Subject: A replacement of the previously signed off NDA review document (NDA-205831; S-005)

The present review document replaces the previously finalized review document dated 19 February 2019, Statistical Review and Evaluation (DARRTS Reference ID: 4392619) for Supplemental NDA (NDA205831: S-005) of Aptension XR.

The reason for this replacement is that the additional information was submitted by the Sponsor on March 14, 2019.

The previous NDA review should be disregarded.

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Eiji Ishida, MS (Primary Reviewer)

May 1, 2019

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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

STATISTICAL REVIEW AND EVALUATION (REVISION)

CLINICAL STUDIES

NDA/BLA #:	NDA 205-831
Supplement #:	SUPPL-005
Drug Name:	Aptensio XR (methylphenidate hydrochloride extended-release)
Indication(s):	ADHD
Applicant:	Rhodes Pharmaceuticals L.P.
Date(s):	Stamp date: September 14, 2018
	PDUFA goal date: March 14, 2019
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Eiji Ishida, MS
Concurring Reviewers:	Peiling Yang, PhD; James Hung, PhD
Medical Division:	Division of Psychiatry Products
Clinical Team:	John Umhau, MD, Bernard Fischer, MD
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Keywords: NDA Efficacy Supplement Review, Pediatric Study, Double-Blind, Randomization on Optimized-Dose, ANOVA

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1 EXECUTIVE SUMMARY

The primary efficacy objective of Study EF-003 was to evaluate the efficacy of Aptensio XR in comparison with Placebo at the endpoint of the 2-week randomized double-blind period on responders defined as subjects who meet Randomization Criteria, based on the efficacy assessments with ADHD-RS-IV total score and CGI-I score, over the 6-week open label Aptensio XR exposure. The target patient population was preschool children of 4 or 5 years old with a diagnosis of Attention-Deficit Hyperactivity Disorder (ADHD).

Statistical Review Conclusion: In Study EF-003, although the efficacy data has shown statistical significance based on *post hoc* analyses that seem more sensible than the pre-specified, it may not be adequate to support an efficacy indication in labeling because it was conducted in an enriched patient population and the double-blind duration was two weeks only.

The study protocol defines the primary endpoint as change from baseline (Visit 13) to Visit 15 in ADHD-RS-IV total score (see 3.2.2). Visit 15, the second post-baseline visit, was scheduled at the end of the 2-week double-blind phase.

The Applicant's primary analysis result may be difficult to interpret for an evaluation of the protocol-defined primary efficacy, because of the systematic discontinuation based on observed ADHD-RS-IV total score and CGI-Improvement score (Section 3.2.3.2).

At the first post-baseline visit (Visit 14) of the 2-week double-blind phase, because the majority of 20 discontinued subjects had worsened conditions in ADHD symptoms, the mean ADHD-RS-IV total score of Placebo group got worsened by 16.9 points on the scale (Figure 5 and Table 9). Similarly, at the first post-baseline visit (Visit 14), because the majority of 9 discontinued subjects had worsened conditions in ADHD symptoms, the mean ADHD-RS-IV total score of Aptensio XR group got worsened by 7.0 points on the scale (Figure 4 and Table 9). The mean difference in ADHS-RS-IV total score between Aptensio XR and Placebo changed from 1.7 points to -8.4 points on the scale, which difference was -10.1 = -8.4-1.7 (Table 9). This may be considered the efficacy advantage of Aptension XR compared to Placebo, but much of it may be attributed to the fact of more worsening of Placebo group observed at the first post-baseline visit. On the other hand, the mean difference between Aptensio XR and Placebo was much the same at the first post-baseline visit (-8.4) and at the primary efficacy endpoint (-9.4); there was not much improvement from the first post-baseline visit to the primary efficacy endpoint visit. In other words, after a substantial number of placebo subjects who got worsened were discontinued at the first post-baseline visit, the mean difference between the two groups remained much the same. Therefore, the mean difference between Aptensio XR and Placebo may be interpreted as a reflection from the difference in efficacy performance of discontinued subjects between the two groups (Section 3.2.5.3). Whether or not this difference is considered meaningful efficacy evidence may be a clinical matter.

Although the Applicant's primary analysis may not provide a straightforward conclusion as the primary efficacy analysis, collective evidence suggests the efficacy of Aptensio XR. This reviewer finds evidence of efficacy of Aptensio XR in his *post hoc* statistical analyses (see Sections 3.2.5.3.1 and 3.2.5.3.2). However, because Study EF-003 used a design different from

one which the agency recommended, the interpretations of the efficacy evidence may need clinical considerations beyond the statistical analysis.

2 INTRODUCTION

2.1 Overview

Aptensio XR (methylphenidate hydrochloride extended-release) was approved on April 17, 2015. In the current supplement (NDA205831 Supplement-05), the applicant included the following pediatric efficacy study to fulfill the PREA postmarketing requirement:

Study RP-BP-EF003 – "*A randomized, double-blind, placebo controlled, flexible-dose titration study of methylphenidate hydrochloride extended release capsules (Aptensio XR) in children ages 4 to 5 years diagnosed with ADHD*".

The present statistical review provides an evaluation of the efficacy of Aptensio XR for the children ages 4 to 5 years diagnosed with ADHD using the data of Study RP-BP-EF003, abbreviated as Study EF-003. Study EF-003 consists of 6 phases, and the efficacy evaluation was based on Phase 5, 2-Week Randomized Double-Blind phase. Key information of Study EF-003 is presented in Table 1. The Applicant chose the study design (as summarized in Table 1) to assess efficacy for patients that are randomized to Drug or Placebo following 6-Week exposure to Drug. The agency had a concern with the proposed study design. The DPP (Division of Psychiatry Products) recommended in a Written Request that a study with a different design be conducted. More details are provided in the following section, Section 2.2.

Table 1: Key Information of a PREA PMRs WR pediatric study (Study EF-003)

Design	Multi Center, Randomized, 2-Week Double-Blind, Parallel Group, Placebo Control phase, following 6-Week Open Label Aptensio XR exposure phase
Treatment/ Sample Size of Randomized Patients	Aptensio XR/ N_A=39 Placebo/ N_P=50
Primary Endpoint	Change in ADHD-RS_IV total score from the end of open label phase (Study Visit 13) to end of 2_week double-blind phase (Study Visit 15)

Abbreviation: PREA: Pediatric Research Equity Act, PMRs: postmarketing requirements, WR: Written Request
Note: Study EF-003 consists of 6 phases, and the efficacy evaluation was based on Phase 5, 2-Week Randomized Double-Blind phase.

2.2 Regulatory Communications

Aptensio XR (methylphenidate hydrochloride extended-release capsules) was approved for the treatment of ADHD in patients aged $\geq$ 6 years on April 17, 2015. The Approval Letter included PREA PMRs (Pediatric Research Equity Act Postmarketing Requirements). Study EF-003, the study to be reviewed in this review, was originally one of the studies the applicant proposed to request an FDA Written Request for Pediatric Studies. The primary study endpoint for this study is comparison of the change in ADHD-RS-IV Preschool Version Total Score during the double-blind phase between the placebo group and the optimized dose group. The applicant planned to enroll up to 150 subjects, with the goal of study completion by at least 74 subjects to ensure adequate statistical power. On May 11, 2016, the Agency issued a Written Request (WR) for Pediatric Studies to the applicant, in which it was communicated to the applicant that to obtain needed pediatric information on methylphenidate at, least one adequate and well-controlled randomized double-blind and placebo-controlled trial in the preschool children (ages 4 and 5

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years) population would be necessary. The Agency provided the applicant with important recommendations for the required study as guidance in the WR as follows[1]:

Number of patients to be studied:
- Preschool-aged children (ages 4 and 5 years) to reflect the distribution of those affected with this condition.
- The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.
- The gender distribution of participants in this study must reflect the distribution of those affected with this condition.

Study Design:
- You must conduct a randomized, double-blind, placebo-controlled trial with a recommended duration of at least 6 weeks in preschool-aged children (ages 4 and 5 years). A flexible dose titration design may be used. This trial must provide the opportunity to detect a treatment effect of the drug in this population to inform labeling recommendations on dosing. For patients who discontinue study medication or discontinue from the trial, the reasons underlying such decisions must be collected and submitted (withdrawal of consent does not constitute an adequate explanation for such actions). The protocol must be submitted for comment prior to initiation of this study. You must obtain agreement on the final protocol prior to initiation of this study.

Statistical Information:
- Study 2 (the required study) must have a detailed statistical plan. The preliminary statistical analysis plan must be submitted for review and comment prior to initiation of this study. You must obtain agreement on the final statistical analysis plan prior to initiation of this study.
- The study must be designed with at least 85% statistical power to detect a clinically meaningful treatment effect (probably based on typical effects in children and adolescents) at a Type I error rate of 5% (two-sided). You must obtain agreement with the Division on the estimated size of the treatment effect prior to initiating the study. With respect to the primary efficacy analysis, the protocol will describe the estimand of primary interest. If the estimand of interest is the treatment effect in all patients randomized regardless of adherence, you should include provisions to limit missing data through study design and education of investigators and patients, and pre-specify analysis methods to account for missing data for the primary and key secondary efficacy analyses. We recommend designs that encourage continued collection of efficacy data even after study treatment discontinuation, following the recommendation from the National Academy of Sciences report on missing data in clinical trials. If you believe the treatment effect in all patients randomized regardless of adherence is not the most clinically important estimand, the protocol should specify which estimand is of most clinical

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[1] Quoted from Written Request issued on May 11, 2016

importance and why. Statistical methods to quantify this estimand should be specified in the protocol.

- To ensure your study is adequately powered, you must obtain an estimate of variability from an interim analysis and then follow a pre-specified rule to adjust the sample size to achieve the specified target power. The interim analysis must be performed when the study is close to completion (for example, at >75% of initially randomized patients who have completed/discontinued). You may estimate the variability based on a blinded and pooled analysis of all groups, in which case no alpha-spending adjustment is required for the interim analysis. If, however, you want to perform an efficacy assessment at these or some other interim analyses, an appropriate alpha adjustment would be required. Please provide the postulated magnitude of treatment effect and its standard deviation in your sample size planning.

The protocol and its amendments of the efficacy study (Study EF-003) was submitted on August 10, 2015, November 1, 2017. On October 18, 2016, the applicant submitted the draft SAP of the study for the first time and requested that the Agency ░░░░░░░░░░░░░░░░░░░░░░░ (b) (4) ░░░░░░░░░░░░░░░░░░░ and in addition, the applicant requested changes to the Agency's Written Request for Pediatric Studies. The most significant change was to specify that the efficacy and safety study (Study EF-003) would be comprised of a six-week, open-label, dose-optimization phase followed by a two-week, double-blind treatment phase. The Agency responded on February 2, 2017, indicating its disagreement with this strategy, because it would lead to a double-blind phase enriched for patients who tolerated and responded to the drug, potentially diminishing any safety signal. At a guidance meeting held on November 29. 2017, this disagreement was re-iterated and advised the Sponsor to submit a new request to amend the Written Request.

The applicant submitted the amendments of the SAP (Version 1.1 Final dated 30 October 2017, Version 1.2 Final dated 7 November 2017, and Version 2.0 Final dated 15 February 2018). The final version (Version 2.0) of the SAP was not submitted until the submission day of the current supplement. SAP Version 1.2 was submitted[2] on November 7, 2017. The final submission of the protocol (Version 2.0 dated 15 February 2018) was made on February 26, 2018.

Importantly, regarding the study design of Study EF-003, the Agency communicated its disagreement on the proposed design as a six-week, open-label, dose-optimization phase followed by a two-week, double-blind treatment phase, but the study design remained unchanged.

2.3 Data Sources

The applicant submitted CDISC SDTM and ADaM datasets of Study EF-003. The electronic path of the data of this study is:

\\CDSESUB1\evsprod\NDA205831\0065\m5\datasets\rp-bp-ef003

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[2] The submission is located at: \\Cdsesub1\evsprod\IND104624\0035\m5\53-clin-stud-rep\535-rep-effic-safety-stud\adhd\5351-stud-rep-contr\stf-ef003-protocol-amendxml

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The final version of the protocol of Study EF-003, Protocol Version 2.0 Final dated 15 February 2018, was included in the current NDA Supplement application. The applicant submitted SAP Version 1.1 Draft 2 on October 18, 2016, SAP Version 1.1 Final on November 3, 2017, SAP Version 1.2 Final on November 7, 2017, and SAP Version 2.0 Final on February 26, 2018. The statistical review was performed on SAP Version 1.1 Draft 2, and statistical comments were conveyed to the applicant. The SAP versions later submitted did not have major changes, and thus no further statistical comments were communicated to the sponsor.

