CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	NDA 20583, Supplement 005; IND 104624
Priority or Standard	Standard for pediatric data supplement (6 months)
Submit Date(s)	September 14, 2018
Received Date(s)	March 30, 2018
PDUFA Goal Date	Originally March 30, 2018; extended to June 14, 2019
Division / Office	DPP/ODE I
Reviewer Name(s)	John C. Umhau MD MPH
Review Completion Date	June 6, 2019
Established Name	Methylphenidate hydrochloride (MPH) extended-release
(Proposed) Trade Name	Aptensio XR
Therapeutic Class	Stimulant
Applicant	Rhodes Pharmaceuticals, a subsidiary of Perdue Pharma
Formulation(s)	Extended-Release Capsules: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg of methylphenidate hydrochloride, equivalent to 8.6 mg, 13.0 mg, 17.3 mg, 25.9 mg, 34.6 mg, 43.2 mg, and 51.9 mg of methylphenidate free base, respectively, per capsule
Dosing Regimen	10 mg once daily with or without food in the morning. Dosage may be increased weekly in increments of 10 mg per day.
Indication(s)	Indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).
Intended Population(s)	Patients (b) (4)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Weighed against questionable evidence of a meaningful benefit of Aptensio XR in these young children, the significant unresolved questions about safety compel me to recommend (b) (4) [redacted]. As a matter of public health, I recommend that appropriate safety data in this Application be added to a revised label for Aptensio XR.

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1.2 Benefit-Risk Integrated Assessment

Summary

In the United States in 2013, approximately 2.6% of the nearly 2.4 million methylphenidate (MPH) extended release prescriptions written for children and adolescents were written off-label for children under 6 years of age. (b) (4) . The evidence for safety and effectiveness contained in this Application is derived from a study which, because of its design, is difficult to interpret. (b) (4)

The use of MPH in preschool children has been debated in the literature for decades. This debate includes questions of overdiagnosis, the lack of documented benefit for children not yet in school, and ethical problems created by the treatment of a vulnerable population for the benefit of caregivers. The Applicant has not adequately addressed these issues or characterized the benefit-risk ratio in this population of preschool children. In children ages 4 and 5, the effect of MPH to reduce growth and cause psychiatric adverse effects was confirmed in the data submitted with this Application. In addition, preclinical literature indicates that treatment with MPH during development has the potential to cause significant neuropsychiatric dysregulation in adulthood. Considering international standards, sufficient long-term data on the safety of MPH in 4- and 5-year-old children is lacking. (b) (4)

Discussion of Submitted Studies

The Applicant studied 10 children in a single-dose pharmacokinetic (PK) study, (RP-BP-PK003). The Applicant obtained efficacy and safety data from 119 subjects in a 6-week open-label, ~2-week double-blind study (RP-BP-EF003) and from 31 subjects who completed a 52-week open-label extension study (RP-BP-EF004).

The PK study demonstrated that preschoolers have 2-3 times greater exposure (Cmax, AUC) compared to school-aged children. However, preschool-aged children are not prescribed a commensurately lower dose on a mg/kg basis. This increased exposure has the potential to cause distinctive adverse effects, yet this information did not lead to a reduced starting dose in the studies.

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The design of the pivotal efficacy study, RP-BP-EF003, was not agreed to by FDA, and several design issues complicated interpretation. First, the double-blind population was an enriched population consisting only of subjects who could tolerate Aptensio XR. Secondly, a 2-week double-blind period is not of sufficient length to appropriately characterize the adverse effects occurring on drug. Thirdly, there was no was washout period, creating the potential for a carryover effect from the open label phase directly preceding it. Fourth, the protocol stipulated criteria for subjects in the double-blind phase whose condition became worse to discontinue. Therefore, RP-BP-EF003, does not qualify as a well-controlled study, and it does not allow an analysis of the risk-benefit ratio.

Study RP-BP-EF004 as submitted provides long-term (i.e., 52-week) data on 31 children. This is a smaller population than recommended by ICH guidelines, and fewer subjects than FDA required the Applicant to provide in fulfilment of a Written Request.

Benefits of treatment

Study RP-BP-PK003 exposed subjects to Aptensio XR for 6 weeks during the lead-in phase. During the subsequent double-blind phase, a placebo group (n=50) compared to a group continuing Aptensio XR (n=39) had more ADHD symptoms detected by a significant difference in ADHD-RS-IV scores in a post-hock analysis and complicated by the issues noted above. The magnitude of the difference between groups as presented by the Applicant is considered to be “minimal improvement.”

The Applicant has not provided information indicating that treatment of preschoolers with ADHD prevents significant disability. A search of available scientific literature in English suggests that treatment of ADHD in children ages 4 and 5 has benefits for caregivers.

Long-term Safety in Humans

Although MPH is often used off-label for children ages 4 and 5, the potential for MPH to have adverse effects when administered at this age continues to be a concern and is clearly noted in the literature. There exists inadequate long-term safety data to evaluate and quantify the risks of long-term use of MPH, including Aptensio XR, in preschool-aged children.

Weight loss is a prominent issue when MPH is used in preschool children; in Study RP-BP-EF003, 35% of the patients experienced weight loss during the 6-week open-label treatment phase (N=119). The average weight loss in those patients was 0.68 kg.

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Psychiatric adverse events (AEs) are a known risk of stimulants, however, 4- and 5-year olds exhibit an excessive number of such events when compared to previous studies with Aptensio XR and as documented with MPH in the literature. If the AEs of irritability and affect liability are combined with emotional disorders, 42 of the 119 subjects treated in the 6-week open-label dose optimization phase developed emotional disorders compared with none of the 152 preschoolers in the 6-week off-treatment phase. Supporting this observation, at least 11 of the 32 discontinuations during this phase were, at least in part, related to psychiatric side effects. The AE of aggression was also described in this Application; this is a known side effect of MPH in preschool children. This and other neuropsychiatric safety signals are noted in the literature, however they appear to be less prominent in older age groups dosed with MPH. The reason for this effect may relate to the immaturity of the nervous system in the pre-school age group.

