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Reviva Pharmaceuticals Holdings, Inc. (RVPH: NASDAQ)

RVPH: Update to Brilaroxazine Safety vs. Efficacy Comparison – Adding RECOVER Data

Research Note

Reviva Video Series

Reviva Pharmaceuticals Holdings, Inc.'s (NASDAQ: RVPH) CEO Laxminarayan Bhat participated in a video series which covered several topics germane to the company. This included reviewing the most recent key opinion leader (KOL) event, elaborating on the unmet needs in schizophrenia, summarizing the results of the RECOVER trial, looking ahead to the RECOVER 2 trial and evaluating recent merger and acquisition activity in the CNS space. Follow the links on the next page to access the interviews.

Exhibit I – Reviva CEO Dr. Laxminarayan Bhat

Source: Screenshot from Reviva Pharmaceuticals Upcoming RECOVER 2 Trial Video Clip

- Reviva Pharmaceuticals RECOVER Trial Findings
- RECOVER Trial Results
- RECOVER Trial Additional Findings
- What's Going on with M&A in CNS?
- Unmet Needs in Schizophrenia
- Reviva's Upcoming RECOVER 2 Trial
- Key Opinion Leader Event
- Reviva Pharmaceuticals CEO Fireside Chat

Update on Brilaroxazine Comparison

In an April 2021 report, we developed an analysis that compared efficacy benefits against the side effect profile for the leading antipsychotics and brilaroxazine and found that brilaroxazine produced above average efficacy with the best side effect profile for the group. This analysis was updated using data from Reviva's 2023 RECOVER trial using the same methodology.

The 2021 analysis used data from brilaroxazine's Phase II trial and Huhn *et al*. published in The Lancet. Huhn *et al.* is the largest known, most comprehensive systematic review and network meta-analysis comparing the efficacy and side effects of 32 oral antipsychotics in acute treatment of adults with multi-episode schizophrenia.[1] The publication provided a comprehensive comparison of first- and second-generation antipsychotic drugs. The meta-analysis evaluated each of the antipsychotics on measures of efficacy and side-effects. The study employed a meta-analysis that combined the results from 402 studies, including 53,463 participants and built on the group's past efforts. The 32 drugs were compared, in terms of efficacy, by reduction in overall, positive, and negative symptoms. Dropout, depression, quality of life and functioning were also assessed. Side effects compared included use of antiparkinsonian drugs, extrapyramidal side effects, akathisia, weight gain, prolactin levels, sedation, QTc prolongation and anticholinergic side effects.

Comparison parameters included in the review were standardized to accommodate studies of varying measures. The studies' results were standardized via Standardized Mean Difference (SMD), Risk Ratio (RR) and Mean Difference (MD) where appropriate. To facilitate our comparison, data from the Phase II study of RP5063 (brilaroxazine) (NCT01490086) was standardized in a similar manner, using SMD, RR and MD, to the extent the collected data was analogous[2] and the data compared against those published in the meta-analysis.

REFRESH: Phase II Evaluation of Brilaroxazine in Schizophrenia
Reviva's Phase II (REFRESH) was a randomized, double blind, placebo controlled, multi-center trial intended to assess safety and efficacy of brilaroxazine in acute exacerbation of schizophrenia or schizoaffective disorder.[3] 22 clinical sites located in the Philippines, India, Malaysia, Moldova and the United States participated in the trial. The primary endpoint for the study was reduction in total PANSS at end of treatment from baseline vs placebo. Secondary endpoints included change from baseline to day 4, 8 15, 22 and 28 on PANSS total, positive and negative subscales, 20% improvement in PANSS total and one-point improvement on the clinical global impressions scale severity (CGI-S).[4] 234 subjects were enrolled. Patients were randomized into five arms including 15 mg (n=60), 30 mg (n=60) and 50 mg (n=60) doses as well as placebo (n=40) and aripiprazole 15 mg (n=20). Approximately one week of screening was followed by 28 days of dosing and follow up afterward of one and two weeks for men and women, respectively. Pharmacokinetic analysis was also performed. 186 of 234 enrolled subjects completed the study.