This reviewer confirmed that the applicant's primary efficacy analysis may be reproduced from the original data source (CDISC SDTM data). The analysis datasets are consistent with the study database data.

However, during the review, it was found that an SDTM dataset and an analysis dataset for ADHD-RS-IV total score and CGI-Improvement score were not given correct visit information. Although the number of subjects with both the first and second visit assessments was 59 and the remaining 30 subjects had the first visit efficacy assessment alone, all randomized subjects but two (i.e., 88 subjects) were recorded as a 2-Week randomized phase completer and their primary endpoint efficacy data were recorded as those of Visit 15 (Primary Endpoint) assessment. The FDA review team discovered that this incorrect information had been recorded in the case report forms (CRFs), which created great confusion in the agency's efficacy and safety review activities.

3.2 Evaluation of Efficacy

3.2.1 Study Design (Study EF-003)

Primary Objective: The primary objective of this study was to determine whether an optimal dose of Aptensio XR was associated with a significant reduction in ADHD symptoms compared with placebo in children ages 4 to under 6 years.

Study Design: The protocol defines the primary objective of Study EF-003 as determining whether an optimal dose of Aptensio XR was associated with a significant reduction in ADHD symptoms compared with placebo in children ages 4 to under 6 years. The applicant designed Study EF-003 as a six-week open-label (OL) treatment phase allowed for dose optimization, followed by a 2-week double-blind (DB) treatment phase in which subjects were randomized to receive their optimal dose of Aptensio XR or placebo.

**Reviewer's Note on the overall design:** As the Agency recommended in WR dated 11 May 2016, the primary objective may be achieved with a randomized, double-blind, placebo-controlled trial with a recommended duration of at least 6 weeks in preschool-aged children (ages 4 and 5 years), with a flexible/optimal dosing scheme. However, the Applicant stayed with the open label enrichment design, and the study population of Study EF-003 as an enriched (responder) population for two weeks post Open Label dose optimization.

Study Population: Male and female children ages 4 years, 0 months to 5 years, 8 months (inclusive) with a diagnosis of ADHD (combined, inattentive or hyperactive/impulsive presentation) based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria were enrolled.

Study Site: Eleven clinical sites participated in the study. Up to 150 subjects were planned to be enrolled in RP-BP-EF003 to allow for subjects who either improved significantly during the behavior parent training phase (hence not requiring pharmacological treatment and withdrawn from the study) or early terminated.

Study Phases: The study comprised of six sequential phases. Once 74 subjects had completed the DB phase, no additional subjects were to be enrolled. Subjects who were already enrolled at that time were permitted to continue and complete their participation in the study. The description of the phases is summarized in Table 2 (See also Figure 1).

Sample Size Calculation: The applicant described the sample size calculation as follows: Assuming a mean change from baseline in ADHD-RS-IV total score of +1.5 points in the optimal Aptensio XR dose (a conservative estimate since, as noted above, the data for RP-BP-EF-001 indicate that with continued treatment the mean ADHD-RS-IV total score decreased during the double-blind phase) and +10 points in the placebo group, and assuming a standard deviation of 11 for the mean change in either group (since the preschool population may be more variable than children and adolescents), if 74 subjects (37 per treatment group) complete the double-blind parallel treatment phase, study RP-BP-EF003 would have 90% power to detect a treatment difference (active group mean change from baseline minus placebo group mean change from baseline) of -8.5 total score points in ADHD-RS-IV total score at a 2-sided significance level of 0.05. This sample size determination is based on a two-sample t-test.

Figure 1: Study Design (Study EF-003)
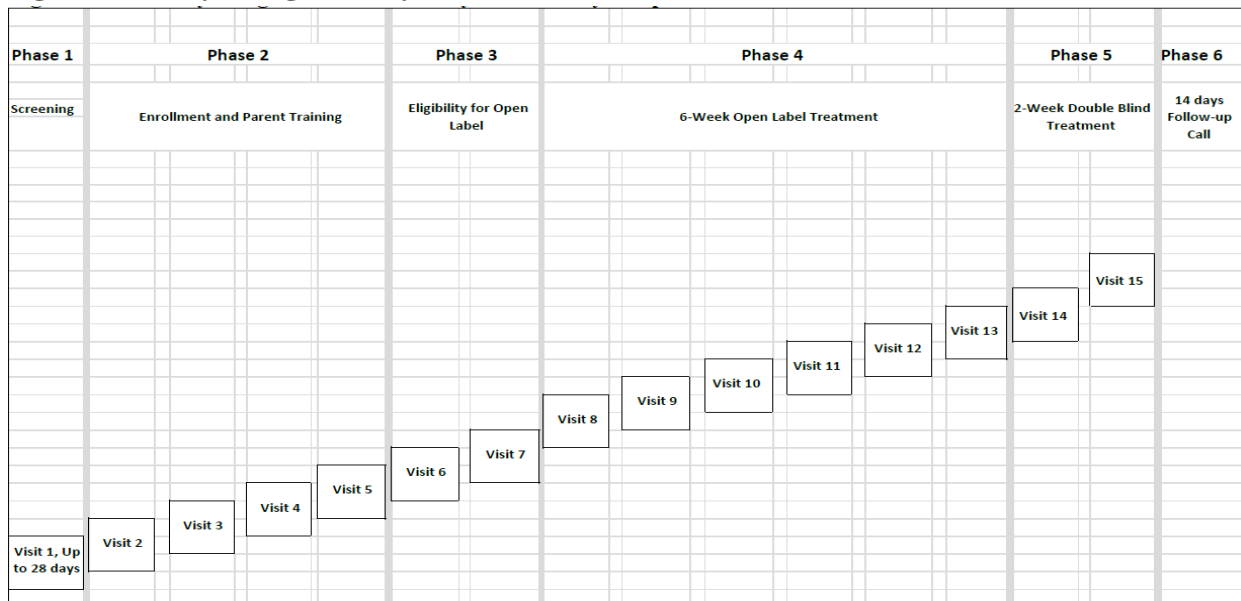
Note: Subjects could enter an OL Safety Study if they completed Visit 15 procedures. Subjects continuing in the OL Safety Study did not enter Phase 6.
Source: Figure 2 of Study Report (page 37)

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Table 2: Important Information of Phases of Study EF-003

Phase 1	**Screening phase of up to 4 weeks** (inclusion & exclusion criteria), which included, if applicable, washout of any prior ADHD-related medication
Phase 2	**4-week enrollment and behavior parent training phase:** The purpose of this study phase was to assess whether non-pharmacological intervention was efficacious prior to the initiation of study medication. Subjects for whom behavior parent training was deemed to provide adequate management of their ADHD symptoms were excluded from the study at the end of the behavioral management training and, therefore, not receive any study medication.
Phase 3	**2-week phase to determine eligibility for the OL phase** <u>At Visit 6</u>, clinical status (including AEs) was assessed, and ADHD-RS-IV, CGI-S, and CGI-I instruments were administered. Criteria to permit continuation to the OL phase were <30% improvement in ADHD-RS-IV (Preschool Version) score (versus screening), and a CGI-I score of $\geq$3 (minimally improved or less). <u>At Visit 7</u>, subjects were required to still meet the ADHD-RS-IV eligibility criteria. Subjects who continued to meet study eligibility requirements were permitted to transition to the OL treatment phase. Study drug was subsequently dispensed, and participants were scheduled for their next visit.
Phase 4	**6-week OL dose titration phase** <u>First Dosing</u>: Subjects started Aptensio XR (10 mg) on the morning immediately following Visit 7. <u>At subsequent weekly visits (Visits 8 to 13)</u>, the previous dose strength was either maintained, decreased, or increased, until an optimal dose or the maximum allowed dose of 40 mg was reached. The ADHD-RS-IV rating scale was used to determine the optimal dose. The optimal dose was defined as the dose associated with a reduction of ADHD symptoms of at least 30% versus Visit 7, and a CGI-I score of "much improved" or "very much improved" compared to Visit 7 with tolerable side effects.
Phase 5	**2-week DB phase for Aptensio XR responders** Subjects who have $\geq$30% response on the ADHD-RS-IV and a CGI of "much improved" or "very much improved" at the end of Visit 13 will enter the two-week parallel double-blind phase where they will be randomized to receive their best optimal dose of Aptensio XR or placebo. Subjects who have a $\geq$50% worsening of symptoms on the ADHD-RS-IV from Visit 13 and a CGI-I of 6 or 7 (much worse or very much worse) at Visit 14 will be eligible to discontinue the double-blind phase and enter the open-label extension study at investigator discretion after completing end of study (Visit 15) procedures.
Phase 6	**Follow-up phone call:** 2 weeks after study completion or early discontinuation to assess for ongoing adverse events (AEs) and concomitant medications

[Source: Study EF-003 study protocol]

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3.2.2 Statistical Methodologies

Applicant's Prespecified Statistical Method for Primary Efficacy Evaluation

1. **Null and Alternative Hypotheses:** The applicant specified the test hypotheses as follows: The null hypothesis associated with the primary efficacy endpoint is that during the Double-blind Treatment (Phase 5), the mean change from baseline (Visit 13) in ADHD-RS-IV total score at Visit 15 does not differ between the two treatment arms, Aptensio XR® and placebo, tested against the alternative hypothesis that the mean change from baseline in ADHD-RS-IV total score at Visit 15 is different between the Aptensio XR® treatment arm and the placebo treatment arm.

2. **Primary Analysis Model:** The null hypothesis will be tested using a two-way ANOVA. The ANOVA model will have two fixed factors, one for treatment group and one for investigative site; the dependent variable is the change from baseline in ADHD-RS-IV total score; the change score will be calculated as Visit 15 total score minus Visit 13 (baseline) total score. Treatment will have two levels: Aptensio XR or placebo. Sites with fewer than 10 subjects in the analysis population will be combined into a single site 99 for the analysis. The model will include a term for treatment by site interaction.

3. **Primary Efficacy Endpoint and Evaluation:** The primary endpoint is the change in a subject's ADHD Rating Scale – 4th Edition (ADHD-RS-IV) total score at Visit 15 compared to baseline (where the baseline value was the ADHD-RS-IV total score at Visit 13). Visit 13 is the end of the Open-Label Phase (Phase 4) of the study and Visit 15 is the end of the Double-Blind Phase (Phase 5). The primary efficacy evaluation is based on the difference (Aptensio XR minus placebo) in least squares mean estimates of the change from baseline score, obtained from the ANOVA application.

4. **Analysis Set for Primary Efficacy Evaluation:** The primary analysis will be conducted for the ITT-E population, which is defined as the set of all subjects in the ITT population who complete ADHDRS- IV assessments at the end of the open-label phase (Visit 13) (i.e., Double Blind phase baseline) and have at least one post-baseline ADHD-RS-IV assessment.

5. **Sensitivity Analysis Plan for Primary Efficacy Evaluation:** In order to assess the sensitivity of the primary analysis to missing values of the primary endpoint, the primary analysis will be repeated in the ITT-E population in two ways using last observation carried forward (LOCF), where the last non-missing value of the ADHD-RS-IV total score obtained prior to the missing value is imputed for the missing value: (1) missing values of ADHD-RS-IV total scores post baseline will be imputed using LOCF; (2) missing values of ADHD-RS-IV total scores post baseline will be imputed by using the baseline score plus 10 points (the assumed minimum value of a clinically significant change in ADHD-RS-IV total score). In addition, multiple imputation, assuming missing values are missing at random (MAR), will be employed to generate imputed values of missing post-baseline ADHD-RS-IV total scores using the fully conditional specification (FCS) method in SAS PROC MI to generate 10 complete data sets, which in turn are

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analyzed by a linear mixed-effects model analysis, and the analysis results combined via SAS PROC MIANALYZE for final inference.

Reviewer's Note on Applicant's Primary Efficacy Analysis Model

The Applicant's pre-specified primary analysis model had factors of Treatment, Study Site and their interaction. Including the interaction in the primary analysis model may not be appropriate.

Reviewer's Note on Handling Missing Data

The SAP did not specify a plan to handle missing Visit 15 Primary Efficacy data that may be caused by the protocol discontinuation scheme. Visit 15 is scheduled as the end of the 2-week randomized treatment period. The discontinuation eligibility assessment was scheduled at Visit 14, one week after the randomization and led to many discontinued subjects with no Visit 15 efficacy data. During the IND stage, we asked the Applicant to clarify the potential issue of this missing data, but no clarification was made. The final SAP does not address the issue, either. During the NDA review, the reviewer discovered that Visit 14 ADHD-RS-IV total score data of discontinued subjects were recorded as Visit 15 data in the case report forms (CRFs) and the SDTM data. This made the Applicant's primary analysis to look as if the primary efficacy data consisted of Visit 15 data alone. The Applicant's analysis may be analytically equivalent to an analysis based on LOCF imputed data.

