September 16, 2024

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Reviva Pharmaceuticals Holdings, Inc. (RVPH: NASDAQ)

RVPH: RECOVER Biomarker KOL Event

Research Note

RECOVER Vocal Biomarker Data

On September 4, 2024, Reviva Pharmaceuticals Holdings, Inc. (NASDAQ: RVPH) held a key opinion leader (KOL) event to discuss results from the RECOVER trial. RECOVER was a global Phase 3, randomized, double-blind, placebo-controlled, multicenter study designed to assess the safety and efficacy of brilaroxazine in 412 patients with acute schizophrenia compared to placebo. Brilaroxazine was administered at fixed doses of 15 mg or 50 mg once daily for 28 days. The primary endpoint was a decrease in the Positive and Negative Syndrome Scale (PANSS) total score compared to placebo from baseline to Day 28. Key secondary endpoints include clinical global impression (CGI) severity, positive and negative symptoms, social functioning and cognition. Topline for the trial was first announced in October 2023. The primary endpoint was met with the trial producing a 10.1-point reduction in PANSS score relative to placebo at four weeks for the 50 mg dose. Brilaroxazine also achieved statistically significant and clinically meaningful reductions in all major symptom domains and secondary endpoints at week 4 with the 50 mg dose vs. placebo. The 15 mg dose of brilaroxazine was numerically superior to placebo on the primary endpoint and most secondary endpoints, and reached statistical significance on two key secondary endpoints.

On February 15th, Reviva hosted its first post-RECOVER key opinion leader (KOL) event. It featured Dr. Mark Opler, the Chief Research Officer at WCG Inc and Executive Director of the PANSS Institute and Dr. Larry Ereshefsky, retired professor of Psychiatry, Pharmacology and Psychiatry at the University of Texas. Along with Reviva's CEO Laxminarayan Bhat, the presenters summarized schizophrenia's epidemiology with a review of prevalence and positive and negative symptoms. Scales and tools used to evaluate schizophrenia and the measures used in the RECOVER trial were discussed along with RECOVER trial design and demographic details. The event participants provided a history of antipsychotic drugs and side effects.

The February KOL event provided the first round of data and analysis. Additional analysis was underway, especially in the areas of biomarkers. This follow-on data was provided in another KOL event held on September 4th, 2024. The September event again featured Drs. Bhat and Opler. There was also a new face that joined to introduce viewers to the vocal biomarkers: Brian Kirkpatrick, MD. He is Professor, Psychiatric Research Institute at the University of Arkansas for Medical Sciences. The event began with a review of previously shared RECOVER data and background on schizophrenia. It also reviewed previously released data regarding another biomarker called brain-derived neurotrophic factor (BDNF). Low BDNF levels are associated with negative symptoms and cognitive deficits in schizophrenia. In the RECOVER trial, brilaroxazine arms were associated with an increase in BDNF levels compared to baseline while BDNF levels in placebo declined over the duration of the trial.

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Exhibit I – Improvements in BDNF (ng/mL) Over Duration of RECOVER Trial



Source: Reviva September 4, 2024 KOL Event Presentation

Vocal biomarkers (VBMs) have been used for some time in patients with schizophrenia and other neurodegenerative disorders such as Alzheimer's disease.[1] The approach uses an automated, objective method such as natural language and acoustic processing to generate highly reliable data. Supported by meta-analyses[2], speech production and speech latency are validated measures that can correlate to PANSS severity. Turn latency, in particular, is a useful measure. Turn latencies in speech analysis refer to the time intervals between speaking turns in a conversation. They provide insights into conversation dynamics, speaker relationships and communication efficiency. It is usually measured in milliseconds or seconds using speech analysis software. Turn latencies are further able to aid in the evaluation of schizophrenia pathology, clarifying the integration of cognitive, social and motivational systems. They indicate the psycho-motor retardation in a subject. As part of the conduct of the RECOVER trial, subject interviews were recorded, which provided the input data necessary to analyze the speech. Machine learning was used to identify response times and break subjects into two groups of slow and fast response time. Slower response times were associated with more severe negative symptoms while faster response times were more closely associated with more severe positive symptoms.