Although complaints of neuropsychiatric dysfunction typically resolved after Aptensio XR was withdrawn, there is preclinical data suggesting a potential for exposure to MPH in development to cause brain dysfunction. Recent research indicates that MPH damages the blood brain barrier (BBB) and causes neuroinflammation. Other preclinical studies indicate that behavioral abnormalities induced by MPH (e.g., anxiety) persist into adulthood. In short, preclinical research indicates that MPH given to preschool children with ADHD has the potential to cause life-long neuropsychiatric consequences.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• ADHD is a common diagnosis in preschool children ages 4 and 5; the Applicant estimates that the prevalence of ADHD in this population is 0.5 to 12.2% • ADHD symptoms are distressing to parents and caregivers • MPH is used off-label for children ages 4 and 5 with ADHD • Although ADHD symptoms have the potential to disrupt learning in school-aged children, there was no data presented regarding this possibility in preschool children. • Those who care for preschool children may experience a benefit when ADHD behavior is treated with medication	• There were no data presented suggesting that ADHD symptoms in preschool children present the same potential for harm as in older, school age children • Treating ADHD symptoms in school-aged children provides a different benefit compared to younger, preschool-aged children

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• First line therapy for ADHD in children younger than 6 is parent training and other behavioral interventions • Behavioral interventions show benefit in a significant proportion of cases; benefits persist and are measurable after 6 months. • Second line therapy for preschool aged children is pharmacologic • Amphetamine products are indicated for the treatment of ADHD in children age 3 and above, however their use was grandfathered, so there is less safety data on preschool children. • MPH is commonly used off-label for ADHD in preschool children ages 4 and 5	• Parent behavioral-training-type behavioral interventions do not meet the need of many children with ADHD • The current pharmacological treatment of children ages 4 and 5 with ADHD incudes the off-label use of MPH • No data was found indicating that the long-term academic benefits reported to occur with MPH treatment of school-aged children will also occur with the treatment of preschool-aged children
Benefit	• In Study RP-BP-EF003, the FDA biometrics reviewer found that the mean difference in the change from baseline score of ADHD-RS-IV total score at the Week 2 endpoint between Aptensio XR and placebo was 7.3 points in favor of Aptensio XR (59 subjects had their Week 2 measurement). The magnitude of this difference is considered to be a “minimal improvement” based on the literature (Goodman, Faraone et al. 2010). • The secondary measures, CGI-S and the Conners EC BEH-P(S), did not provide supportive evidence of efficacy • In the follow-up Study RP-BP-EF004, 31 subjects received Aptensio XR for 52 weeks and 43 subjects discontinued for reasons that included the of loss of benefit from Aptensio and the emergence of adverse events. Efficacy measured with the CGI-S score, assessed monthly, became worse over time, consistent with a general worsening of ADHD symptoms.	• The design of this study is not considered acceptable by FDA; there is insufficient time for placebo / drug comparison, there is no washout period, subjects whose condition became worse were discontinued early, and the study population was enriched for responders to MPH. • Based on this analysis, the results of this study do not indicate that Aptensio XR produced a meaningful clinical response • The Applicant does not present evidence that the improvement in ADHD symptoms provides a significant benefit for preschool aged children

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Dimension	Evidence and Uncertainties	Conclusions and Reasons

Risk and Risk Management	• Psychiatric SOC related AEs occurred in more than half of treated subjects in Study RP-BP-003
	• Existing animal studies do not support safety in regard to neuropsychiatric issues. Recent studies indicate that MPH administration in development is associated with neuroinflammation and blood brain barrier dysfunction
	• The study does not provide a sufficient length of placebo comparison to the drug to adequately evaluate the potential for adverse events
	• Enriching the population with responders obscures the risk of Aptensio XR to cause AEs
	• It is unknown if the observed effect of Aptensio XR was confounded by parents who exaggerated their child's symptoms to obtain this stimulant for illicit use
	• Forty percent of enrolled subjects dropped out in the dose-optimization phase before randomization to double-blind placebo or drug; this enrichment of the study population with subjects who can tolerate the drug makes interpretation of placebo-controlled phase difficult
	• The literature notes that the side-effect profile of MPH in preschool aged children is different when compared to older children
	• For a given mg-per-kg dose, the systemic exposure to MPH in children 4 to 5 years of age is 2-3 times higher than that for older children and adolescents
	• The use of a lower dose may reduce the risk of MPH in this population, but the data does not allow this conclusion
	• The long-term significance of psychiatric adverse reactions induced by the drug is unknown, and may represent
		• As suggested in the animal literature, the potential exists for MPH to induce neuroinflammation in children
		• Although off-label MPH is commonly used in children ages 4 and 5, the safety profile is not well characterized
		• The long-term safety database does not contain sufficient preschool aged subjects to provide an assurance that uncommon adverse effects have been detected
		• There is a potential for children prescribed MPH to become addicted to it
		• Unresolved potential issues for the use of Aptensio XR in preschool children include:
		  ○ Growth retardation (i.e., weight loss)
		  ○ Increased blood pressure
		  ○ Aggressive reactions
		  ○ Long-term neurobehavioral damage causing maladaptive behaviors in adulthood; e.g., anxiety disorders, stimulant addiction
		• Based on the existing data, the use of Aptensio XR in preschool children cannot be rendered safe through labeling or by limiting the duration of use
		• Part of the risk associated with Aptensio XR in this age group may be related to the design of this formulation to be extended release.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	neuropsychiatric insults to the central nervous system which have the potential to alter brain development, especially when MPH is used at a high dose and for long periods • Some children who are administered MPH will eventually become addicted to it; the extent of this risk is not known • The reason for the apparent increased incidence of adverse effects in preschool children is unknown	

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1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Although not addressed in this application, there exists a potential for all stimulant medications, including Aptensio XR, to cause disability and death from addiction. A strategy to mitigate the risk of addiction and illicit use could be developed in consultation with appropriate groups and experts.

1.4 Recommendations for Postmarket Requirements and Commitments

Additional studies are needed to evaluate safety in this vulnerable population. When considering neurobehavioral aspects of development, there are insufficient animal data evaluating the youngest age and dose level at which MPH is safe and without adverse effects on adult behavior. Further animal studies have the potential to identify protective factors that could mitigate the adverse effect of MPH on the developing nervous system. Epidemiological studies, e.g. surveillance, have the potential to provide information about long-term safety for humans. Such concern extends to other stimulants as well.

The demonstrated higher blood exposure to MPH in children ages 4 and 5 compared to older children, together with the high rate of side effects, suggests that a lower dosage should be evaluated. For some children, a lower dose may provide efficacy with less adverse effects. Clinical studies that relate pharmacokinetic analysis of Aptensio XR to safety and efficacy data may provide important information. If studies using lower doses show efficacy, new, lower dose formulations will be required.

(b) (4)

2 Introduction and Regulatory Background

Methylphenidate (MPH) is the most commonly prescribed psychotropic medication for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children, including the subgroup of children 4 to 5 years of age, even though it does not have Food and Drug Administration (FDA) approval for use in children under 6 years of age (Wigal, Gupta et al. 2007).