Reviewer's Note on Proposed Sensitivity Analysis Plan

(1) LOCF: Discontinuations were based on worsened results in ADHD-RS-IV total score at Visit 14. With the LOCF imputation, the imputed missing observations of Visit 15 would have the same mean parameter as those of Visit 14. Unless the equality of mean parameters at Visits 14 and 15 is assumed, even though there would be a positive correlation between the two observations (at Visits 14 and 15), a bias will be induced.

(2) Imputing a missing observation by an addition of 10 points to the baseline score may not be meaningful.

Note: Additionally, regarding (1) and (2), it is noted that per ICH E9, a single value imputation is not recommended.

3.2.3 Study Implementation: Randomization and Discontinuation

3.2.3.1 Randomization Eligibility Assessment

The Randomization Criteria base on ADHD-RS-IV total score and CGI-I assessment was planned at the end of Open Label (OL) phase, Visit 13. Visit 7 (the pre-dose visit (end of OL phase)) was the baseline visit of the assessment. Out of 92 OL phase completers, 2 subjects discontinued, while 90 subjects continued into Double Blind phase, which may suggest that the Randomization Criteria assessment was not performed in accordance with the plan pre-specified in the study protocol. As seen in

Figure 2, 13 subjects were randomized without meeting the Randomization Criteria. One of the 77 Open Label completers discontinued and had no efficacy measurements in the randomized phase, and thus the set of 76 subjects would provide the pre-specified efficacy data consisting of responders, those who are to be evaluated for the primary efficacy. This number matches that of the sponsor's re-analysis.

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Figure 2: Assessment of Randomization Eligibility
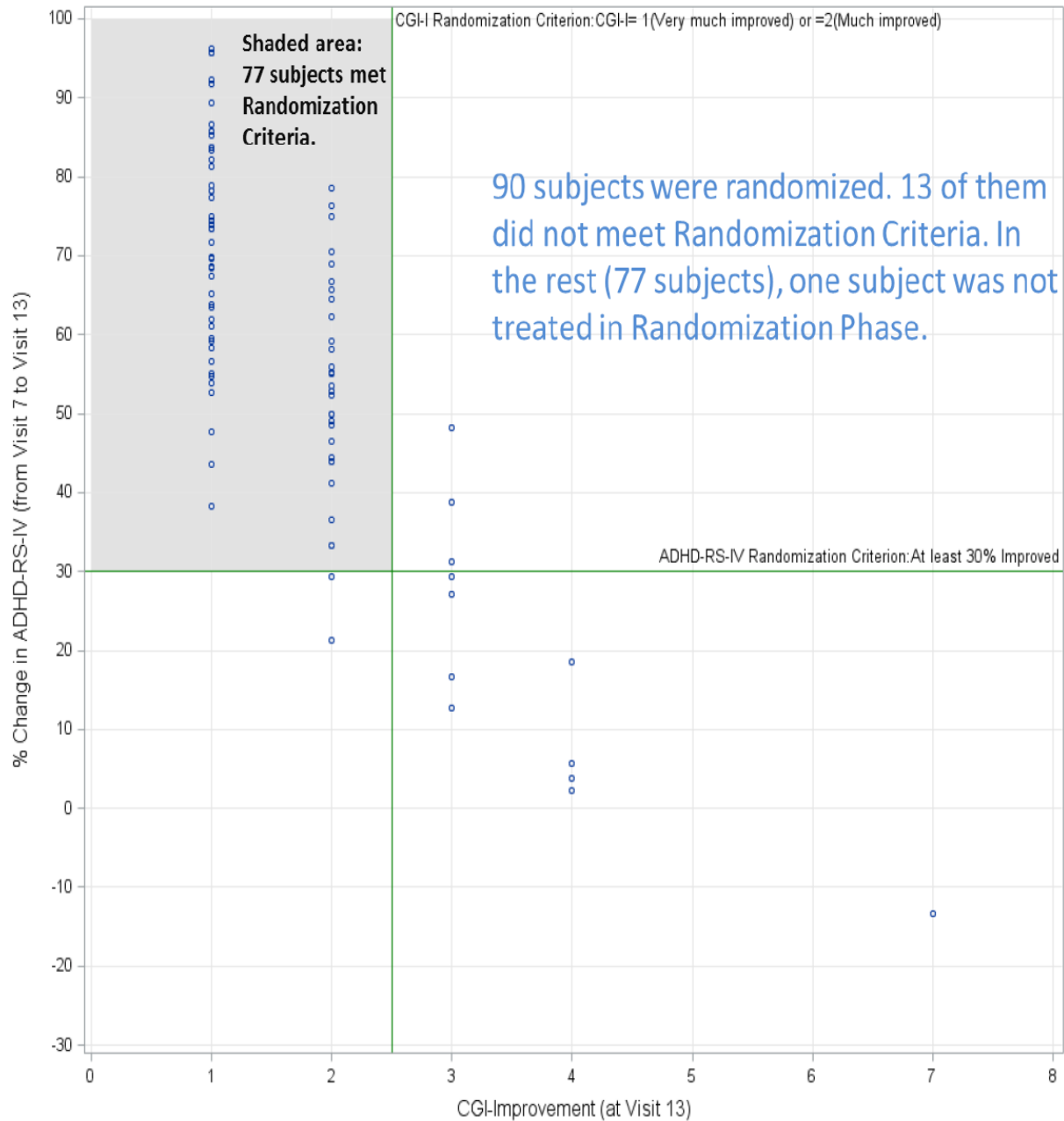
Note: The shaded area represents subjects (77 subjects) who met Randomization Criteria, defined as meeting two criteria (CGI-I = 'Very much improved' or 'Much improved' AND at least 30% improved in ADHD-RS-IV total score).
[Source: Reviewer's analysis]

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Reviewer's Note on Applicant's implemented assessment of Randomization Eligibility Criteria

On November 2, 2018, the applicant submitted an amendment, titled Note Regarding RP-BP-EF003 Randomization Eligibility[3]. According to the submitted document, the applicant had randomized 90 subjects (almost all Open Label phase completers) to the DB phase, but later found that *14 of the randomized subjects did not meet Randomization Criteria, consisting of a reduction of ADHD symptoms (at least 30% decrease) from Visit 7 and CGI-I score of "much improved" or "very much improved" compared to Visit 7*.

Reviewer's Note on Applicant's Re-analysis of Primary Efficacy based on a set of subjects who met Randomization Eligibility Criteria

In the submitted amended re-analysis, the applicant claims: *The re-analysis of the primary endpoint demonstrates that the removal of 14 subjects included in the original analysis who were not eligible for randomization does not affect the efficacy conclusion.*

This reviewer confirmed the analysis provided in the amendment submission may be reproduced from the submitted data. In the reviewer's analysis, the number of the randomized subjects who did not meet the randomization eligibility criteria was 13, as seen in Figure 3.

It may not be sensible to conclude that "the removal of 14 subjects included in the original analysis who were not eligible for randomization does not affect the efficacy conclusion". Since the Applicant's "14" incorrectly randomized subjects are removed from the analysis, the re-analysis may not be considered a randomization-based analysis. The efficacy data of the subset of a randomized set does not provide a basis for an analysis of the randomized subject set of the intent-to-treat population.

3.2.3.2   Discontinuation Eligibility Assessment

The Applicant's study report states that only three subjects discontinued from the 2-Week randomized double-blind phase. In fact, however, 29 subjects were discontinued at their first post-baseline visit (Visit 14) and they did not have their efficacy assessment at Visit 15 (Primary Endpoint). The Applicant's assessment of Discontinuation Eligibility (Table 2), which was scheduled at Week 1 visit (Visit 14) by protocol, were not performed in compliance with the pre-specified eligibility criteria.

As shown in Table 3, during the 2-Week randomized double-blind phase, 29 of the 90 randomized subjects were discontinued, but 6 of the 29 discontinued subjects were not eligible for a discontinuation (although subjects might discontinue themselves for any reason), while 27 subjects were eligible for a discontinuation, but 23 of them were discontinued.

shows plots of each subject's fold change from baseline in ADHD-RS-total score and CGI-Improvement score at the first post-baseline visit. Subjects plotted in the shaded are those who met the discontinuation eligibility criteria. The Applicant specified Discontinuation Eligibility Criteria as follows: At Visit 14, a subject meets the two conditions of ≥50% worsening of

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[3] The location of the submission is \\CDSESUB1\evsprod\NDA205831\0069

symptoms on the ADHD-RS-IV from Visit 13 AND a CGI-I score of 6 or 7 (much worse or very much worse). This figure visually shows that 27 subjects met the criteria. Of these 27 subjects, 23 were discontinued and thus 4 were not. Of the 89 randomized and treated subjects, 62 were not eligible for discontinuation (refer to Table 3).

Additional figures (Figure 4 for Aptensio XR and Figure 5 for Placebo) provide a visual description of how discontinuations were implemented in terms of ADHD-RS-IV total score. The line of the figures labelled as "50% worsened" distinguish subjects who are eligible or not eligible for a discontinuation based on one of the discontinuation eligibility criteria, ADHD-RS-IV total score. All subjects above this line are eligible for a discontinuation in terms of the criterion of ADHD-RS-IV total score, because their score at the first post-baseline visit got worsened by 50% from Baseline visit. A visual inspection of the figures shows that a few subjects who were not eligible (qualified for a discontinuation) were discontinued, and a few qualified subjects were not discontinued.

As seen in Figure 4 and Figure 5, six subjects (2 in Aptensio XR and 4 in Placebo) were not qualified (eligible) for a discontinuation but were discontinued, while four placebo subjects were eligible for a discontinuation but were not discontinued.

Table 3: Discontinued Subjects vs Discontinuation Eligibility

	Not discontinued			Discontinued			Total
	Aptensio	**Placebo**	**Total**	**Aptensio**	**Placebo**	**Total**	
Eligible for Discontinuation	0	4	4	7	16	23	27
Not eligible for Discontinuation	30	26	56	2	4	6	62
#Randomized and treated Subjects (N=89)	30	30	60	9	20	29	89

[Source: Reviewer's analysis] Note: One of the 90 randomized subjects was not treated.

Reviewer's Note on Discontinuations

- A large proportion of subjects were discontinued based on discontinuation eligibility criteria. This may undermine the fair comparison background the randomization prepares, thus causing the pre-specified primary efficacy analysis evaluation to be inappropriate for the primary efficacy objective. As mentioned above, not all discontinuation eligible subjects were discontinued, and some discontinued subjects were not eligible for a discontinuation.
- It appears that discontinuation eligibility assessment was mainly planned to rescue placebo subjects who greatly worsened one week after the switching from Aptensio XR to placebo. The discontinued placebo subjects were eligible to enroll in the extension study, so they would get back on Aptensio XR treatment. It is noteworthy that Aptensio XR subjects also showed a great worsened efficacy result about one week after the randomization.

Figure 3: Assessment of Discontinuation Eligibility (ADHS-RS-IV total score and CGI-I)

Checking ADHD-RS-IV and CGI-Improvement for Discontinuation Criteria at the first post-baseline visit

Randomized Treatment Group (N=89)   △ Aptensio (N=39)   △ Placebo (N=50)

Fold Change (0.5 means 50% worsening)

CGI-Improvement

1) Discontinuation Criteria at Visit 14:(1)50% worsening in ADHD-RS-IV total score from Baseline and (2) CGI-Improvement score of "Very Much Worse" or "Much Worse" (Shaded area)
2) This figure shows that 27 subjects met Discontinuation Criteria. In fact, 23 of the 27 subjects were discontinued. Because 29 subjects were discontinued at the first post-baseline visit, 6 of the 29 discontinued subjects did not meet the criteria.
3) Two subjects are not included in the figure (Both worsened by 2000%, but their CGI-Improvement score was "No change".
4) When multiple subjects had an identical pair of values, the numbers of subjects are shown in the figure.