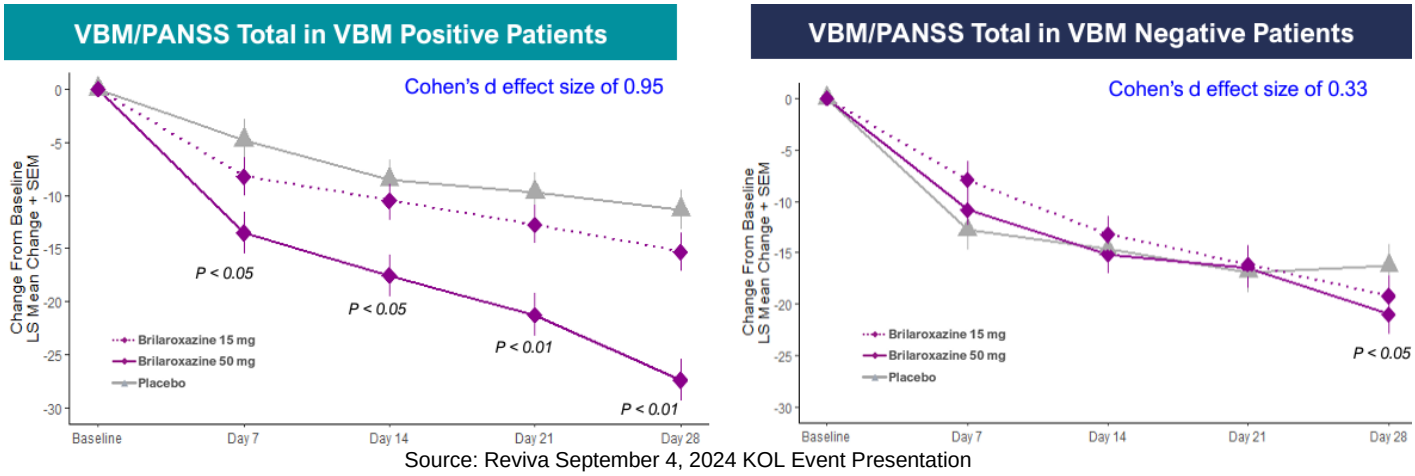
Dr. Kirkpatrick took the baton for the third leg of the KOL event to discuss the data behind the VBM. The VBM was determined from the screening recording of the interview and was divided into two groups of VBM positive and VMB negative subjects. The VBM positive group had responses of about 550 milliseconds slower than the average for the group. This was about 2.0 seconds after the patient was asked a question. Characteristics of the VBM positive group were more severe negative symptoms and a slightly younger age. The VBM negative group produced fast responses that delayed an average of 1.4 seconds after the question to respond. This group was characterized by more severe positive symptoms

During the recorded screening interview, VBM positive subjects spoke less and at a slower pace, had shorter interviews with fewer turns and evaluators gave them higher negative symptom scores. When treatment response to brilaroxazine was examined, there was a significant separation in curves for vocal biomarker positive patients. However, the separation was less pronounced for VBM negative patients. VBM positive patients show significantly greater reduction in:

- PANSS total scores, but both groups had a significant improvement
- positive symptoms, but both groups had a significant improvement
- PANSS negative symptoms
- in cognitive/disorganization scores, but both groups had a significant improvement
- CGI scores, but both groups had a significant improvement

[1] Hajjar, I., *et al*. Development of digital voice biomarkers and associations with cognition, cerebrospinal biomarkers, and neural representation in early Alzheimer's disease. Alzheimer's & Dementia Journal. 2023.
[2] Cohen, *et al*. 2014 and Parola, *et al*. 2020.