2.1 Product Information

Methylphenidate is a central nervous system stimulant first approved in 1955 and classified as a Schedule II controlled substance in the United States. Aptensio XR is a (b) (4)-release formulation of methylphenidate indicated for the treatment of ADHD. Aptensio XR has a biphasic plasma profile, achieving a first peak concentration similar to immediate-release methylphenidate followed by a second peak approximately 8 hours later. Aptensio XR was developed by Rhodes Pharmaceuticals L.P. for the United States market and originally developed by Purdue Pharma L.P. (Purdue) in Canada (approved for marketing in Canada under the trade name Biphentin in March 2006).

2.2 Table of Currently Available Treatments for Proposed Indication

(b) (4) treatment of ADHD in children ages 4 and 5. MPH and other stimulants have been used extensively in this population, despite limited data on their safety and efficacy. Although significant data are available for the treatment of ADHD in subjects aged 6 years and older, there is much less data available regarding the medical treatment of ADHD in children younger than 6 years old.

The American Academy of Pediatrics Clinical Practice Guidelines for the Diagnosis, Evaluation, and Treatment of Attention-deficit/Hyperactivity Disorder in Children and Adolescents recommend behavior therapy as first-line treatment in these young children. In school-aged children, parent behavior training is a commonly recommended intervention. This behavioral intervention for the treatment of ADHD is delivered in a variety of programs and has been shown in metanalysis to have beneficial effects, which continue after the intervention is completed; e.g., at 6 months (Charach, Carson et al. 2013). In reality, however, the guidelines are not followed, as no more than 55% of children with ADHD received psychological services annually, regardless of insurance type, whereas approximately three-fourths received medication (Visser 2016).

Other interventions used to treat ADHD include psychological interventions, complementary and alternative remedies, and dietary management. Although these modalities are all used, the mainstay of treatment is pharmacological.

Methylphenidate is commonly used “off-label” in preschool children younger than 6 years old; it does not have regulatory approval in the United States in these young children. Other drugs used include amphetamine products and antidepressants used off-label (e.g., desipramine, nortriptyline, imipramine, and bupropion).

Methylphenidate and amphetamine are available in a multitude of drug delivery systems that extend the duration of action of these medications. Intermediate-acting formulations are designed to cover the school hours with a once-daily dose preparation. Long-acting compounds are designed to cover both the school day and afterschool hours with a single dose given in the morning before school. Longer-acting formulations can then be complemented with immediate-release preparations for additional ADHD

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coverage as needed. A methylphenidate-IR solution formulation and a long-acting methylphenidate extended release solution preparation are available for children who have difficulty swallowing pills and capsules. Amphetamine, dextroamphetamine, and combination products are currently approved for preschool-aged children.

Table 1. Currently Available ADHD Medications.

Class	Active Moiety	Dosage Form	Strength
Stimulant	Methamphetamine	Tablet	5, 10 mg
		Tablet, extended release	5, 10 mg
	Methylphenidate	Tablet	2.5, 5, 10 mg
		Tablet, chewable	2.5, 5, 10 mg
		Tablet, extended release	10, 18, 20, 27, 36, 54 mg
		Tablet, extended release, chewable	20, 30, 40 mg
		Capsule, extended release	5, 10, 15, 20, 25, 30, 35, 40, 50, 60 mg
		Transdermal	10, 15, 20, 30 mg/9hrs
		Suspension, extended release	5 mg/mL
		Solution	5, 10 mg/mL
	Dexmethylphenidate	Tablet	2.5, 5, 10 mg
		Capsule, extended release	5, 10, 15, 20, 25, 30, 35, 40 mg
	*Amphetamine	Suspension, extended release	2.5 mg/mL
		Tablet	5, 10 mg
		Tablet, extended release, orally disintegrating	EQ 3.1, 6.3, 9.4, 12.5, 15.7, 18.8 mg base
	*Dextroamphetamine	Tablet	2.5, 5, 7.5, 10, 15, 20, 30 mg
		Capsule, extended release	5, 10, 15 mg
		Solution	5 mg/mL
	Mixed Amphetamine Salts*	Capsule, extended release	Total active ingredients: 5, 10, 15, 20, 25, 30 mg
		Tablet	Total active ingredients: 5, 7.5, 10, 12.5, 15, 20, 30 mg
	Lisdexamfetamine	Tablet, chewable	10, 20, 30, 40, 50, 60 mg
		Capsule	10, 20, 30, 40, 50, 60, 70 mg
Non-stimulant	Atomoxetine	Capsule	10, 18, 25, 40, 60, 80, 100 mg

	Clonidine	Tablet	0.1, 0.2, 0.3 mg
		Tablet, extended release	0.1 mg
		Transdermal	0.1, 0.2, 0.3 mg/24 hrs.
	Guanfacine	Tablet	EQ 1, 2, 3 mg base
		Tablet, extended release	EQ 1, 2, 3, 4 mg base

*Approved for use in children age 4 to 6.

Other Treatments used for ADHD

- Approved Pharmaceuticals used off-label
  - Antidepressants: bupropion, desipramine, venlafaxine, reboxetine
  - Other Drugs: modafinil
- Complementary and alternative medicine interventions
  - Dietary therapy
  - Polyunsaturated fatty acids
  - Amino acids (L-carnitine)
  - Minerals (zinc, iron)
  - Herbal therapy (St John's wort, Ginkgo biloba)
- Psychological interventions
  - Behavioral therapy: parent training; child, parent and/or teacher training
  - Cognitive training: working memory training; attention training
  - Other psychotherapies

Reviewer note:

Although MPH is widely used off-label for children ages 4 and 5, literature reports suggest that PBT interventions may have greater evidence of effectiveness than MPH for treatment of preschoolers, but with no risk for adverse drug effects (Charach, Carson et al. 2013).

2.3 Availability of Proposed Active Ingredient in the United States

Methylphenidate is currently Schedule II in the United States. It is available by prescription as a brand-name product and generic in a variety of formulations (see Table 1).

2.4 Important Safety Issues with Consideration to Related Drugs

Stimulants carry a boxed warning for abuse and dependence as well as sudden death and serious cardiovascular adverse reactions when misused. Other warnings and precautions include risk of increased blood pressure, psychosis or mania, long-term suppression of growth, seizure, peripheral vasculopathy (including Raynaud's phenomenon), serotonin syndrome (when combined with serotonergic agents or in an overdose setting), blurred vision, and exacerbation of tics.

