseline in PANSS total or any PANSS factor scores, or worsening in CGI-S by at least 3 points or a score of 6/7 in CGI-I at two consecutive visits excluding the first post-baseline visit, or 2) a stricter definition of relapse defined as 30% worsening from baseline in PANSS total or any PANSS factor scores, or worsening in CGI-S by 3 or a score of 6/7 in CGI-I at two consecutive visits excluding the first post-baseline visit. Odds ratios of meeting relapse criteria were calculated for each risk factor.

Results: The odds of meeting one of the operational thresholds for relapse after antipsychotic discontinuation were not statistically significantly increased in the subjects who were unstable on the PANSS total or on one of the five PANSS Marder factors before antipsychotic discontinuation. In addition, the severity of PANSS total and Marder factor scores at screening and baseline were not statistically significantly associated with odds of relapse. Lastly, nor age nor gender had any effect on relapse rates.

Conclusion: Mild to moderate symptomatic variations in severity of symptoms during screening and more severe symptomology at baseline as measured by the PANSS were not predictive of increased risk of subsequent relapse in schizophrenic patients with predominantly negative symptoms in a 12 week, double-blind, placebo-controlled clinical trial.

INTRODUCTION

The realization that negative symptoms are at least as burdensome as psychosis for individuals suffering from schizophrenia has led investigators in academia and the pharmaceutical industry to focus research efforts on these illness aspects. To reduce the confounding effects of psychosis and agitation, most but not all published trials targeting negative symptoms involved symptomatically stable patients and used an add-on design in which the experimental compound or placebo was added to an antipsychotic. A potential disadvantage of the add-on design is the risk of confounding effects of antipsychotics which may cause secondary negative symptoms. In contrast, a potential risk of the monotherapy design, i.e. experimental versus placebo, is the potential for symptomatic worsening and exacerbation. This is particularly relevant since most trials targeting negative symptoms are conducted in out-patient settings and tend to last 3 to 6

months (1-2). Regardless of the add-on or monotherapy designs, to reduce the risk of including into trials patients who are unstable or who might undergo rapid symptomatic exacerbation, an observation period is included into the trial design. It is hypothesized that patients whose symptoms vary during the 1-3 weeks observation period preceding randomization - beyond a predetermined threshold - are more likely to destabilize. By trial design, these patients are excluded from the trial. However, because the hypothesis that more severely ill or unstable patients are more likely to undergo symptomatic exacerbation aligns with clinical common sense the hypothesis is rarely tested and was never tested in patients with predominately negative symptoms.

METHOD

This retrospective analysis included all randomized patients assigned to placebo (n=83) in the double-blind, placebo-controlled outpatient trial of MIN-101 (roluperidone) for the treatment of negative symptoms in schizophrenia. A detailed description of the trial design and patient population can be found in reference 3. 79 subjects had at least one post baseline visit. Subjects in the trial were required to be 18 to 60 years of age, inclusive; meet the diagnostic criteria for schizophrenia as defined in the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5); be stable in terms of positive and negative symptoms of schizophrenia over the last 3 months and have a PANSS negative subscore of at least 20. . The screening period lasted up to 28 days. After at least 2 days washout from all psychotropic medication, patients were randomly assigned to receive placebo or experimental medication for 12 weeks.

At baseline, the mean total PANSS score was 80.5, and for the five PANSS Marder factors (4), the mean Uncontrolled hostility/excitement factor score was 6.8, the mean Anxiety/depression factor score was 8.7, the mean Positive symptom

factor score was 19.4 , the mean Disorganized thought factor score was 20.5, and the mean Negative symptom factor score was 25.1.

For purposes of this retrospective analysis, subjects at risk for exacerbation were hypothesized to be those with the highest 10% of absolute change from the screening visit to baseline in the PANSS total or one of the five PANSS Marder factors. Additionally, we tested for the effect of screening or baseline severity in PANSS total or any of the five PANSS Marder factors, as well as for the effect of age and gender on relapse rates. For analysis purposes, we operationally defined 2 criteria of relapse: 1) A 20% increase in PANSS total or one or more of the 5 PANSS Marder factors; or worsening of CGI-S by at least 3 points; or a CGI-I score of 6 or 7 at two consecutive post baseline visits excluding the first post-baseline visit; or 2) A stricter definition requiring a minimum of 30% increase in PANSS total or at least one of the five PANSS factors or worsening in CGI-S by 3 points or a CGI-I score of 6/7 at two consecutive post baseline visits excluding the first post-baseline visit.

In the first step logistic regression was performed to assess the effect of individual risk factors on relapse. In the subsequent step we performed an age and gender corrected logistic regression on the individual risk factors. The analyses were carried out using SAS 9.4. Results are presented in odds ratios for each risk factor described above. Given the post-hoc nature of the analysis and the relatively large number of tests performed, the alpha value of significance was corrected using Bonferroni correction, dividing the alpha value of 0.05 by the number of test conducted within an analysis to determine the threshold of statistical significance.