Data Compilation and Presentation
Data from the REFRESH study was compared to the data presented in the Huhn meta-analysis. The meta-analysis compared 32 antipsychotics by their reduction in overall, positive, and negative symptoms, dropout, depression, quality of life and functioning. Side effects compared included use of antiparkinsonian drugs, extrapyramidal side effects, akathisia, weight gain, prolactin levels, sedation, QTc prolongation and anticholinergic side effects. Of these parameters, overall, positive and negative change in symptoms, dropout, akathisia, weight gain, change in prolactin

[1] Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., Krause, M., Samara, M., Peter, N., ... & Leucht, S. (2019). Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *The Lancet*, *394*(10202), 939-951.
[2] Cantillon, M., Prakash, A., Alexander, A., Ings, R., Sweitzer, D., & Bhat, L. (2017). Dopamine serotonin stabilizer RP5063: a randomized, double-blind, placebo-controlled multicenter trial of safety and efficacy in exacerbation of schizophrenia or schizoaffective disorder. *Schizophrenia research*, *189*, 126-133.
[3] Schizoaffective disorder is a combination of schizophrenia symptoms and mood disorder symptoms
[4] The CGI-S is a measure of clinician's view of patient's global functioning

levels and sedation were comparable based on data available from the REFRESH study publication. As positive and negative symptom reduction were endogenous to overall symptom reduction, reduction in overall symptoms was solely used as a measure of efficacy. Side-effects ultimately compared included akathisia, weight gain, change in prolactin levels and sedation. All-cause discontinuation is compared on its own to evaluate treatment adherence across the antipsychotics. The analysis was centered on data specific to the 15 mg dose. Furthermore, though the *Lancet* review featured 32 antipsychotics, we focused our attention on the major antipsychotics that are most frequently prescribed: olanzapine, risperidone, quetiapine, aripiprazole, cariprazine and brexpiprazole.

REFRESH study data was then standardized to be comparable with the meta-analysis data. Symptom reduction measures were standardized using Standardized Mean Difference (SMD), where the mean difference between symptom reduction in the 15 mg and placebo arms was determined, and the standard deviation (SD), derived from standard error (SE) of the placebo arm was used to standardize the therapeutic reduction. This number was then directly compared to the results presented in the *Lancet* meta-analysis review which were also presented in SMD. This was performed for change in total PANSS, which correlated with the meta-analysis' change in overall symptoms parameter.

Other parameters, such as all-cause discontinuation, were presented as Risk Ratio (RR) in the meta-analysis, and REFRESH data was treated accordingly, taking the percentage discontinued in the 15 mg arm, and dividing by the same in the placebo arm. Akathisia and sedation parameters were processed in the same manner. We note that no placebo arm patients experienced akathisia in the REFRESH trial, rendering an error in the RR calculation. We used a surrogate datapoint for akathisia placebo prevalence of 3.7%.[5] No patients experienced sedation in treated and placebo arms and the RR was taken to be one.

Finally, in cases where Mean Difference (MD) was compared, such as change in weight, the mean weight gain for the placebo arm was subtracted from the treatment arm. Change in prolactin, another factor compared using MD, was in mIU/L, or milli-international units per liter, in the REFRESH trial, and was converted at a rate of 21.2 µg per mIU to ng/mL, as presented in the meta-analysis.

Data was compiled from REFRESH and the meta-analysis, and percentile rankings were determined for each antipsychotic, for each parameter. Missing data was ignored. The efficacy (y) axis reflected only the overall reduction in symptoms parameter to rank the antipsychotics, where no average was taken. Side-effect parameters were averaged with equal weighting. An equal weighting was determined to be best practice, in this application, as assigning weights to the side effects implied that one side effect was less desirable than another. The ranking and averaging also reconciled differences between the standardization measures and minimized distortion from missing data. The overall reduction in symptoms and average of side effect ranking were used to produce a two-dimensional projection of efficacy versus side effects. A higher efficacy ranking and lower side effect ranking are most desirable.