[Source: Reviewer's analysis]

Figure 4: ADHD-RS-IV total score at Baseline and First Post-Baseline Visit (Aptensio XR)
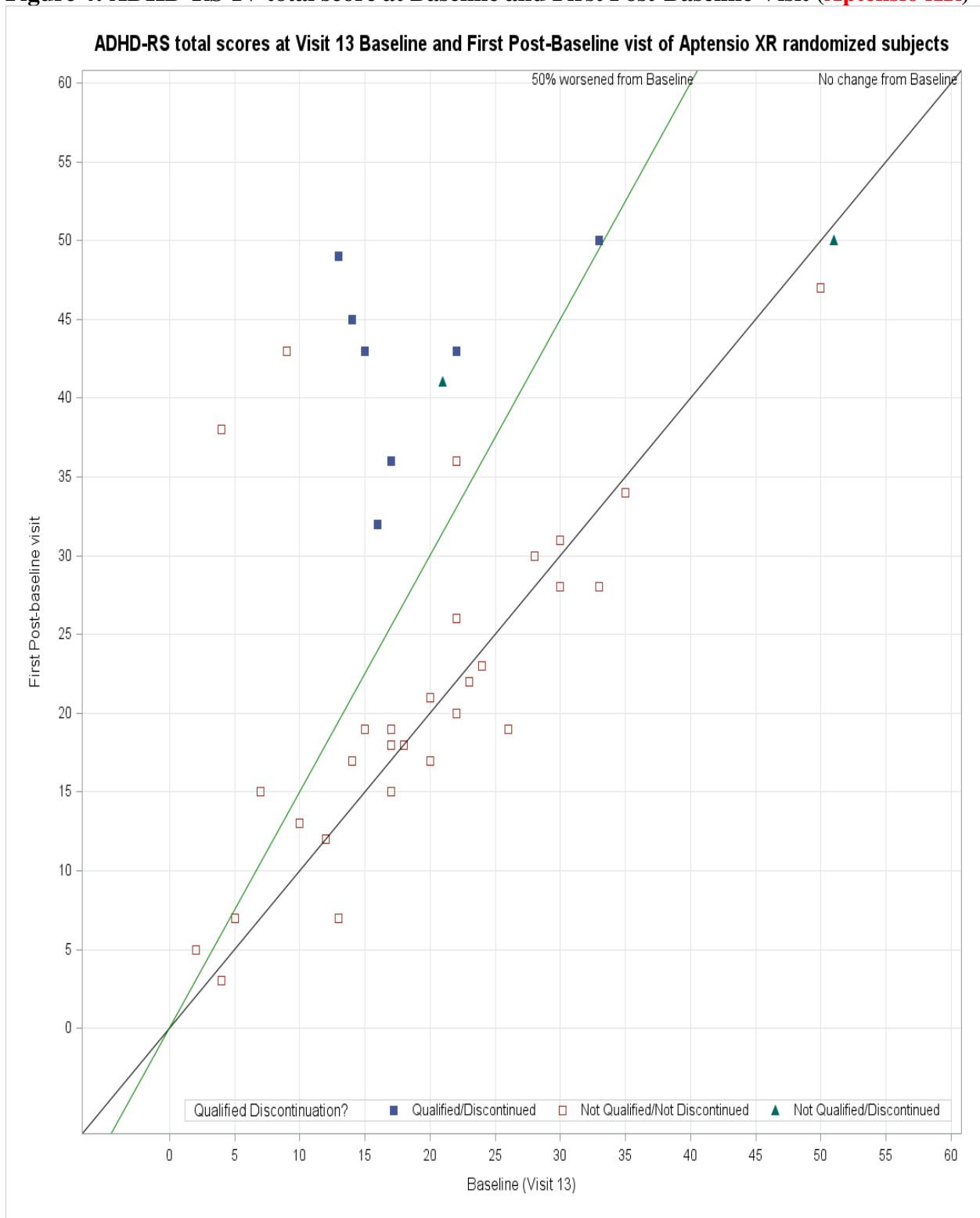
ADHD-RS total scores at Visit 13 Baseline and First Post-Baseline vist of Aptensio XR randomized subjects

Note: Qualified means Eligible for discontinuation due to worsened symptoms
[Source: Review's analysis]

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Figure 5: ADHD-RS-IV total score at Baseline and First Post-Baseline Visit (Placebo)
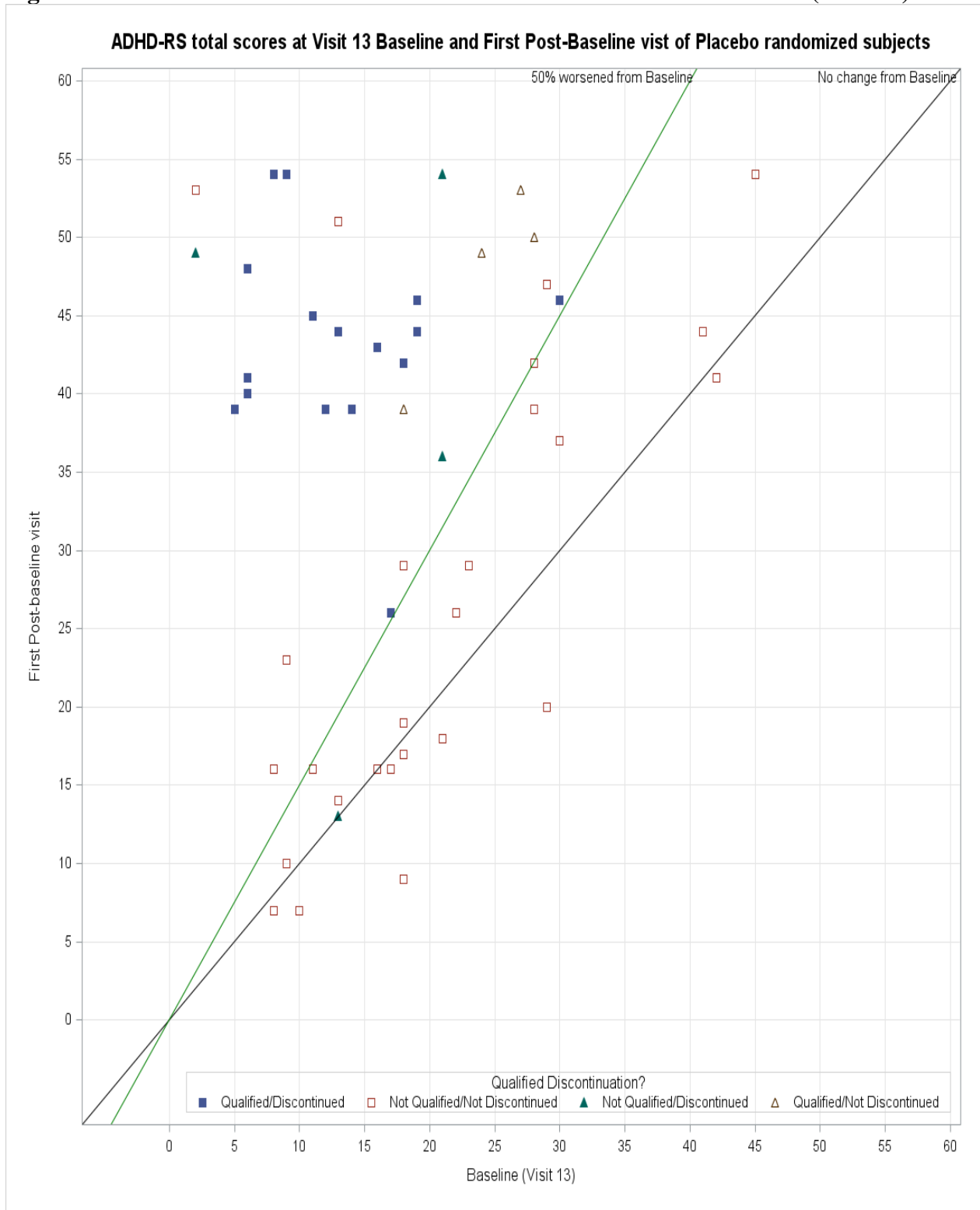
ADHD-RS total scores at Visit 13 Baseline and First Post-Baseline vist of Placebo randomized subjects

Note: Qualified means Eligible for discontinuation due to worsened symptoms
 [Source: Reviewer's analysis]

3.2.4 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

The applicant reports the patient disposition data as follows:

One hundred and thirty-two were enrolled out of 194 screened subjects. Of the 132 enrolled subjects, 119 entered the OL Treatment Phase and 90 were randomized to the DB Treatment Phase. In total, 86 subjects completed the study, 104 subjects discontinued prior to randomization (including 36 subjects who failed screening) and 4 subjects discontinued following randomization.

Of the 119 subjects who enrolled in the OL phase, 29 subjects discontinued from treatment. Of the 90 subjects who enrolled in the DB phase, 4 subjects discontinued from treatment. This included 2 subjects in the Aptensio XR® group and 2 subjects in the placebo group. Two subjects, one in the placebo group and one in the Aptensio XR® group, were discontinued due to protocol deviations, one subject was lost to follow-up and was not assigned a treatment group, and one subject in the placebo group was withdrawn due to non-compliance with protocol and drug administration. (Refer to Table 4 and Figure 6).

Table 4: Applicant's Subject Disposition

	Aptensio XR®	Placebo	Overall
Number of Subjects Screened	-	-	194
Number of Subjects Who Failed Screening	-	-	36
Number of Subjects Enrolled	-	-	158
Number (%) of Subjects Who Bypassed Parent Training Phase	-	-	20 (12.7)
Number (%) of Enrolled Subjects Who Entered Parent Training Phase	-	-	132 (83.5)
Number (%) of Subjects Who Completed Parent Training Phase but Were Not Eligible for Open Label Treatment Phase	-	-	8 (5.1)
Number (%) of Subjects Who Discontinued prior to Open Label Treatment Phase	-	-	30 (19.0)
Number (%) of Subjects Eligible for Open Label Treatment Phase	-	-	128 (81.0)
Number (%) of Subjects Who Did not Enter Open Label Treatment Phase	-	-	9 (5.7)
Number (%) of Subjects in Open Label Treatment Phase	119 (75.3)	-	119 (75.3)
Number (%) of Subjects Randomized to Double-blind Treatment Phase	40 (25.3)	50 (31.6)	90 (57.0)
Number (%) of Subjects Who Completed the Study	38 (24.1)	48 (30.4)	86 (54.4)
Number (%) of Subjects Discontinued from the Study Before Randomization	29 (18.4)	-	104 (65.8)
Number (%) of Subjects Discontinued from the Study After Randomization	2 (1.3)	2 (1.3)	4 (2.5)

Note: The Consented population = all subjects who signed informed consent. Percentages are based on the number of subjects in the Enrolled population. (Enrolled Population = all subjects who were not screen failures.)
[Source: Table 8 of Study Report (page 63-64)]

Figure 6: Subject Disposition
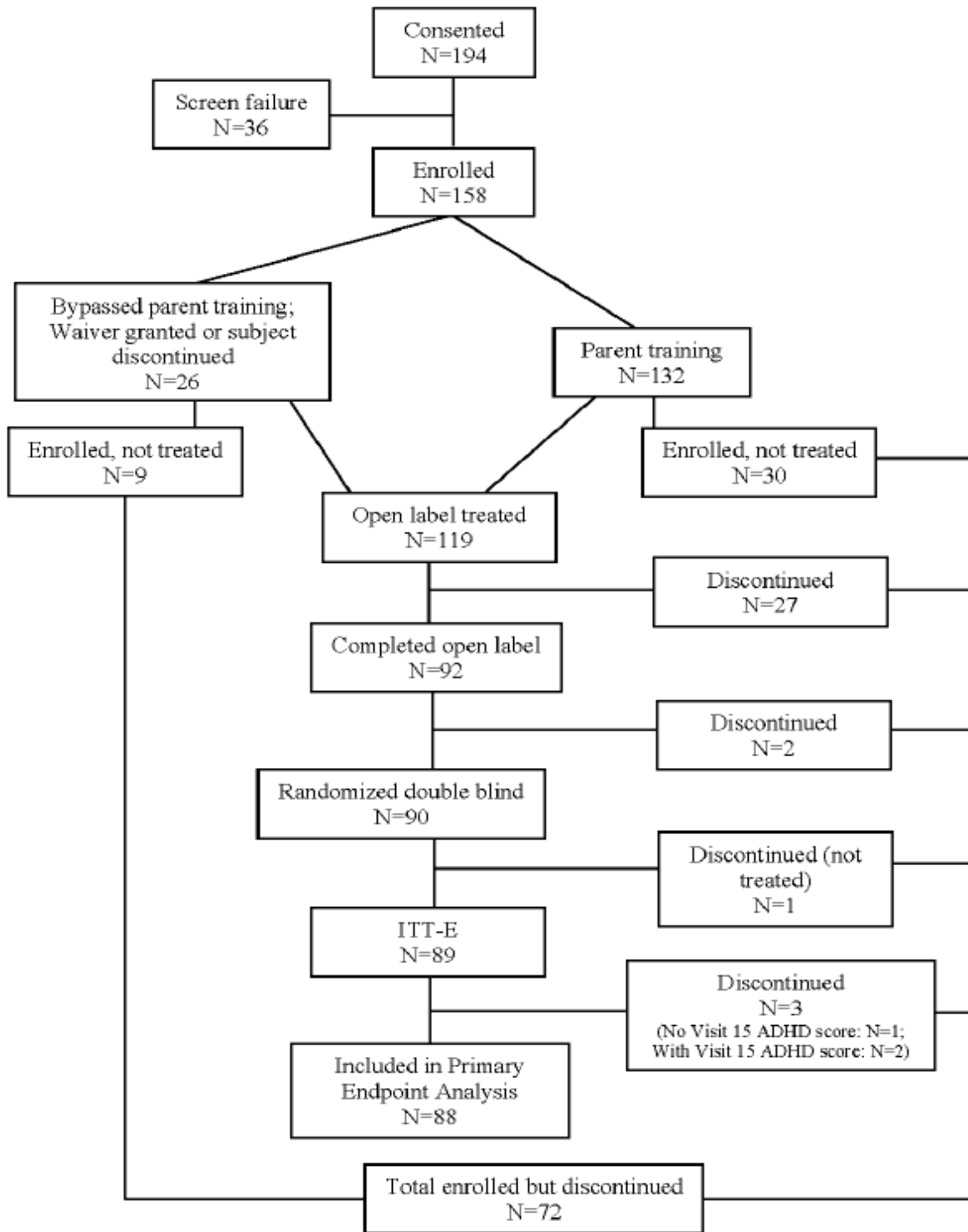
[Source: Figure 3 of Study Report (page 65)]