Exhibit II – Effect on the VBM Positive & Negative Patient Groups – Total PANSS Score



Source: Reviva September 4, 2024 KOL Event Presentation

As the two groups were measured, the vocal biomarker positive and the vocal biomarker negative groups, the results shows that brilaroxazine produces a greater impact in the total PANSS score for VBM positive patients (slower responses) than it did in VBM negative patients (faster responses), although both were statistically significant at day 28 (see above). Additional slides in the KOL presentation illustrated a large effect size for VBM positive patients for PANSS positive symptoms, PANSS negative symptoms, cognition, VBM positive and clinical global impression-schizophrenia (CGI-S) stores. VBM negative patients (faster responses) had a much smaller effect size for each of these measures.

Personal and social performance (PSP) subscales examined groups divided by the speech latency VBM. For PSP total, socially useful activities, and disturbing and aggressive behavior, the VBM negative patients produced a greater effect size as measured by Cohen's D score for PSP total, socially useful activities and disturbing and aggressive behavior. VBM positive patients saw a greater effect size as measured by Cohen's D for personal and social relationships and self-care. Guided by the information in the VBM, Dr. Kirkpatrick asserted that brilaroxazine produces a robust improvement in both VBM positive and negative groups, but in different functional areas. Brilaroxazine's benefits differ because the patients receiving treatment have different symptom profiles.

Exhibit III - Personal and Social Performance (PSP) Subscales / Speech Latency in Brilaroxazine vs Placebo

	Full sample		VBM-pos		VBM-neg	
Outcome measure	Cohen's D	p value <	Cohen's D	p value <	Cohen's D	p value <
PSP Total	0.48	0.05	0.34	NS	***0.62***	***0.05***
Socially useful activities	0.51	0.01	0.30	NS	***0.72***	***0.01***
Personal and social relationships	0.37	0.05	***0.62***	***0.05***	0.18	ns
Self-care	0.54	0.01	***0.77***	***0.01***	0.35	ns
Disturbing & aggressive behavior	0.42	0.05	0.27	ns	***0.57***	***0.05***

Source: Reviva September 4, 2024 KOL Event Presentation

Speech turn latency is an automated, objective measure supported by extensive literature in schizophrenia. In the RECOVER trial, turn latency distinguished between two groups that differed in the severity of negative and positive symptoms. In both vocal biomarker groups, brilaroxazine demonstrated efficacy for total PANSS score and many of its subcategories. The VBM positive group, which was characterized by more speech latency, had a higher proportion of moderate to severe negative symptoms; brilaroxazine produced robust efficacy for negative symptoms. Furthermore, the turn latency measures and human raters' scale scores cross validate each other. In summary, the turn latency vocal biomarker provides further support for the efficacy of brilaroxazine for both symptoms and function.

The KOL event concluded with an opportunity for analysts to ask questions of the experts which ranged from regulatory considerations to the use of biomarkers for categorizing different symptoms of schizophrenia.

Summary

As it continues to conduct its long-term safety trial and seek capital to begin its RECOVER 2 trial, Reviva holds a KOL event to discuss the analysis of additional biomarkers used in RECOVER. The focus of this event was to examine the use of voice biomarkers in patients to see their relationship with brilaroxazine treatment and PANSS score. VBM positive patients, which had more latency in their speech, showed robust effect sizes in a number of measures. Some of the outcome measures that benefitted from brilaroxazine differed by VBM positive and VBM negative patients because their symptom profiles were also different.

Investor eyes are focused on an anticipated capital raise in the near term that if completed and if in sufficient magnitude will allow Reviva to begin its RECOVER 2 trial and complete its pivotal studies required to submit a new drug application (NDA) to the FDA. We are also following the progress of the open label extension (OLE) safety study which is expected to read out in 4Q:24. We continue to see a best-in-class safety and efficacy profile for brilaroxazine which has been demonstrated in a Phase II and Phase III study. While it has been frustrating that capital providers have not recognized brilaroxazine's opportunity, we do think there are investors that understand the potential and that in time, when there is more market certainty, this will be reflected in the valuation.

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