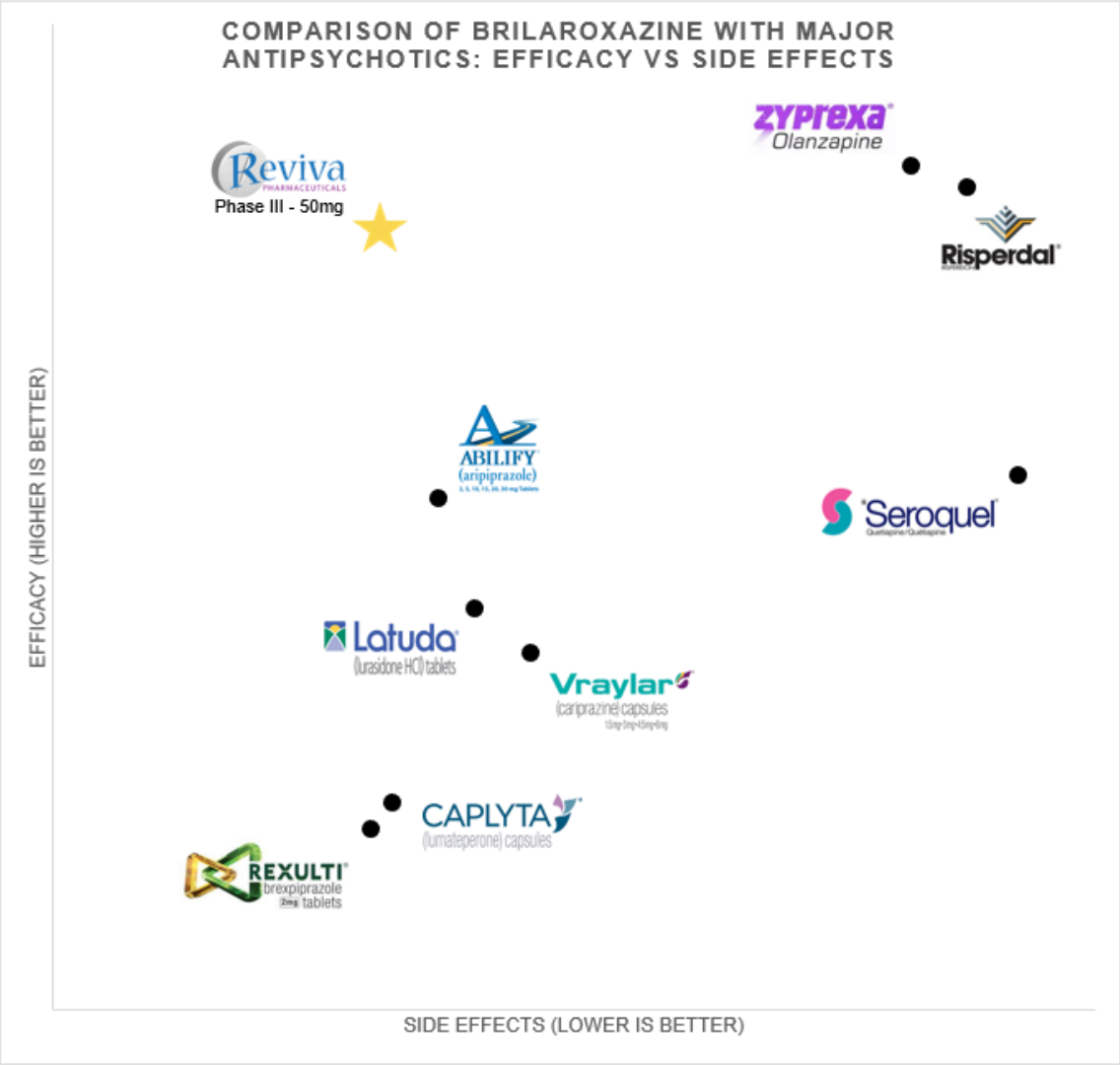
Based on the analysis, 15 mg brilaroxazine is differentiated among the major antipsychotics. Brilaroxazine efficacy is above average compared with other treatments but really differentiates itself with its class-leading lack of side-effects. Side effects are a material deterrent to treatment adherence and patients are forced to consider this when seeking the benefits. Also noteworthy is that brilaroxazine is superior to aripiprazole in both efficacy and side effects. It is a chemical evolution of aripiprazole, sharing the same underlying structure but replacing a carbon atom with an oxygen atom in the quinoline ring, resulting in a benzoxazinone ring. Brilaroxazine is also structurally similar to cariprazine and brexpiprazole. The attributes of above average efficacy combined with class-leading lack of side effects holds up when the analysis is extended to all 32 available antipsychotics included in the meta-analysis.