**Reviewer's Note on Applicant's Patient Disposition Report**: From the perspectives of the primary efficacy evaluation, the subject disposition information of the above quoted description and of Table 4 and Figure 6 may be misleading. Four subjects are recorded as discontinued subjects in Table 4. One of them did not take the assigned treatment. Three are recorded as a discontinued subject, but they had their ADHD-RS-IV total score records for the post-baseline two visits. In fact, 29 subjects (20 in Placebo and 9 in Aptensio XR) were discontinued at the first visit, and without completing their second efficacy assessment, they were enrolled into the extension study (EF-004). The efficacy data obtained at the first post-baseline visit were recorded as the data of the second post-baseline visit.

Demographics (Screening Visit)

Demographics Baseline Characteristics are shown in Table 5.

Table 5: Baseline Characteristics (Demographics: Age, Gender, Race)

	ITT Population			Enrolled Population
	Aptensio XR® (N=40)	Placebo (N=50)	Overall (N=90)	Overall (N=158)
Age (months)				
n	40	50	90	158
Mean	58.5	59.2	58.9	58.8
SD	5.59	6.42	6.05	6.24
Median (Q1, Q3)	57.0 (55.0, 63.5)	59.0 (54.0, 64.0)	59.0 (55.0, 64.0)	58.5 (53.0, 64.0)
Minimum	49	48	48	48
Maximum	69	70	70	70
Gender, n (%)				
Male	29 (72.5)	39 (78.0)	68 (75.6)	121 (76.6)
Female	11 (27.5)	11 (22.0)	22 (24.4)	37 (23.4)
Race, n (%)				
White/Caucasian	24 (60.0)	30 (60.0)	54 (60.0)	82 (51.9)
Black or African American	15 (37.5)	18 (36.0)	33 (36.7)	70 (44.3)
Asian	0	1 (2.0)	1 (1.1)	1 (0.6)
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Other				
1/2 Black & 1/2 White	0	1 (2.0)	1 (1.1)	1 (0.6)
Biracial	1 (2.5)	0	1 (1.1)	3 (1.9)
Two Or More Races				1 (0.6)

[Source: Study Report (Table 14.1.6.1 and Table 14.1.6.2)]

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ADHD-RS-IV total score Baseline (Visit 13) Characteristics
The baseline measurements of ADHD-RS-IV total score are provided for both randomized subjects and re-analysis (responder) subjects in Table 6.

Table 6: Baseline ADHD-RS-IV total score

		N	Mean	Standard Deviation	Minimum	Maximum
Randomized Subjects	**Aptensio XR**	39	19.5	11.06	2	51
	Placebo	50	17.8	9.93	2	45
Responder Subjects	**Aptensio XR**	32	16.1	7.55	2	33
	Placebo	44	15.3	7.38	2	30

N: Number of Subjects
[Source: Reviewer's analysis]

3.2.5 Results and Conclusions

3.2.5.1 Statistical and Data Issues in Applicant's Primary Efficacy Evaluation

Inappropriateness of pre-specified primary analysis to support the definition of the primary efficacy evaluation: The study protocol defines the primary efficacy objective as: to evaluate efficacy of Aptensio XR in its comparison with placebo based on the ADHD-RS-IV total score assessment at the 2-week randomized exposure, following a 6-week open label Aptensio XR treatment. However, 29 subjects were discontinued by the investigator due to worsened symptoms right after the first post-baseline assessment. The Applicant's primary analysis, which essentially imputed missing data using the last observed carried forward method does not seem to be appropriate.

Varied timings of ADHD-RS-IV total score assessments: As shown in
the first post-baseline visit data ranged from Day5 to Day22, while the second post-baseline visit data ranged from Day 9 to Day21. The numbers of days after randomization at the first and second post-baseline visits did not necessarily correspond to the design scheduled visit days (7 days and 14 days). Some subjects had their primary efficacy assessment a time that was very different from 2 weeks (14 days) although most subjects had the visits around the scheduled days.

Concern with duration of the DB phase: It may not be clear if an efficacy comparison between Aptensio XR and Placebo of the 2-week randomized, double-blind treatment duration was sufficiently long. As seen in Table 9, the standard deviations of ADHD-RS-IV total score at the two post-baseline visits of DB phase were relatively larger, in Placebo, than in OL phase.

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Reviewer's Note on Statistical and Data Issues in Applicant's Primary Efficacy Evaluation

- The study protocol defines the primary endpoint as change from baseline (Visit 13) to Visit 15 in ADHD-RS-IV total score (see 3.2.2). Visit 15, the second post-baseline visit, was scheduled at the end of the 2-week double-blind phase.

- Although the study report states that 86 subjects of the 90 randomized subjects completed the randomized DB phase, the study had more than 30% of discontinued subjects in terms of their efficacy assessments at the primary endpoint visit. The Applicant's primary analysis result alone might not sufficiently communicate efficacy information obtained in Study EF-003.

3.2.5.2 Applicant's Primary Efficacy Analysis

The applicant used an ANOVA with the treatment group, study site and a treatment by study site interaction for the primary analysis model. The primary efficacy endpoint was evaluated based on the difference between the two treatment groups (Aptensio XR vs Placebo) in the mean change from baseline (Visit 13) to Visit 15 endpoint. The applicant reports that the mean change in ADHD-RS-IV Total Score from Visit 13 to Visit 15 was statistically significantly greater in the placebo group versus the Aptensio XR group (p=0.002). This reviewer reproduced the result for validation, and it is provided in Table 7. In Figure 7, this reviewer provides the plots of mean ADHD-RS IV measurements by Visit (Screening, Visit 2-Visit 15) by Group (the set of subjects treated with Aptensio XR in the OL phase and Placebo in the DB phase versus the set of subjects treated with Aptensio XR in the OL phase and Aptensio XR in the DB phase). The plots are based on the Applicant's primary analysis set, whose endpoint included the records of discontinued subjects' ADHD-RS-IV total scores taken at the first post-baseline visit. Figure 7 shows a very different efficacy profile than Figure 8, which provides an efficacy profile with Visit 14 ADHD-RS-IV total scores of discontinued subjects as they were observed at Visit 14. In Figure 7, the mean ADHD-RS-IV total score at Visit 15 was worse than at Visit 14 for both treatment groups. On the other hand, in Figure 8, the mean score was better at Visit 15 than Visit 14 for both treatment groups. Those who got worsened in efficacy at Visit 14 were discontinued and had missing observations of their efficacy assessment at the second post-baseline visit (Visit 15). They may be likely to remain worse in symptoms at Visit 15.

Reviewer's Note on Applicant's Primary Efficacy Analysis
- The Applicant's primary efficacy analysis may not be useful for the labeling purpose. The applicant's primary analysis is indeed equivalent to an analysis based on the LOCF approach, which was proposed for a sensitivity analysis. The Applicant's pre-specified primary analysis might be meaningful if no discontinuations had occurred or a negligible number of subjects had discontinued.
- The Applicant's primary efficacy model may not be meaningful because it has a factor of Treatment/Study Site interaction. This is inadequate (see Reviewer's Note on Applicant's Primary Analysis Model in Section 3.2.2).

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Table 7: Applicant's Primary Efficacy Analysis Result (Randomized Subjects)
The first post-baseline visit (Visit 14) data of 29 discontinued subjects were recorded as the primary efficacy endpoint data (Visit 15) in CRFs, CDISC SDTM data and the efficacy analysis dataset.

ADHD-RS-IV Total Score	Change from Baseline* to Endpoint of 2-week Double-Blind Randomized Phase		
	ITT Analysis set of 90 randomized subjects**		
	Note 13 subjects who did not meet Randomization Criteria were mistakenly randomized		
	Aptensio XR N=39	Placebo N=50	Difference: Placebo-Aptensio XR (95% Confidence Interval) [p value]
Applicant's initial submission			
LS Mean Estimate (SE) (ANOVA; N=89)	5.7 (2.48)	16.9 (2.34)	-11.2 (-18.0, -4.4) [0.002]
Note: The model with factors of Treatment, Study Site and Treatment-Study Site interaction			

* Baseline visit is the last visit of 6-week Open Label Aptensio XR treated Phase. SE: Standard Error
** After randomization, one subject did not take the assigned treatment.
Note: Applicant's results were reproduced by this review for validation.
[Source: Reviewer's Replication of the Applicant's Pre-specified Primary Analysis]

Table 8: Applicant's Post Hoc Primary Efficacy Analysis (Responder Subjects)

ADHD-RS-IV Total Score	Change from Baseline* to Endpoint of 2-week Double-Blind Randomized Phase		
	Post Hoc Analysis set of 77 randomized subjects (subjects who met Randomization Criteria) **		
	Aptensio XR N=32	Placebo N=44	Difference: Placebo-Aptensio XR (95% Confidence Interval) [p value]
Applicant's re-submission			
LS Mean Estimate (SE) (ANOVA; N=76)	8.5 (2.56)	19.8 (2.21)	-11.3 (-18.0, -4.5) [0.001]
Note: The model with factors of Treatment alone (Study Site was removed because Study Site was found statistically non-significant)			

* Baseline visit is the last visit of 6-week Open Label Aptensio XR treated Phase. SE: Standard Error
** After randomization, one subject did not take the assigned treatment.
Note: Applicant's results were reproduced by this review for validation.
[Source: Reviewer's Replication of the Applicant's Re-submitted (*Post Hoc*) Primary Analysis]

3.2.5.2.1 Applicant's Resubmitted Re-analysis of Primary Efficacy

The Applicant states in the resubmission that: *Rhodes has undertaken a re-analysis of the study data for the 76 subjects in the ITT-E population who were eligible for randomization to the double-blind phase of the study. ... The re-analysis of the primary endpoint demonstrates that the removal of 14 subjects included in the original analysis who were not eligible for randomization does not affect the efficacy conclusion. Since the intent of the two eligibility criteria was to remove those subjects who were not responding to Aptensio XR from participation in the double-blind phase of the study, their inclusion in the analysis is in effect a more conservative analysis of subjects who completed the open-label portion of the study since not all non-responders were prevented from being randomized to the double-blind phase of the study as was the original intent of the study design.*

Reviewer's Note on Applicant's Resubmitted Primary Analysis: The statistical analysis provided in the resubmitted primary analysis may not be useful for the labeling purpose. See Reviewer's Note (Section 3.2.3.1).