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Serious adverse events, such as psychosis and mood disorders, are reported to affect approximately 3% of children treated with MPH (Storebø, Pedersen et al. 2018). Psychiatric side effects can include irritability, emotional blunting, depression, anhedonia (Morton and Stockton 2000). Other adverse reactions include loss of appetite, insomnia, abdominal pain, nausea and vomiting, nervousness, headache, dry mouth, and fever.

Relatively little safety information is available from the use of stimulants in children ages 4 and 5. At the time of its publication, one review (Connor 2002), noted over 200 controlled trials of stimulants in school-aged children compared with only 9 in the preschool-age group; of 5768 children, adolescents, and adults studied under controlled conditions in stimulant drug trials for ADHD, only 206 subjects were in the preschool-age range. Literature reports indicate that more severe and more variable side effects occur in preschool-age children treated with methylphenidate compared to elementary-age children (McGoey, Eckert et al. 2002, Safer 2011). In addition, longitudinal studies indicate that MPH impairs both children's height and increases in weight (Swanson, Greenhill et al. 2006).

Reviewer note:

Although MPH is widely used, there is a relative lack of data regarding safety and efficacy in preschoolers.

2.5 Summary of Presubmission Regulatory Activity

Aptensio XR was approved by FDA on April 17, 2015 for the treatment of ADHD in patients aged > 6 years. At the time of approval, FDA specified that the Applicant conduct studies in children following the requirements of the Pediatric Research Equity Act (PREA), which included:

1) Pharmacokinetic (PK) study for subjects ages 4 to 5 years;
2) Efficacy and safety study for subjects ages 4 to 5 years with ADHD;
3) Open-label safety study for subjects ages 4 to 5 years with ADHD.

The final version of the protocol of the efficacy and safety study, RP-BP-EF003, was submitted under IND 104624 on August 10, 2015, and was amended on August 10, 2015, December 17, and February 24, 2016.

On 14 January 2016, the Applicant submitted a Proposed Pediatric Studies Request to request an FDA Written Request (WR) for pediatric clinical studies. In the WR, dated May 11, 2016, FDA noted that 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 dose titration dosing scheme could acceptably demonstrate efficacy and safety. On June 9, 2016, the FDA requested a detailed statistical plan for

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review, and that this should include an interim analysis to be agreed upon prior to initiation of the study. Please refer to the Statistical review of this application for additional details. On October 18, 2016, the Applicant submitted the draft SAP of the study for the first time and requested (b) (4) ; the Applicant requested changes to the Agency's Written Request for Pediatric Studies. The Applicant specified that the efficacy and safety study (Study AR-BP-EF003) would be composed of a 6-week, open-label, dose-optimization phase followed by a 2-week, double-blind treatment phase.

The Agency responded on February 2, 2017, indicating disagreement with this strategy, because such a study design would lead to a double-blind phase enriched for patients who tolerated and responded to the drug, potentially diminishing any safety signal. The Agency noted that a flexible dose design would be acceptable, but that the treatment should be double-blind and placebo-controlled to ensure that safety data is collected from a non-enriched population.

At a guidance meeting held on November 29. 2017, this disagreement was re-iterated. In the meeting notes, FDA stated that:

> *"we do not agree with a study design that would involve a very short period of double-blind, placebo-controlled treatment. "*
>
> *"…we do not agree with the strategy of an open-label, dose-optimization phase followed by a double-blind treatment phase. We remain concerned that this strategy would result in a double-blind phase enriched for patients who tolerated and responded to the drug…, we want to ensure that you collect sufficient data to make meaningful safety comparisons between a drug-treated group and a placebo group".*
>
> *"We recommend a study design that is double-blind and placebo-controlled from the beginning of the study."*
>
> *"We believe that a trial duration of six weeks for Study RP-BP-EF003 would provide sufficient safety and efficacy data…"*

At this meeting, the Applicant reported that they had already initiated Study RP-BP-EF003 in response to PREA requirements. FDA expressed uncertainty as to whether the completed study would be sufficient to fulfill the Written Request; stating, "Our primary concern is whether the completed study provides sufficient safety data."

FDA advised the Applicant to submit a new request to amend the Written Request, and the Agency revised the WR (WR Amendment 1 date 18 June 2018).

The Applicant submitted three amendments of the SAP (Version 1.1 dated October 30, 2017, Version 1.2 dated 7 November 2017, and Version 2.0 dated 15 February 2018). The final submission of the protocol was made on February 26, 2018.

On 11 April 2018, the Applicant submitted the finalized pharmacokinetic report and, with this sNDA, submitted reports from the efficacy study, RP-BP-EF003, and preliminary data from the open-label safety study, RP-BP-EF004. Completion of these studies and submission of a supplement to the NDA by September 19, 2018 was deemed necessary to request pediatric exclusivity.

In a subsequent communication on November 2, 2018, the Applicant noted that 14 of the 90 subjects randomized to the double-blind phase of Study RP-BP-EF003 did not meet eligibility criteria intended to remove non-responders from the double-blind phase of the study. The Applicant submitted a re-analysis suggesting that this error did not alter the conclusions of the study.
What about IR?????

Reviewer Note:

FDA disagreed with the design of Study RP-BP-EF003 because it utilized a double-blind period of only 2 weeks and because it was enriched for subjects who had already demonstrated that they could tolerate the drug. These factors render Study RP-BP-EF003 of limited value in determining the safety of Aptensio XR and the risk-benefit ratio. The meeting minutes noted above indicate that the Division did not believe that the design of Study RP-BP-EF003 could permit meaningful safety and efficacy comparisons between a drug-treated group and a placebo group. The Applicant did not follow suggestions or adapt Study RP-BP-EF003 in response to FDA's concerns about the program. Unfortunately, the PK study was conducted last; if it had been conducted first, as requested by FDA, the excessive exposure noted in children age 4 and 5 might have led the Applicant to study lower initial doses, potentially avoiding some AEs.

Currently, the Division requires that studies for the same purpose have a parallel design and evaluate different fixed doses instead of employing dose optimization. The new guidelines are noted in the FDA document, "Attention Deficit Hyperactivity Disorder: Developing Stimulant Drugs for Treatment Guidance for Industry".

2.6 Other Relevant Background Information

The use of MPH for the treatment of children with ADHD has been the focus of significant scientific, cultural, and ethical discussion in the literature. Despite extensive clinical use, and evidence from the literature that treating school-aged youth with ADHD 6 to 18 years of age decreases the risk for subsequent comorbid psychiatric disorders (Biederman, Monuteaux et al. 2009), treatment of young children with stimulants has

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been criticized from both a scientific and ethical perspective (McCubbin and Cohen 1999, Kean 2004).