Meta-Analysis Comparison with RECOVER Data

Reviva commissioned a study in 2024 to update this analysis for data provided in the RECOVER trial. RECOVER data was announced in October 2023 promulgating the results from 411 patients with acute schizophrenia. Patients in the trial were randomized into placebo, 15 mg and 50 mg groups, respectively enrolling 137, 140 and 134 patients. The comparative analysis standardized the data in Huhn *et al*. along the dimensions of efficacy and side effects and applied the same methodology as used in the 2021 analysis to the RECOVER data and new addition lumateperone (Caplyta) which was approved in 2019. The updated results from RECOVER were placed in a scatter plot along with the meta-analysis data from Huhn. On the x axis is a measure for side effects, where lower is better and on the y axis is efficacy, where higher is better. The optimal region on the scatter plot is in the Northwest corner which is associated with an effective antipsychotic producing low side effects. In the following image we share a graphical comparison provided in Yu, 2024[6].

[5] Chow, C. L., Kadouh, N. K., Bostwick, J. R., & VandenBerg, A. M. (2020). Akathisia and Newer Second-Generation Antipsychotic Drugs: A Review of Current Evidence. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 40(6), 565-574.
[6] Yu, Theodore. Reviva Pharmaceuticals. Brilaroxazine vs. Major Antipsychotics: A Reduction in Side Effects. March 2024. Unpublished.

Exhibit II – Efficacy vs. Side Effects: Brilaroxazine and Other Major Antipsychotics, 2024 Analysis



Source: Reviva commissioned study, Brilaroxazine vs. Major Antipsychotics

As shown in the exhibit, Reviva's brilaroxazine inhabits the most extreme position in the Northwest or upper left corner of the scatter plot demonstrating both better efficacy and a better side effect profile versus the other data points. This position suggests that brilaroxazine provides the best balance of efficacy and side effects which should translate into substantial penetration into the schizophrenia market if the product is approved.

Summary

Now that the first RECOVER trial has ended, the data generated from the study can be put in context with other antipsychotics that are approved for schizophrenia patients. We conducted a comparison using data from the smaller Phase II REFRESH trial several years ago which showed a favorable profile for brilaroxazine that produced fewer and less severe side effects and better efficacy than the other major prescribed antipsychotics. Now that the Phase III RECOVER study has been completed, Reviva commissioned a new study to update the comparison. Results continue to show that brilaroxazine provides the most favorable balance of efficacy and side effects compared with other commonly used agents.

Reviva shared data from its RECOVER trial via other mediums as well, including a video series that summarized the findings of the trial, reviewed the highlights from February's key opinion leader (KOL) event, opined on the merger and acquisition environment and discussed the unmet needs in schizophrenia among other items. We provide links to the interviews in the video series with Dr. Bhat above.

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