Figure 7: Applicant's Efficacy data profiles: Mean ADHD-RS-IV total score by Visit

Note: The first post-baseline visit (Visit 14) data of 29 discontinued subjects were recorded as the primary efficacy endpoint data (Visit 15) in CRFs, CDISC SDTM data and the efficacy analysis dataset.
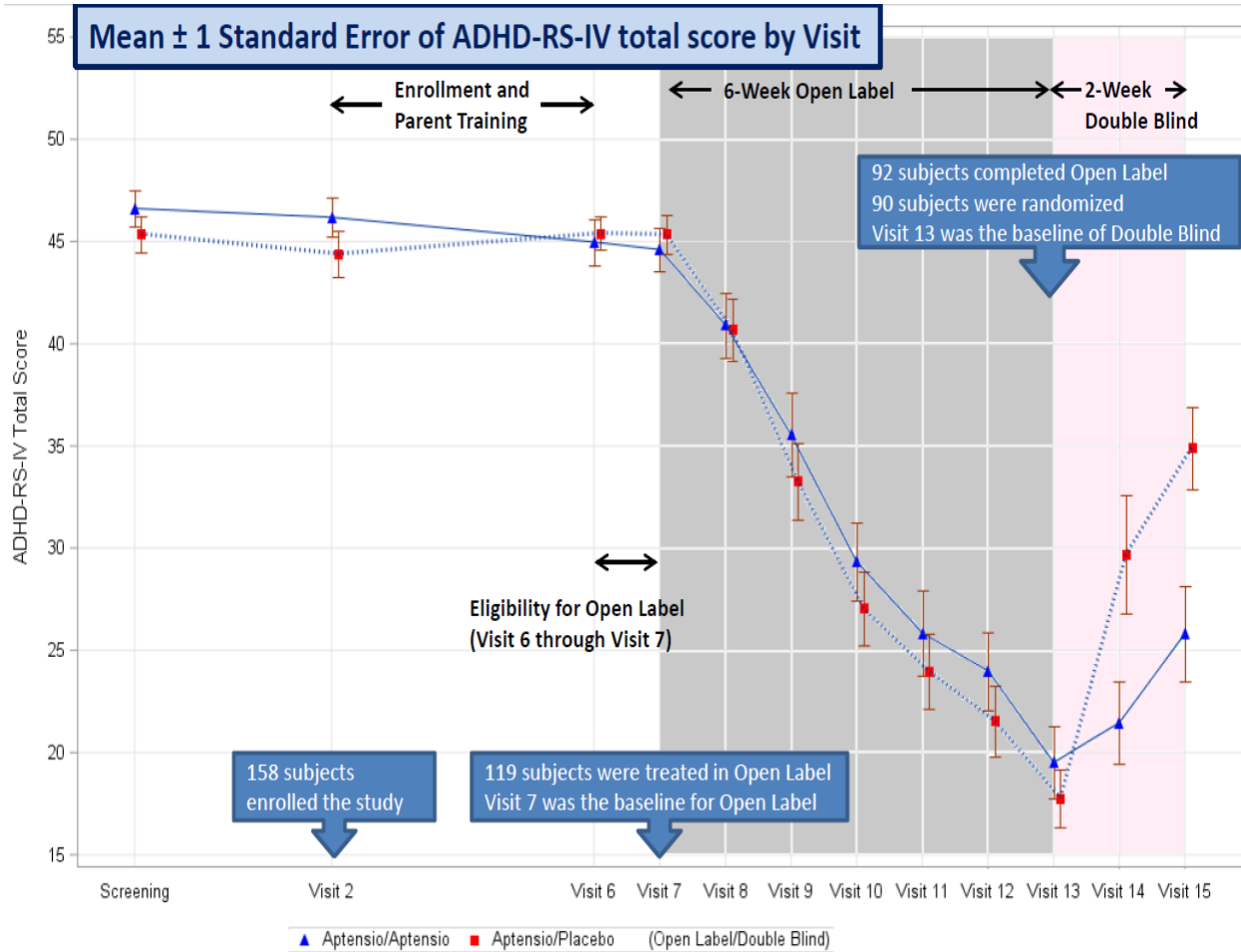
Note: Mean (Standard Error) are that of observed ADHD-RS-IV total scores.
[Source: Reviewer's analysis]

3.2.5.3 Reviewer's Analysis of Primary Efficacy Data

This reviewer provides a summary of descriptive statistics of the ADHD-RS-IV total scores.

The observed ADHD-RS-IV total score data (Table 9) suggest that at the two post-baseline visits, the placebo subtracted mean difference of Aptensio XR in ADHS-RS-IV total score was much the same, i.e., -8.4 (Visit 14) and -9.4 (Visit 15), respectively. However, this reviewer notes that a substantial number of placebo subjects who had worsened symptoms at Visit 14 were discontinued.

Table 9: Descriptive Statistics: ADHD-RS-IV total score by Visit (Study EF-003)

Study Phase		Descriptive Statistics in ADHD-RS-IV total score Study EF-003: Pre-Dose Phase, Open-Label Phase, Double-Blind Phase						
	VISIT	**Aptensio XR in DB phase**			**Placebo in DB phase**			**Mean Difference between Aptensio XR and Placebo**
		N	**Mean**	**SD**	**N**	**Mean**	**SD**	
Pre-Dose Phase	**Screening**	39	46.6	5.57	50	45.4	6.22	1.2
	Visit 2	32	46.2	5.44	39	44.4	6.92	1.8
	Visit 6	39	45.0	6.96	50	45.4	5.79	-0.4
6-Week Open-Label Phase (OL Aptensio XR)	**Visit 7**	39	44.6	6.82	50	45.4	6.66	-0.8
	Visit 8	39	40.9	9.97	50	40.7	10.83	0.2
	Visit 9	39	35.5	12.77	50	33.3	13.24	2.2
	Visit 10	39	29.3	11.84	50	27.1	12.63	2.2
	Visit 11	39	25.8	13.04	50	24.0	12.84	1.8
	Visit 12	39	24.0	11.92	50	21.6	12.28	2.4
2-Week Double-Blind Phase	**Visit 13**	39	19.5	11.06	50	17.8	9.93	1.7
	Visit 14	39	26.5	13.62	50	34.7	14.92	-8.4
	Visit 15	30	20.6	12.03	29	30.0	14.68	-9.4

Note: Randomization to Aptensio XR or Placebo occurred at Baseline (Visit 13). In Open-Label phase, all subjects were treated with Aptensio XR.
[Source: Review's analysis]

The discontinuation was mostly due to worsened conditions, and more placebo subjects were discontinued than Aptensio XR subjects (20 on placebo versus 9 on Aptensio XR). For placebo subjects, the observed difference between the two post-baseline visits may be related with the switching from Aptensio XR to placebo. However, as many as 9 Aptensio XR subjects got worsened from Visit 13 (baseline visit) to Visit 14 (the first post-baseline visit), in which they were on the same Aptensio XR dose as before entering the DB phase.

Figure 8 and Figure 9 visualize the impact of discontinuations at the first post-baseline visit on the mean profiles of ADHD-RS-IV total scores at the primary endpoint/second post-baseline visit (Visit 15). The mean ADHD-RS-IV total score improved (lowered) from Visit 14 (the first post-baseline visit) to Visit 15 in both Placebo and Aptensio XR. The removal of subjects who showed poor efficacy at the first post-baseline visit appears to have brought about a better average response at the primary efficacy endpoint visit. As seen in Table 9, the standard deviations of ADHD-RS-IV total score at the two post-baseline visits of DB phase were relatively larger, in Placebo, than in OL phase.

Table 10: Descriptive Statistics: Change from Baseline in ADHD-RS-IV total score by Visit

	VISIT	Aptensio XR in DB phase			Placebo in DB phase			Mean Difference between Aptensio XR and Placebo In change from baseline
		N	Mean	SD	N	Mean	SD	
2-Week Double-Blind Phase	Visit 14	39	7.0	12.2	50	16.9	16.2	-9.9
	Visit 15	30	2.0	9.0	29	9.3	14.8	-7.3

Note: Randomization to Aptensio XR or Placebo occurred at Baseline (Visit 13). In Open-Label phase, all subjects were treated with Aptensio XR.

**Table 11: Reviewer's Subject Disposition of Randomized Double-Blind Phase**

Number of Days from Randomization Baseline (Visit 13)	Randomized Subjects (N=89)						Subjects discontinued at the first post-baseline visit (N=29)		
	Total		Aptensio XR		Placebo		Total	Aptensio XR	Placebo
	1st Visit	2nd Visit	1st Visit	2nd Visit	1st Visit	2nd Visit			
5 (Day5)	5	0	0	0	5	0	4	0	4
6 (Day6)	3	0	2	0	1	0	1	0	1
7 (Day7: Visit 4)	16	0	6	0	10	0	4	2	2
8 (Day8)	47	0	24	0	23	0	12	5	7
9 (Day9)	9	1	5	0	4	1	4	1	3
10 (Day10)	2	0	1	0	1	0	2	1	1
11 (Day11)	3	1	1	0	2	1	0	0	0
12 (Day12)	2	1	0	1	2	0	1	0	1
13 (Day13)	1	2	0	2	1	0	0	0	0
14 (Day14: Visit 15)	0	13	0	6	0	7	0	0	0
15 (Day15)	0	28	0	15	0	13	0	0	0
16 (Day16)	0	6	0	3	0	3	0	0	0
17 (Day17)	0	3	0	2	0	1	0	0	0
18 (Day18)	0	1	0	0	0	1	0	0	0
19 (Day19)	0	1	0	0	0	1	0	0	0
20 (Day20)	0	1	0	0	0	1	0	0	0
21 (Day21)	0	1	0	1	0	0	0	0	0
22 (Day22)	1	0	0	0	1	0	1	0	1
Total	89	59	39	30	50*	29	29	9	20

*One subject was not given the assigned treatment
[Source: Reviewer's analysis]

The observed Change from baseline in ADHD-RS-IV total score data (Table 10) suggest that at the two post-baseline visits, the placebo subtracted mean difference of Aptensio XR in Change from baseline in ADHS-RS-IV total score was much the same, i.e., -9.9 (Visit 14) and -7.3 (Visit 15), respectively. However, this reviewer notes that these are raw means and a substantial number of placebo subjects who had worsened symptoms at Visit 14 were discontinued.

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Figure 8: Efficacy Profile (Individual and Mean) in ADHD-RS-IV total score by Randomized Treatment (Aptensio vs Placebo) in Study EF-003 (Pre-Dose/Open Label/Double-Blind phases)
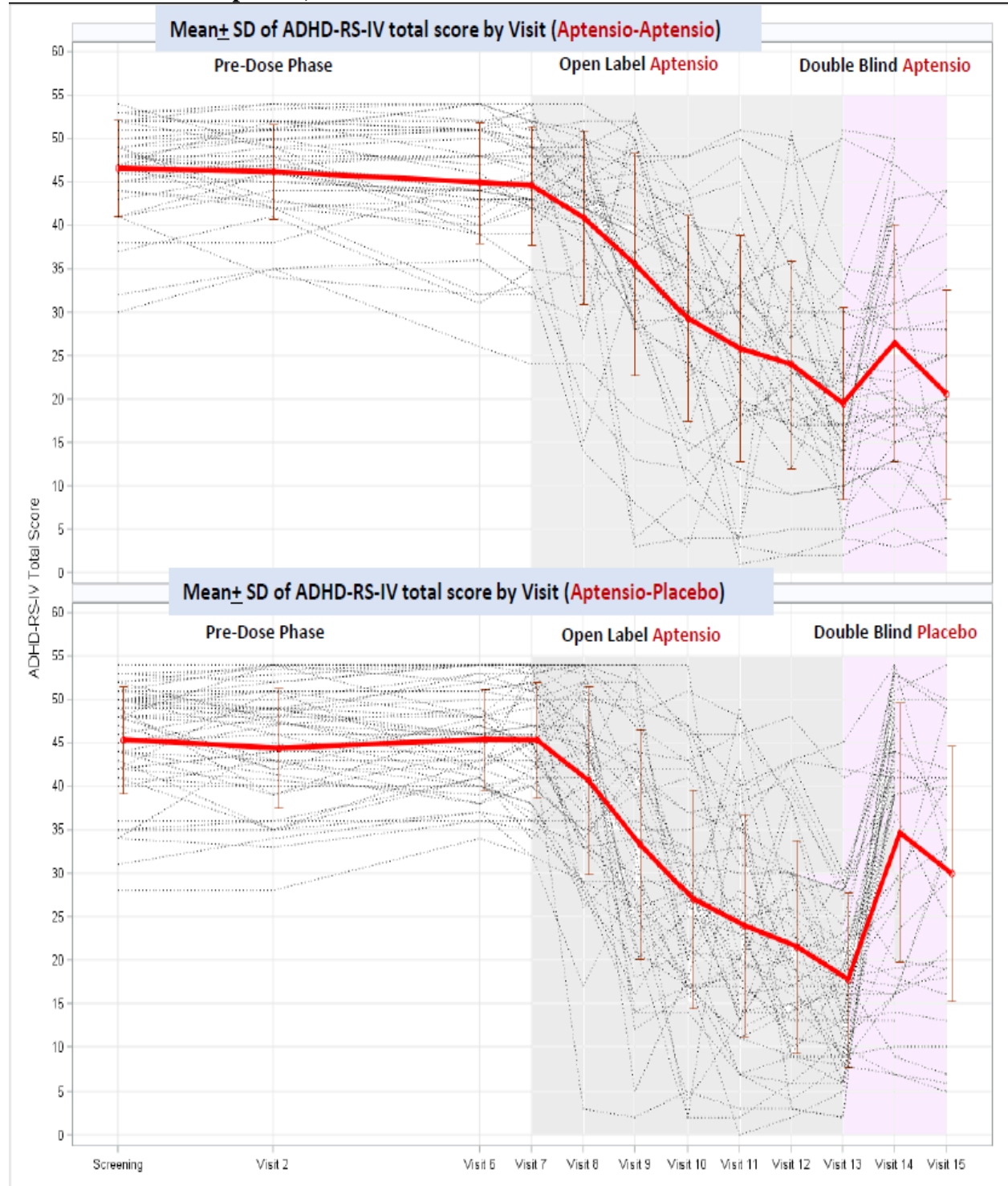
Note: Labeling visits in the figures: Visit 13 is Baseline, Visit 14 is the first post-baseline visit, and Visit 15 is the second post-baseline visit of the DB phase. (For larger sized figures, see figures of Appendix). [Source: Reviewer's analysis]