RESULTS

Depending on the definition of relapse, 26 or 17 subjects met the operational criteria for relapse based on worsening of their PANSS total, worsening of one of the five Marder factors or worsening of the CGI scores. As shown in Figures 1 and

2, the odds of meeting one of the operational thresholds for relapse, regardless of how strict the definition was, were not statistically significantly increased in the subjects who were most unstable on the PANSS total or on one of the five PANSS Marder factors. Relapse rates were as well not affected by subject's age or gender.

The severity of the PANSS total score at baseline was statistically significantly associated with meeting the milder relapse criteria prior to application of the Bonferroni correction for multiple comparisons (OR (95% CI) 0.95 (0.91, 1.00) P= .0493. After the application of the correction for multiple comparisons (dividing the alpha value of 0.05 by 12 given the number of test performed) the p value was not significant. As shown in Tables 1 and 2 none of the other PANSS measures at screening or baseline was statistically significantly associated with either milder or more severe operationally defined relapse. No differences in the results were observed when we corrected for age and gender (data referenced in appendix).

DISCUSSION

In this post-hoc analysis of stable clinical trial subjects with moderate to severe negative symptoms who were washed out of their previous antipsychotic medication and assigned to placebo for 12 weeks as outpatients, instability of psychopathology during the screening period, age or gender were not associated with increased risk of subsequently meeting the operational relapse criteria.

Severity of psychopathology at screening or baseline measured by the five Marder factors was also not statistically significantly predictive of increased relapse in this placebo treated population. The severity of the total PANSS score at baseline was weakly, but statistically significantly associated with meeting the milder relapse criteria (OR (95% CI) 0.95 (0.91, 1.00) P= .0493), but statistical significance did not survive a Bonferroni correction for multiple comparisons. An association of milder psychopathology with modestly higher odds of relapse would

be contrary to clinical experience and might reflect a chance finding or the phenomenon of regression to the mean. The results did not change when data were analyzed correcting for age and gender.

Studies attempting to predict relapse for stable patients with predominately negative symptoms who are withdrawn from antipsychotics are of upmost importance. These trials tend to be lengthy (typically 12-24 weeks) and are preferentially conducted in the outpatient community. However, mild to moderate symptomatic variations during screening and greater severity of symptoms as measured by the PANSS were not predictive of increased risk of relapse, in this predominantly negative symptom sample over 12 weeks of double-blind placebo-controlled treatment. These findings are tentative due to the relatively modest sample size and relatively small number of relapses. Larger placebo treated samples will be useful in making more definitive interpretations.

Figure 1: Association of Percentile Rank of PANSS Change between Screening and Baseline with Subsequently Meeting Relapse Criteria – Relapse criteria one

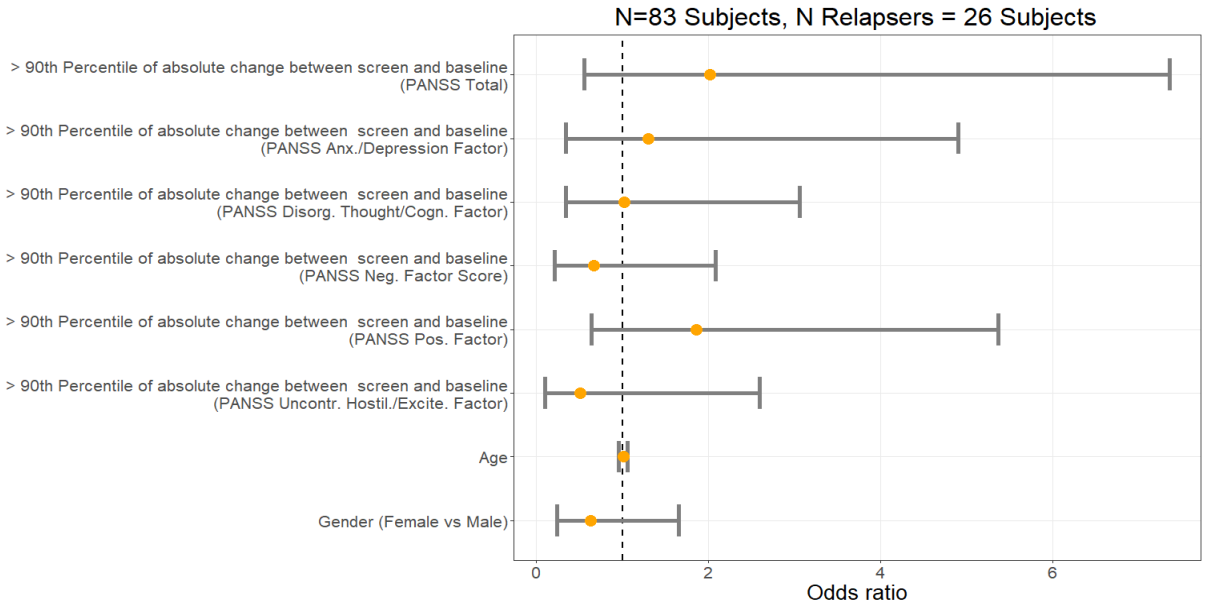

Figure 2: Association of Percentile Rank of PANSS Change between Screening and Baseline with Subsequently Meeting Relapse Criteria Two (more severe).