Some research suggests that the diagnosis of ADHD is influenced by a child's age relative to the ages of classmates and suggests that subjective bias unrelated to a particularly set of ADHD symptoms could affect the likelihood that the child will receive treatment for ADHD (Layton, Barnett et al. 2018).

Research suggests that treatment of preschool aged children with MPH improves parent child interactions and hypothesizes that this may translate into benefits for the child (Barkley 1988). In older, school-aged children with ADHD, treatment provides a small benefit of MPH on academic performance. One recent metanalysis determined that MPH produced a 3% improvement in math accuracy and increased reading speed but not reading accuracy (Kortekaas-Rijlaarsdam, Luman et al. 2018). An earlier review of academic outcomes in nine studies (*N* across studies=8,721) found that that long-term medication use is associated with small improvements in standardized achievement scores but only questionable improvements in grade retention (Langberg and Becker 2012).

(b) (4)

The use of MPH off-label in these younger children, ages 4 and 5, is common throughout the world. In Canada, in 2006 to 2007, 0.3% of preschoolers were prescribed medications for ADHD (Brault and Lacourse 2012). This use is controversial because of the limited data in this population compared with older age groups.

The use of MPH in preschool children was evaluated previously in a landmark study, the Preschool ADHD Treatment Study (PATS) study. PATS was a multicenter, randomized, efficacy trial designed to evaluate the short-term (5 weeks) efficacy and long-term (40 weeks) safety of immediate release (IR) methylphenidate in preschoolers 3 to 5 years of age with severe ADHD that was unresponsive to a 10-week psychosocial intervention (Greenhill, Kollins et al. 2006, Wigal, Greenhill et al. 2006, March 2011). Of note, some of the investigators in the PATS study were also involved with the conduct of the studies in this Application.

The PATS study reported on a number of measures and included a PK study, which compared children older or younger than 6. This study found increased exposure at similar mg/kg doses in these younger children (Wigal, Gupta et al. 2007); it noted that preschool children have higher circulating levels of MPH than school-aged children for the same weight-adjusted dose. The study reported that clearance of MPH in plasma varies considerably from early childhood (about 100 L/hour) to adulthood (about 500 L/hour). The authors posited that faster clearance of MPH by school-aged children compared to preschool children may be due to the increase in size and maturation of the metabolic enzymes in the older group.

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The PATS study found that immediate-release MPH delivered in 2.5-, 5-, and 7.5-mg doses t.i.d., produced significant reductions on ADHD symptom scales in preschoolers (N=165) compared to placebo, although effect sizes (0.4 vs 0.8) were smaller than those cited for school-age children on the same medication. Blind ratings classified 7 (4%) preschoolers as non-responders; 14 (8%) as placebo responders; 24 (15%) as best responding to 1.25 mg t.i.d. (0.2 mg/kg/day); 26 (16%) as best responding to 2.5 mg t.i.d. (0.4 mg/kg/day); 30 (18%) as best responding to 5 mg t.i.d. (0.8mg/kg/day); 36 (22%) as best responding to 7.5 mg t.i.d. (1.2 mg/kg/day); and 7 (4%) as best responding to 10mg t.i.d. (1.3mg/kg/day). The mean optimal MPH total daily dose was 14.2 (0.7 mg/kg/day). There was no significant correlation between age and MPH absolute dose or MPH dose by weight.

After this optimum dose finding phase, the subjects (N=96) were treated with their optimum dose for 5 weeks in a double-blind parallel group, placebo-controlled phase. The MPH group failed on the primary endpoint, a dichotomous variable, “excellent responder status” based on an experimental classroom measure.

Adverse events, particularly those effecting the central nervous system, (irritability, mood disorders, affect liability) were very common in the PATS study, and were responsible for the large number of subjects who did not tolerate the medication; of the 21 children who discontinued because of AEs, 13 had issues of emotionality/irritability. In addition, one child receiving MPH in the maintenance phase was hospitalized for severe uncontrolled aggression. Also, of the 95 preschool children who remained on medication for a year in the PATS study, annual growth rates were 20.3% less than expected for height (Swanson, Greenhill et al. 2006).

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

On November 2, 2018, the Applicant submitted an amendment, entitled Note Regarding RP-BP-EF003 Randomization Eligibility[1]. According to the submitted document, the Applicant had randomized 90 subjects (almost all of the Open-label Phase completers) to the double-blind phase, but later found that 14 of these randomized subjects did not meet randomization criteria, i.e. a reduction of ADHD symptoms of $\geq$ 30% and a CGI-I score of “much improved” or “very much improved” at the end of the open label phase. The 14 subjects did not have a protocol-defined optimal dose during the randomization phase. All of the analyses are thus *post hoc* in nature. In the submitted amended re-analysis submission, the Applicant claims: “The re-analysis of the primary endpoint demonstrates that the removal of 14 subjects

1 The location of the submission is \\CDSESUB1\evsprod\NDA205831\0069

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included in the original analysis who were not eligible for randomization does not affect the efficacy conclusion."

The office of Surveillance and Epidemiology (OSI) inspected the clinical sites of Drs. Arnold, Brougher, Cure, and Handal and, based on the results of these inspections, OSI had concerns about potential under-reporting of the adverse events (AEs) of hypertension (HTN) and weight loss in Studies RP-BP-EF003 and RP-BPEF004. An information request (IR) was submitted to the Applicant on February 28, 2019 to request the rationale for 1) the definition of an AE of HTN and weight loss as three episodes occurring during three consecutive visits versus a single episode, given that a single episode of HTN or weight loss may be significant as a drug AE; 2) retrospectively deleting reported AEs for HTN and weight loss based on a new Applicant-provided definition. The IR also requested that the Applicant provide a list of episodes of HTN and weight loss that were changed from AE to no AE based on the Applicant/CRO letters sent to all sites, the protocol Version 1.3 definition of HTN and weight loss, and/or BP being 95th percentile at three consecutive visits. The Applicant submitted a response to the information request on March 14, 2019, the original PDUFA Date. The Applicant's response was considered a Major Amendment to the submission by DPP. Therefore, the PDUFA goal date was extended to June 14, 2019. The final compliance classification of the inspections of Drs. Arnold, Cure, and Handal is No Action Indicated (NAI). The final compliance classification of Dr. Brougher's inspection, (because the AE of HTN for two subjects was not reported) was Voluntary Action Indicated (VAI, which indicates that deviations from regulations occurred).