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Figure 9: ADHD-RS-IV total score in Aptensio XR vs Placebo randomized groups (Double-Blind phase)
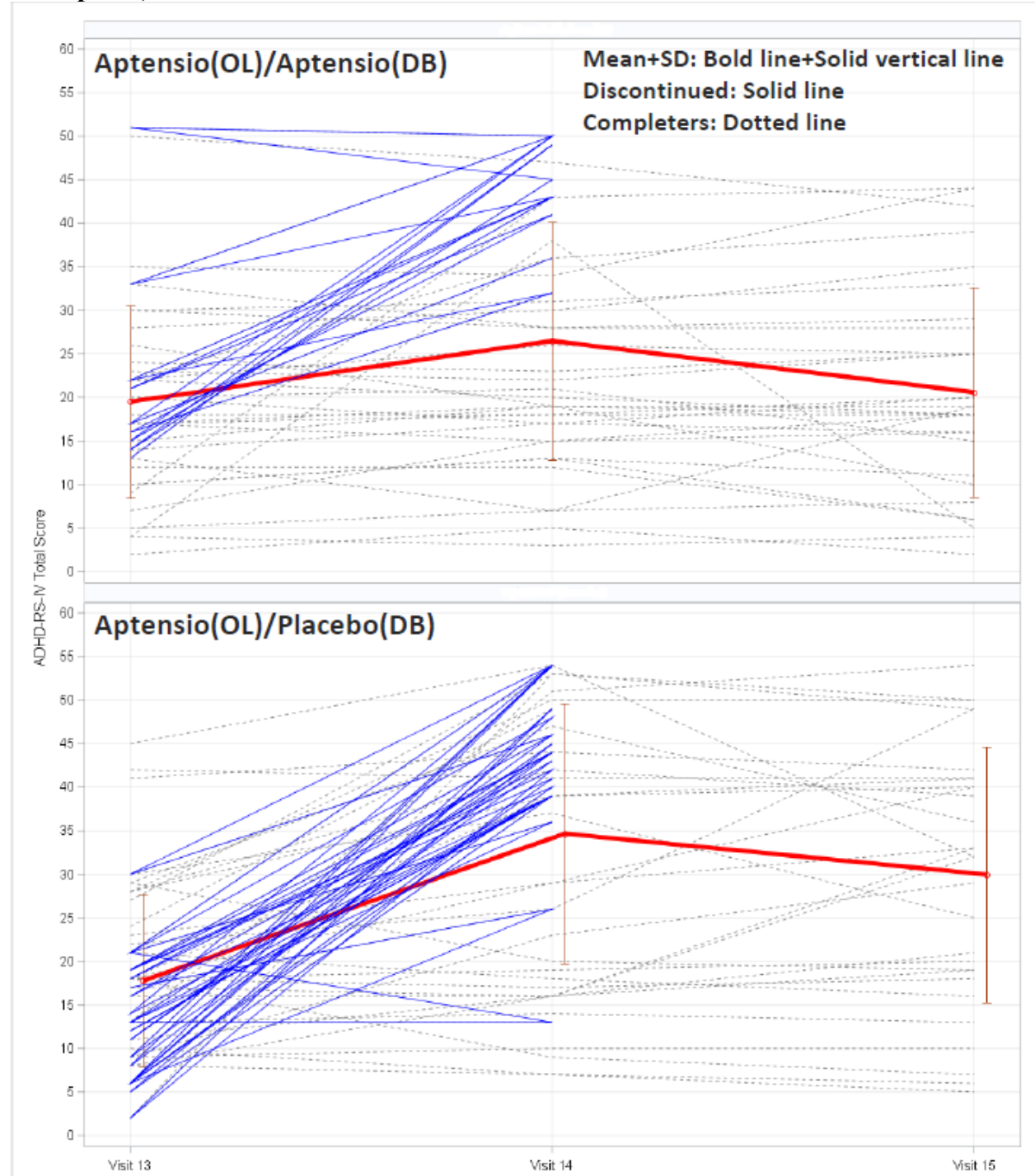
Note: Labeling visits in the figures: Visit 13 is Baseline, Visit 14 is the first post-baseline visit, and Visit 15 is the second post-baseline visit of DB phase
Reference:
[Source: Reviewer's analysis]

This reviewer conducted post hoc efficacy analyses, as shown in the following sections.

3.2.5.3.1 An efficacy analysis based on a set of subjects with the 2-week exposure data

There were 59 subjects who had observed 2-week endpoint data. This reviewer conducted a t test for the difference in change from baseline score in ADHD-RS-IV total score on the set of the 59 subjects with Visit 15 data. The result is shown in Table 12.

Table 12: *t* test for Difference in Change from baseline score in ADHD-RS-IV total score (Aptensio XR vs Placebo) for Protocol defined primary endpoint

ADHD-RS-IV Total Score			
Endpoint: Change from Baseline* to Visit 15 (Endpoint of 2-week Double-Blind Randomized Phase)			
Post hoc **Analysis based on Subset of ITT population (90 randomized subjects**)**			
n=59 (Visit 15)			
Note 13 subjects who did not meet Randomization Criteria were mistakenly randomized			
T test for Difference in Change from baseline score at Visit 15	**Aptensio XR N=29**	**Placebo N=30**	**Difference: Placebo-Aptensio XR (95% Confidence Interval) [p value]**
Mean Estimate (SE) (t test; N=59)	2.0 (1.64)	9.3 (2.75)	-7.3 (-13.7, -1.0) [0.0246]
Note: Pooled method (equal variance) was used for the estimation of the variance of the difference.			
Mean Estimate (SE) (t test; N=59)	2.0 (1.64)	9.3 (2.75)	-7.3 (-13.8, -0.9) [0.0267]
Note: Satterthwaite method (unequal variance) was used for the estimation of the variance of the difference.			

*Baseline visit is Visit 13, the last visit of 6-week Open Label Aptensio XR treated Phase. SE: Standard Error
** After randomization, one subject did not take the assigned treatment.
Note: n is the number of subjects who had ADHD-RS-IV total score at the visit
The analysis was performed with SAS proc ttest.
[Source: Reviewer's analysis]

This reviewer conducted analysis with ANOVA with factors of Treatment and Site. This analysis is not a pre-specified primary analysis. An analysis based on this subset of the randomized subjects is considered a *post hoc* analysis. The result is shown in Table 13.

Table 13: ANOVA Test for Difference in Change from baseline score in ADHD-RS-IV total score (Aptensio XR vs Placebo) for Protocol defined primary endpoint

ADHD-RS-IV Total Score			
Endpoint: Change from Baseline* to Visit 15 (Endpoint of 2-week Double-Blind Randomized Phase)			
Post hoc **Analysis based on Subset of ITT population (90 randomized subjects**)**			
n=59 (Visit 15)			
Note 13 subjects who did not meet Randomization Criteria were mistakenly randomized			
T test for Difference in Change from baseline score at Visit 15	**Aptensio XR N=29**	**Placebo N=30**	**Difference: Placebo-Aptensio XR (95% Confidence Interval) [p value]**
LS Mean Estimate (SE) (t test; N=59)	1.7 (2.29)	7.8 (2.51)	-6.1 (-12.6, 0.3) [0.0619]
Note: The ANOVA model includes factors of Treatment and Site.			

*Baseline visit is Visit 13, the last visit of 6-week Open Label Aptensio XR treated Phase. SE: Standard Error
** After randomization, one subject did not take the assigned treatment.
Note: n is the number of subjects who had ADHD-RS-IV total score at the visit
The analysis was performed with SAS proc glm.
[Source: Reviewer's analysis]

3.2.5.3.2 *Efficacy analyses under an assumption that ADHD-RS-IV total score taken at either Visit 14 or Visit 15 is meaningful for the primary efficacy evaluation*

This reviewer conducted ANOVA and MMRM analysis using the observed data at the primary endpoint visit. The results are shown in Table 14 and Table 15. These analyses use the efficacy data obtained before the 2-week endpoint, and the treatment effect estimates from these analyses are similar to the Applicant's analysis, because of the larger effect at Visit 14 than at Visit 15. It may be important to note that

Table 14: ANOVA (based on Observed Primary efficacy endpoint data)

ADHD-RS-IV Total Score			
Endpoint: Change from Baseline* to Endpoint of 2-week Double-Blind Randomized Phase			
Post hoc Analysis ITT Analysis set of 90 randomized subjects**			
Note 13 subjects who did not meet Randomization Criteria were mistakenly randomized			
	Aptensio XR N=39	**Placebo N=50**	**Difference: Placebo-Aptensio XR (95% Confidence Interval) [p value]**
LS Mean Estimate (SE) (ANOVA; N=89)	5.9 (2.40)	16.5 (2.22)	-10.6 (-16.9, -4.3) [0.0012]
Note: The model with factors of Treatment and Study Site			

* Baseline visit is the last visit of 6-week Open Label Aptensio XR treated Phase. SE: Standard Error
** After randomization, one subject did not take the assigned treatment.
*** The same analysis data as the Applicant's primary analysis was used for the ANOVA.
  [Source: Reviewer's analysis]

Table 15: MMRM Analysis

Note: MMRM method is valid under the assumption that missing data is ignorable.

ADHD-RS-IV Total Score			
Endpoint: Change from Baseline* to Visit 15 (last visit of 2-week Double-Blind Randomized Phase)			
Post hoc Analysis based on ITT population (90 randomized subjects**)			
n=89 (Visit 14)/ n=59 (Visit 15)			
Note 13 subjects who did not meet Randomization Criteria were mistakenly randomized			
Repeated Measure Analysis (Visits 14 and 15)	**Aptensio XR N=39**	**Placebo N=50**	**Difference: Placebo-Aptensio XR (95% Confidence Interval) [p value]**
Reviewer's *post hoc* analysis (2)			
LS Mean Estimate (SE) (MMRM; N=89)	5.0 (2.40)	15.5 (2.34)	-10.5 (-17.0, -4.0) [0.002]
Note: The MMRM model has factors of Treatment, Visit, Treatment by Visit interaction, and Study Site, and an Unstructured Variance-Covariance structure was used. Kenward-Roger denominator degrees of freedom estimation method was chosen.			
Reviewer's *post hoc* analysis (3)			
LS Mean Estimate (SE) (MMRM; N=89)	5.3 (2.40)	16.2 (2.23)	-10.9 (-17.4, -4.4) [0.0014]
Note: The MMRM model has factors of Treatment, Visit, and Treatment by Visit interaction, and an Unstructured Variance-Covariance structure was used. Kenward-Roger denominator degrees of freedom estimation method was chosen.			

*Baseline visit is Visit 13, the last visit of 6-week Open Label Aptensio XR treated Phase. SE: Standard Error
** After randomization, one subject did not take the assigned treatment.
Note: n is the number of subjects who had ADHD-RS-IV total score at the visit
The repeated measure analyses were performed with SAS proc mixed, under the *ignorability* assumption on missing observations.
[Source: Reviewer's analysis]

The MMRM approach may be appropriate when both visit data are meaningful, because the parameter space is not given a strict distributional restriction. The means and variance of ADHD-RS-IV total score at Visits 14 and 15 are not restricted to be equal. The required key assumptions for the MMRM application include the *ignorability* assumption of missing data; The missing

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observations occurred at the second post-baseline visit because of the censoring by discontinuation at the first post-baseline visit. It is assumed that the missing data at Visit 15 is not associated with the missingness at the primary endpoint visit.

