U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Memorandum

Date: April 29, 2019

From: Peiling Yang, PhD.
Statistical Team Lead, Division of Biometrics I
Office of Biostatistics

Subject: Statistical Review of NDA 205-831/S-5

NDA Letter Date:	September 14, 2018
Applicant:	Rhodes Pharmaceuticals L.P.
Drug Name:	Aptensio XR (methylphenidate hydrochloride extended-release)
Indication:	Attention Deficit Hyperactivity Disorder (ADHD)
Submission Location:	\\CDSESUB1\evsprod\NDA205831\0065
Relevant IND:	104624

To: File NDA 205-831

This memorandum summarizes the key conclusion about efficacy from a different perspective than the primary statistical reviewer Mr. Eiji Ishida, who provided a very detailed statistical review.

This submission included one efficacy trial EF-003. In this trial, subjects who met the responder criteria during the open-label phase were randomized to the 2 weeks double-blind phase. Subjects whose symptoms got worsened were discontinued to enter the extension phase. The primary efficacy endpoint was change from baseline to week 2 in the ADHD-RS-IV total score. The pre-specified primary analysis was ANOVA, but the Applicant did not clarify how to handle missing outcomes. Although the FDA's statistical comments were conveyed to the Applicant during the IND review stage, they were not addressed by the Applicant.

Around 30% of the subjects were discontinued after obtaining their week 1 outcomes before reaching the endpoint visit. For these subjects, who were discontinued early, Mr. Ishida found that the Applicant essentially used LOCF (last observed carried forward) method to impute the missing outcomes at week 2. For the sake of convenience, hereinafter I will refer to the primary analysis as LOCF ANOVA. Because these subjects were discontinued due to lack of efficacy, the underlying missing data assumption for the LOCF imputation method (MCAR, *missing completely at random*) was unlikely to hold true. Mr. Ishida performed a *post hoc* MMRM (Mixed Model Repeated Measures) analysis assuming a less rigorous assumption about missing data (MAR, *missing at random*). MAR allows missingness to depend on observed outcomes and treatment arms, but not on unobserved outcomes. Both LOCF ANOVA and MMRM analyses led to statistically significant findings in support of efficacy. Although one cannot verify whether the MAR assumption holds true, in this trial the assumption may be applicable because the missing outcomes at week 2 were essentially due to the worsened symptoms observed at week 1. We also noted that a larger proportion of subjects in the placebo arm were discontinued, so analysis based on a worst-case scenario (which does not depend on the MAR assumption) would also favor the drug arm. Thus, an analysis of giving these dropouts some kind of worst score will also yield a statistically significant treatment effect in favor of Aptensio XR.

In summary, efficacy results were statistically significant regardless of whether based on the prespecified or post-hoc analyses. However, the results were based on merely two weeks duration, and particularly around 30% of the subjects ended up with having one-week efficacy data only. In addition, the patient population was enriched, but some subjects (nearly 15%) who were not eligible to be in the enriched population were also randomized, which raised an uncertainty about the quality of trial conduct. All of these issues undermined the efficacy evidence. Whether the collective evidence for efficacy is adequate (b) (4) is deferred to the clinical review team.

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/s/

PEILING YANG
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