As the database for RP-BP-EF003 was further evaluated, the nature of the data submitted from the double-blind portion of the study was found to be obfuscated by the removal of 20 placebo and 9 active-drug subjects after approximately 1 week of double-blind therapy. A note in one of the case report forms provided clarity and explained why there were irregularities in the data for the double-blind portion of the study. Standard normal clinical study practice stipulates that all study data is preserved, however the CRF notation (for patient (b) (6)) contains this statement:

> "Please delete all entries for Visit 14 as subject did not complete visit as subject had severe worsening of [symptoms] on ADHD-RS-IV from V13 to V 14. Subject entered Open-label."

Also, the Applicant did not send the finalized statistical plan to FDA for approval prior to the end of the study, as stipulated in the WR.

Reviewer note:

The fact that the 14 of the 90 subjects randomized to the double-blind phase of study RP-BP-EF003 did not meet eligibility criteria renders all the analysis of the study post-hoc and suggests a potential for the occurrence of other errors. This particular error, however, leads to a more conservative analysis since these non-responders were not

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excluded from evaluation in the double-blind phase of the study as was the original intent of the study design. The effect of this error appears unlikely to change the conclusions of the study.

3.2 Compliance with Good Clinical Practices

The Applicant certifies that the studies were conducted in accordance with Good Clinical Practices, including the archiving of essential documents.

3.3 Financial Disclosures

Was a list of clinical investigators provided: Yes ☒ No ☐

Total number of investigators identified: _132_

Number of investigators who are Applicant employees (including both full-time and part-time employees): ____0_____

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): ___1___

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: __0_

Significant payments of other sorts: __1__

Proprietary interest in the product tested held by investigator: _0__

Significant equity interest held by investigator in sponsor of covered study: _0__

Is an attachment provided with details of the disclosable financial interests/ arrangements: Yes ☒ No ☐ N/A ☐

Is a description of the steps taken to minimize potential bias provided: Yes ☐ No ☐ N/A ☒

Number of investigators with certification of due diligence (FDA 3454, box 3) __0__

Is an attachment provided with the reason: Yes ☐ No ☐ N/A ☒

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4 Significant Issues from Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Not Applicable.

4.2 Clinical Microbiology

Not Applicable.

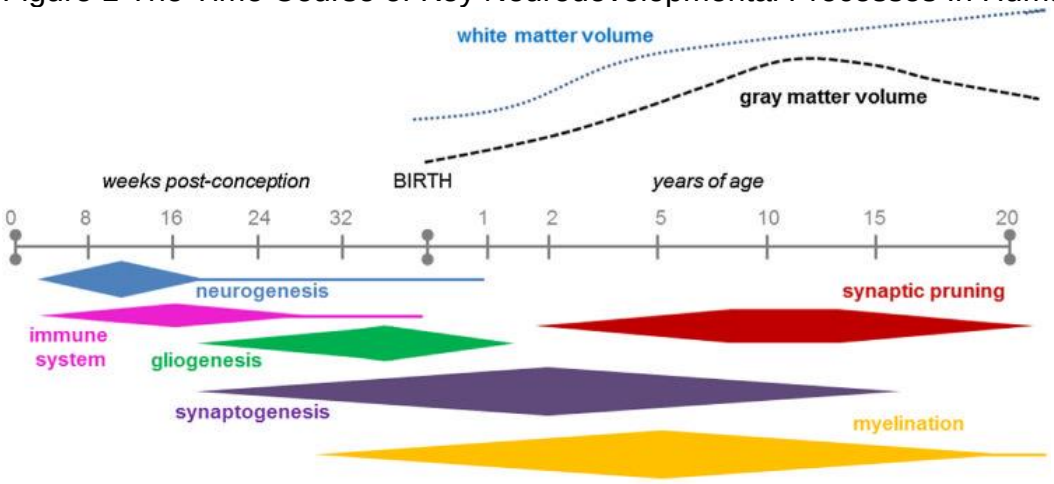
4.3 Preclinical Pharmacology-Toxicology

As there are no studies of the long-term neuropsychiatric effects of MPH dosed in preschool age children, animal studies may help provide information about safety. There were no preclinical studies conducted as part of this Application, however, Aptensio XR draft labeling includes the following:

> "Juvenile Animal Toxicity Data
>
> Rats treated with methylphenidate early in the postnatal period through sexual maturation demonstrated a decrease in spontaneous locomotor activity in adulthood. A deficit in acquisition of a specific learning task was observed in females only. The doses at which these findings were observed are at least 6 times the maximum recommended human dose (MRHD) of 60 mg/day given to children on a mg/m^2 basis.
>
> In the study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (postnatal day 7) and continuing through sexual maturity (postnatal week 10). When these animals were tested as adults (postnatal weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day (approximately 6 times the MRHD of 60 mg/day given to children on a mg/m^2 basis) or greater, and a deficit in the acquisition of a specific learning task was observed in females exposed to the highest dose (8 times the MRHD given to children on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (approximately 0.5 times the MRHD given to children on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown."

As noted in the figure below, the 4 to 5-year-old age is a critical time of synaptogenesis and myelination (Semple, Blomgren et al. 2013), indicating a potential for MPH administered during this vulnerable age to have long-term effects on the development of the brain.

Figure 1 The Time Course of Key Neurodevelopmental Processes In Humans



During ages 4 and 5 years, the brain increases in volume and undergoes synaptogenesis and myelination as well as early synaptic pruning (Semple, Blomgren et al. 2013).

Animal studies that show dosing with MPH during development causes aberrant behavioral adaptations during adulthood are particularly important to consider (Bolanos, Barrot et al. 2003). Chronic exposure to MPH (2mg/kg) during development can damage the BBB in rats, causing neuroinflammation and aberrant behavioral adaptations, which persist through adulthood (Bolanos, Barrot et al. 2003). These alterations in animal behavior may parallel the manifestation of depression, anxiety, and other psychopathology in adult humans (Bolaños, Willey et al. 2008).

One recent study employing pre-adolescent rats found that dose levels of MPH (5 versus 1.5 mg/kg/day) promoted blood-brain barrier (BBB) permeability and induced a robust neuroinflammatory and oxidative response (Coelho-Santos, Cardoso et al. 2018). The dose of MPH given during development maybe a critical factor, as higher doses cause the atrophy of astrocytes and impairment of working memory whereas, in some animals, a lower dose enhances cognitive skills and promotes neuronal plasticity (Coelho-Santos, Cardoso et al. 2018).