This reviewer thinks the MMRM analysis results may show evidence of efficacy. The MMRM results however should be carefully interpreted, because there is a possibility that the discontinuation with worsened ADHD-RS-IV total score at the first post-baseline visit may be correlated with the outcome at the second post-baseline visit. In such a case, the missing observations may be associated with their missingness.

3.2.5.3.3 Conclusion of the post hoc analyses

The *t* test (Table 12) and the ANOVA (Table 13) indicate the efficacy of Aptensio XR. Because they are *post hoc* analyses, the observed *p* value is not most important. In both analysis results, the treatment effect estimate at the primary endpoint visit and its confidence interval are obviously supportive for the efficacy of Aptensio XR.

The MMRM analysis and the ANOVA (Table 14 and Table 15) also shows supportive evidence of efficacy, though the results depend on their model assumptions. Though they are post hoc analyses, the p values of both analyses show statistical significance at the 5% significance level. Their treatment effect estimates are larger and thus look more efficacious than those of the t test and ANOVA, because of the use of data obtained at the first post-baseline visit.

4   FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

No subgroup analyses are performed.

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5   SUMMARY AND CONCLUSIONS

The primary efficacy objective of Study EF-003 was to evaluate the efficacy of Aptensio XR in comparison with Placebo at the endpoint of the 2-week randomized double-blind period on responders defined as subjects who meet Randomization Criteria, based on the efficacy assessments with ADHD-RS-IV total score and CGI-I score, over the 6-week open label Aptensio XR exposure. The target patient population was preschool children of 4 or 5 years old with a diagnosis of Attention-Deficit Hyperactivity Disorder (ADHD).

Statistical Review Conclusion: In Study EF-003, although the efficacy data has shown statistical significance based on *post hoc* analyses that seem more sensible than the pre-specified, it may not be adequate to support an efficacy indication in labeling because it was conducted in an enriched patient population and the double-blind duration was two weeks only.

The study protocol defines the primary endpoint as change from baseline (Visit 13) to Visit 15 in ADHD-RS-IV total score (see 3.2.2). Visit 15, the second post-baseline visit, was scheduled at the end of the 2-week double-blind phase.

The Applicant's primary analysis result may be difficult to interpret for an evaluation of the protocol-defined primary efficacy, because of the systematic discontinuation based on observed ADHD-RS-IV total score and CGI-Improvement score (Section 3.2.3.2).

At the first post-baseline visit (Visit 14) of the 2-week double-blind phase, because the majority of 20 discontinued subjects had worsened conditions in ADHD symptoms, the mean ADHD-RS-IV total score of Placebo group got worsened by 16.9 points on the scale (Figure 5 and Table 9). Similarly, at the first post-baseline visit (Visit 14), because the majority of 9 discontinued subjects had worsened conditions in ADHD symptoms, the mean ADHD-RS-IV total score of Aptensio XR group got worsened by 7.0 points on the scale (Figure 4 and Table 9). The mean difference in ADHS-RS-IV total score between Aptensio XR and Placebo changed from 1.7 points to -8.4 points on the scale, which difference was -10.1 = -8.4-1.7 (Table 9). This may be considered the efficacy advantage of Aptension XR compared to Placebo, but much of it may be attributed to the fact of more worsening of Placebo group observed at the first post-baseline visit. On the other hand, the mean difference between Aptensio XR and Placebo was much the same at the first post-baseline visit (-8.4) and at the primary efficacy endpoint (-9.4); there was not much improvement from the first post-baseline visit to the primary efficacy endpoint visit. In other words, after a substantial number of placebo subjects who got worsened were discontinued at the first post-baseline visit, the mean difference between the two groups remained much the same. Therefore, the mean difference between Aptensio XR and Placebo may be interpreted as a reflection from the difference in efficacy performance of discontinued subjects between the two groups (Section 3.2.5.3). Whether or not this difference is considered meaningful efficacy evidence may be a clinical matter.

Although the Applicant's primary analysis may not provide a straightforward conclusion as the primary efficacy analysis, collective evidence suggests the efficacy of Aptensio XR. This reviewer finds evidence of efficacy of Aptensio XR in his *post hoc* statistical analyses (see Sections 3.2.5.3.1 and 3.2.5.3.2). However, because Study EF-003 used a design different from

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one which the agency recommended, the interpretations of the efficacy evidence may need clinical considerations beyond the statistical analysis.
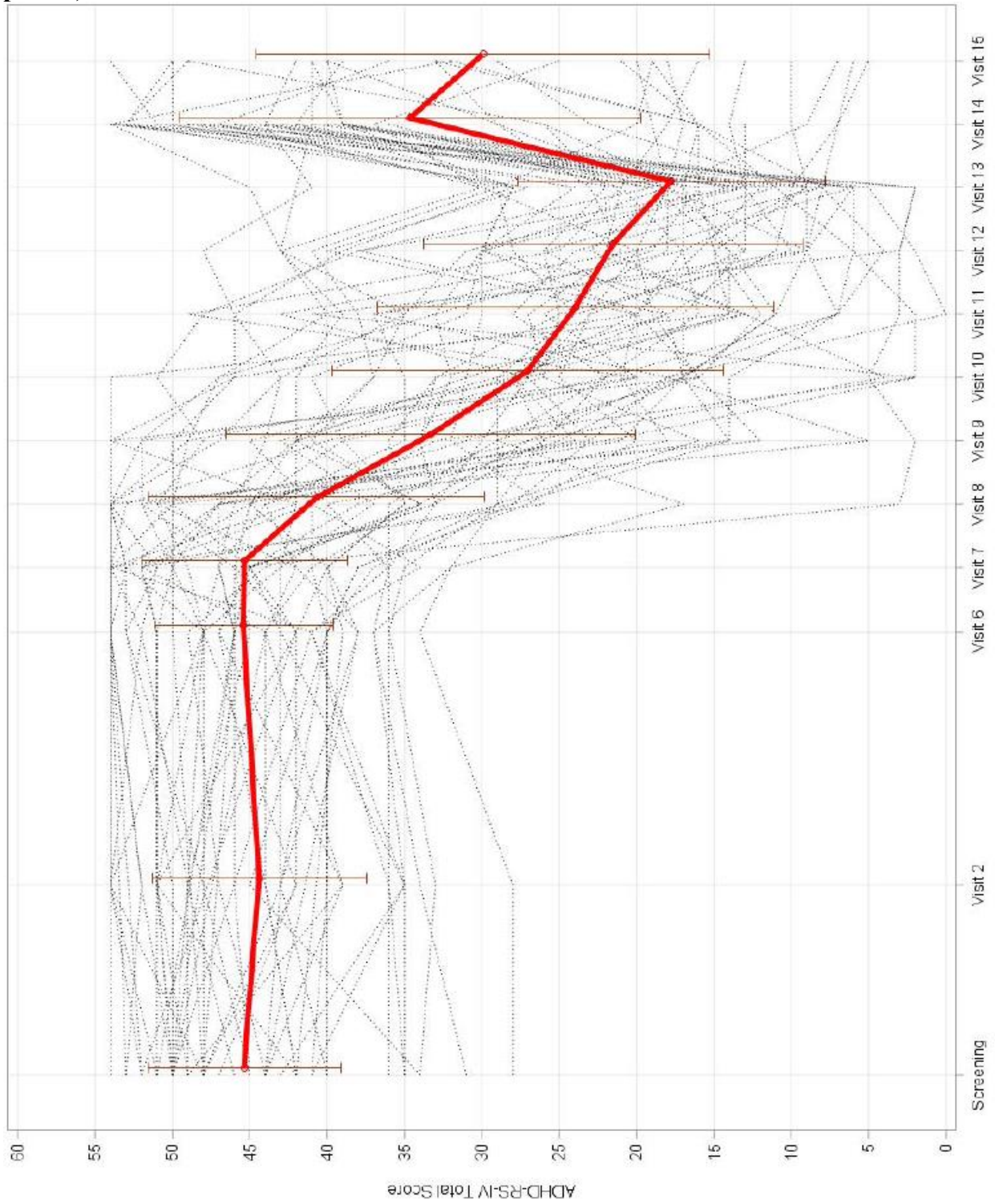
6 Appendix

Figure 10:ADHD-RS-IV total score in Aptensio XR (Randomized) group (Pre-dose, OL and DB phases)
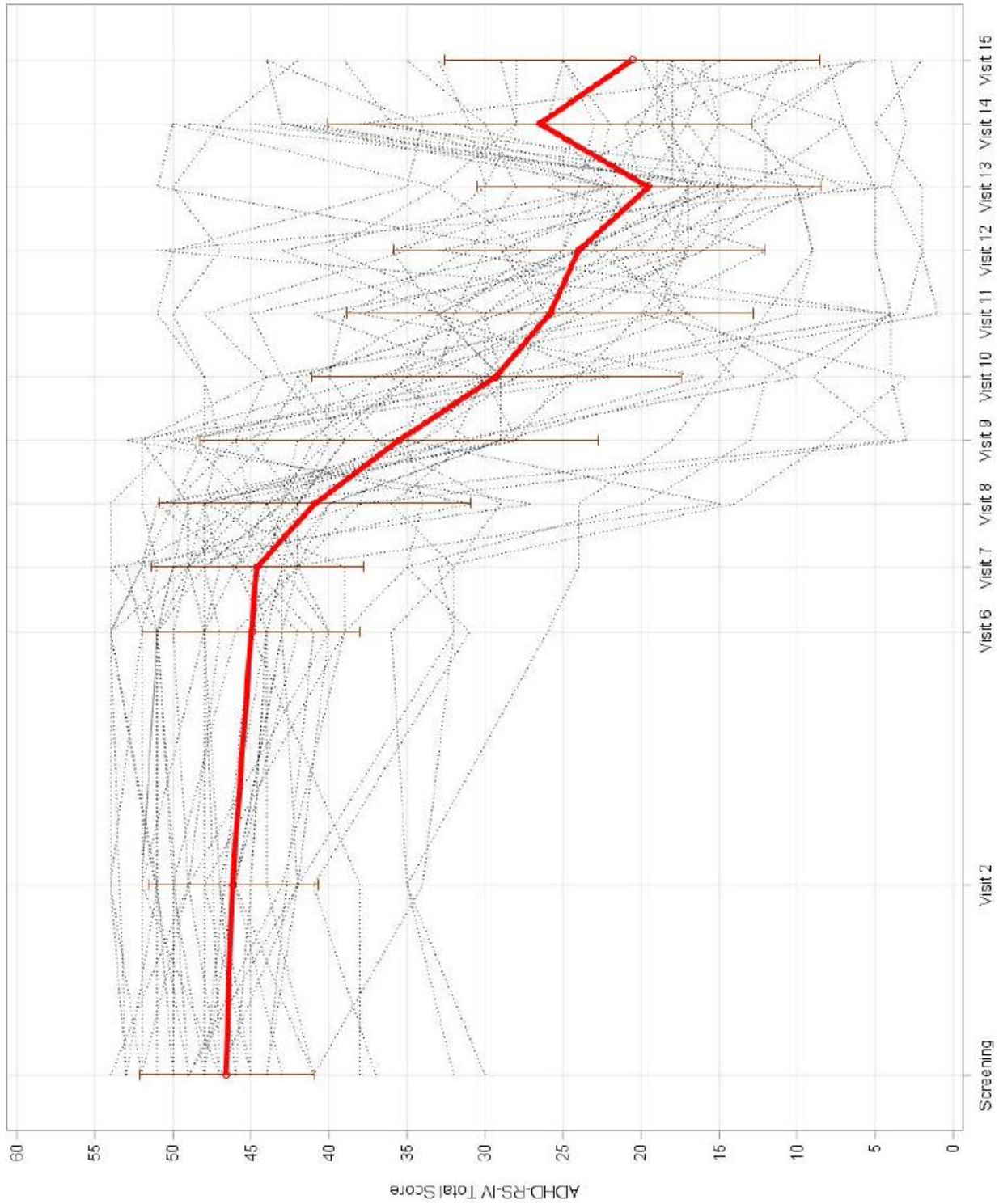
Figure 11: ADHD-RS-IV total score in Placebo (Randomized) group (Pre-dose, OL and DB phases)

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/s/

EIJI ISHIDA
05/01/2019 11:50:39 AM

PEILING YANG
05/01/2019 12:10:41 PM
Refer to my memo for my concluding remarks.

HSIEN MING J HUNG
05/01/2019 05:44:36 PM
I sign this review to acknowledge reading his review. The primary statistical reviewer is very cautious about the uncertainty due to the data quality with respect to imputation. However, the primary analysis and his MMRM analysis and even the analysis assigning some kind of worst scores to the dropouts all seem to suggest there is a drug effect. Other concerns regarding the interpretability due to the trial design are shared in this review and Dr. Peiling Yang's secondary review.