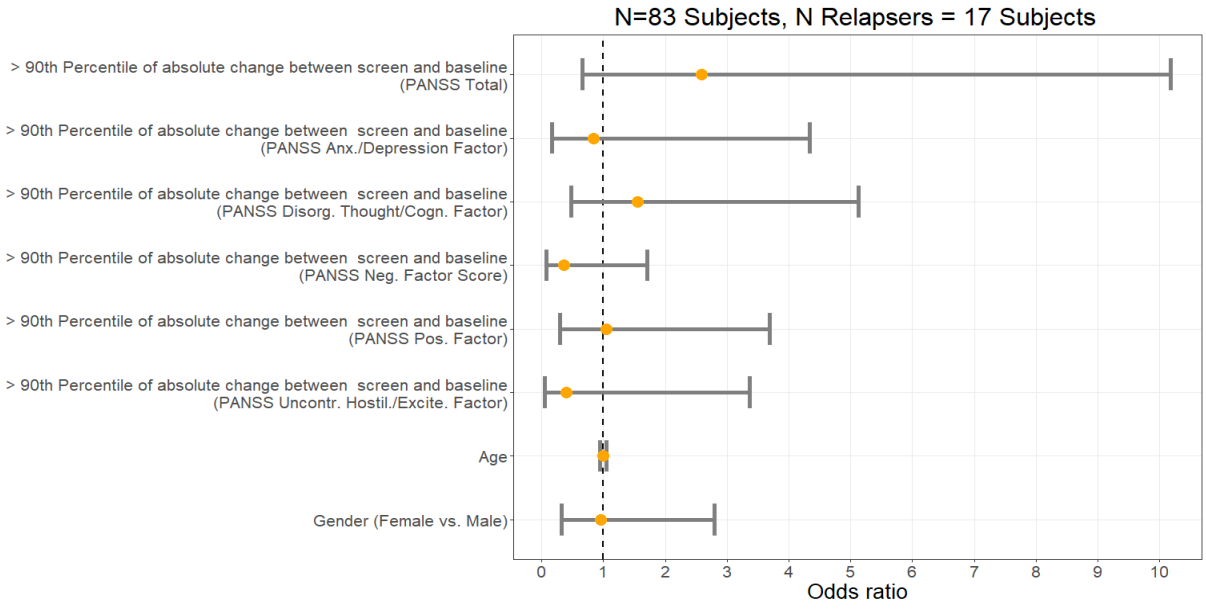

Table 1: Association of PANSS Severity at Screening and Baseline with Subsequently Meeting Relapse Criteria One

Visit	Measure	OR (95%CI)	P_value
Screening	PANSSTOT	0.98 (0.94, 1.02)	0.2469
Baseline	PANSSTOT	0.96 (0.91, 1.00)	0.0493
Screening	PANSS_UF	0.92 (0.75, 1.12)	0.4091
Baseline	PANSS_UF	0.85 (0.70, 1.04)	0.1179
Screening	PANSS_AF	0.99 (0.85, 1.15)	0.8745
Baseline	PANSS_AF	0.92 (0.78, 1.08)	0.3094
Screening	PANSS_PF	0.95 (0.84, 1.09)	0.4767
Baseline	PANSS_PF	0.92 (0.81, 1.06)	0.2551
Screening	PANSS_DF	0.93 (0.82, 1.06)	0.3087
Baseline	PANSS_DF	0.90 (0.79, 1.03)	0.1123
Screening	PANSS_NF	0.93 (0.82, 1.05)	0.2467
Baseline	PANSS_NF	0.91 (0.80, 1.03)	0.1468

Table 2: Association of PANSS Severity at Screening and Baseline with Subsequently Meeting Stricter Relapse Criteria

Visit	Measure	OR (95%CI)	P_value
Screening	PANSSTOT	0.99 (0.94, 1.03)	0.5317
Baseline	PANSSTOT	0.96 (0.91, 1.01)	0.1372
Screening	PANSS_UF	0.93 (0.74, 1.18)	0.5668
Baseline	PANSS_UF	0.87 (0.69, 1.09)	0.2275
Screening	PANSS_AF	1.01 (0.85, 1.20)	0.8869
Baseline	PANSS_AF	0.97 (0.81, 1.17)	0.7717
Screening	PANSS_PF	1.00 (0.86, 1.15)	0.9734
Baseline	PANSS_PF	0.96 (0.82, 1.12)	0.6123
Screening	PANSS_DF	0.94 (0.81, 1.09)	0.4019
Baseline	PANSS_DF	0.88 (0.75, 1.02)	0.0954
Screening	PANSS_NF	0.95 (0.82, 1.09)	0.4372
Baseline	PANSS_NF	0.91 (0.79, 1.05)	0.2043

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