In section M2.4.4, the Applicant provides a summary of available literature concerning MPH. Maximum tolerated doses (MTD) for MPH were identified as 100 mg/kg/day in rats, based upon hyperactivity, hypersensitivity, and self-mutilation, and 10 mg/kg/day in dogs, based upon hyperactivity, salivation, and elevated body temperature. The no-observed-adverse-effect-level (NOAEL) for *d,l*-MPH were <40 mg/kg/day for rats and 2 mg/kg/day for dogs. (For comparison, the maximum dose allowed in the Aptensio XR preschool program was 60 mg, which, for a 20 kg child, is 3 mg/kg/day which is greater than the 2 mg/kg/day NOAEL for dogs).

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These studies indicate that MPH, administered to animals at doses which are relevant for children, have negative effects on the brain, behavior, and the blood brain barrier accompanied by multiple signs of neuroinflammation. This was discussed with Ikram Elayan, PhD , Pharmacology & Toxicology Supervisor, "The animal literature is not reassuring - We do not have animal data to support safety in regard to neurological or psychiatric issues…It is apparent that dose will make the difference and the higher the doses the more toxic effect you will see (and there is a lot) and that these drugs have a potential to be beneficial for ADHD kids but need to weigh the risk to the benefit." "We know that MPH was associated with deficits in learning in juvenile animal studies, and the label says so. There is a lot of literature about the neurotoxicity of amphetamines and MPH…As far as the dose and side effect, it will have to be a risk benefit thing that we always have to deal with. Not sure if some clinical trials or human experience with these drugs can be tracked over the years to see if the risk weighs the benefit of these drugs for ADHD kids. That is what we need, but not sure who will do that."

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The pathological basis for ADHD is currently unknown—as is the reason for stimulant efficacy in the disorder.

4.4.2 Biopharmaceutics/Pharmacokinetics

Study RP-BP-PK003, a single-dose, open-label, pharmacokinetic study of Aptensio XR in children 4 to less than 6 years of age with ADHD demonstrated differences when compared to the results in older individuals. The overall exposures (AUC0-inf and AUC0-t) increased by 2-3-fold in pediatric patients 4 to under 6 years of age compared with adults and pediatric patients 6 to 12 years of age. An approximately 2-fold increase in Cmax was also observed in pediatric patients 4 to under 6 years of age as compared to adults and pediatric patients 6 to 12 years of age. Tmax across different populations are similar (2 to 3 h). In addition, longer half-life was observed in pediatric patients 4 to under 6 years compared with adults and pediatric patients 6 to 12 years of age. Of note, after oral dosing, methylphenidate is rapidly absorbed from the GI tract.

The DPP Clinical Pharmacology study reviewer, Di Zhou, notes that (based on the previous OCP review dated on 3/27/2015) at mean level, Aptensio XR pharmacokinetic profiles in adults and in pediatric patients 6 to 12 years old both show double peaks with similar shape with pediatric patients receiving different doses demonstrating large variability in the shape of their respective mean pharmacokinetic profiles.

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Di Zhou notes that that the Tmax for the second peak varies in pediatric patients 4 to under 6 years of age, ranging from 6 to 12 hours under different doses. See Figure 2. A scrutiny of individual PK profiles of the ten subjects in the study demonstrated that the three peaks observed for the 20-mg group is due to interindividual variability. Excluding this variability, the second peak appears at 10 to 12 hours in general, later than the ones observed in adults and pediatric patients 6 to 12 years (8 hours). An approximately 3- to 4-fold increase in the second Cmax was also observed in pediatric patients 4 to under 6 years of age as compared to pediatric patients 6 to 12 years of age and adults; see Figure 4.

Figure 2, Mean d, l-Methylphenidate Plasma Concentration-Time Profiles Following 10 mg, 15 mg and 20 mg Administered as a Sprinkle Dose to Children (4 to Under 6 Years of age) with ADHD.

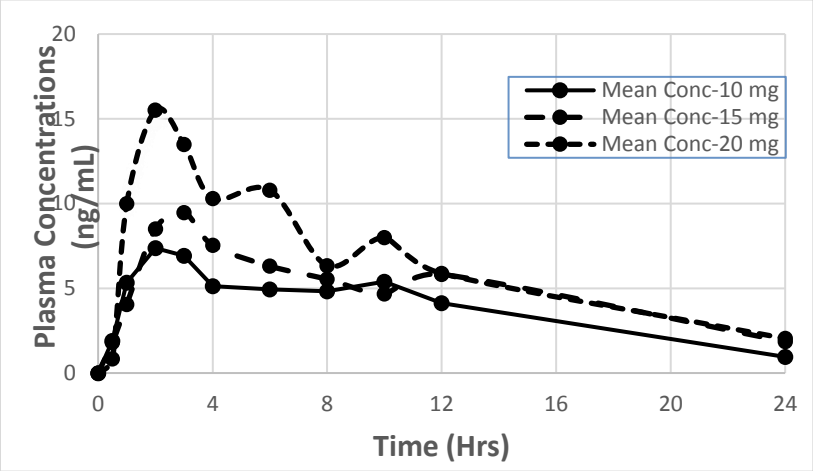

Figure 3, Mean *d, l*-Methylphenidate Plasma Concentration-Time Profiles Following 80 mg Administered as Capsule and Sprinkle Doses in Healthy Adults, from Aptensio XR Label.

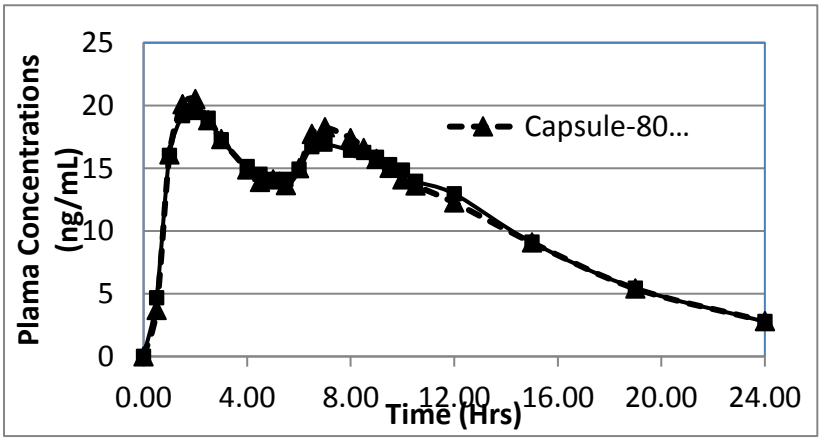

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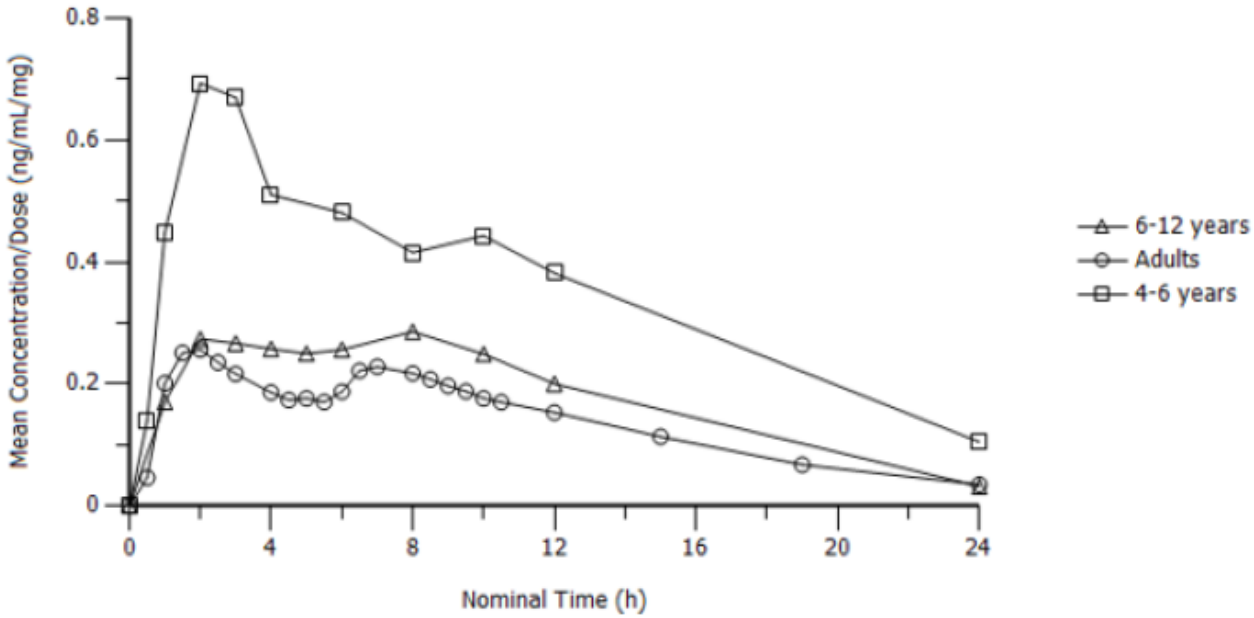
Figure 4, Dose Normalized Cartesian Plot in ng/mL of Methylphenidate HCl Plasma Concentrations as a Function of Time from Studies of Children 4 to under 6 Years, Children 6 to 12 Years and Adults Following Single Dose Administration of Aptensio XR.



Age Group 4-6 years: Study RP-BP-PK003 (10 mg, 15 mg, and 20 mg Aptensio XR® [methylphenidate hydrochloride] ER capsules)
Age Group 6-12 years: Study 022-001 (20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 80 mg Biphentin® CR [methylphenidate HCl] controlled-release capsules)
Adults (aged 18-45 years): Study RP-BP-PK001 (T1, 80 mg Biphentin® CR [methylphenidate HCl] extended-release capsules)

Reviewer note:

*The 2- to 3-fold greater Cmax observed in children age 4 and 5 when compared to adults is striking. This can also be seen in Figures 2 and 3. These figures show that the plasma concentrations achieved by adults given 80 mg (*Figure 3*) are only slightly more than the concentration reached when preschoolers are given 20 mg (*Figure 2*) ¼ of the adult dose.* (b) (4) .

These PK results suggest that the metabolism of MPH is different in older children compared to preschool children who have a higher exposure on a weight for kilogram basis. This increased exposure and the safety signal suggested by a high rate of

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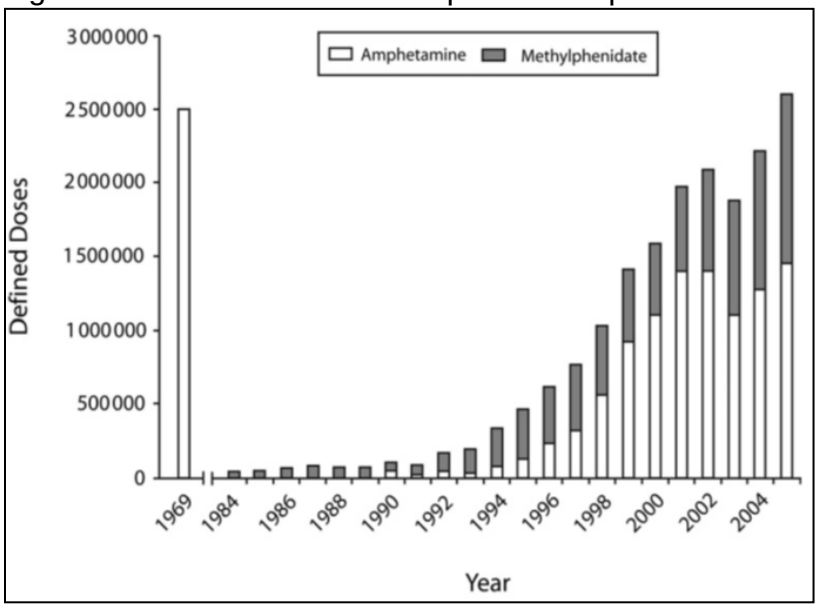
psychiatric AEs, creates concern about the safety of using MPH in this vulnerable population, particularly at the higher doses commonly employed.

Considering the 2+ fold increase in exposure in pediatric patients 4 to 6 years compared with pediatric patients 6 to 12 years of age, the starting dose used in this program appears to be too great. Of note, a lower dose was used in the PATS study. If the double-blind study had been delayed until the PK results were available, as was initially stipulated in the WR, this consideration should have led to the creation of a lower strength dose form to use in these small children. The PK results are consistent with those reported from the PATS study (Wigal, Gupta et al. 2007).

4.5 Controlled Substances

Methylphenidate is currently DEA schedule II and is a known drug of abuse. In a recent national survey, of the approximately 16.0 million U.S. adults who reported prescription stimulant use in the preceding year, 5.0 million reported misuse, and 0.4 million had use disorders. One household survey of stimulant abuse found that approximately half of the 3.2 million individuals who reported non-medical stimulant use in the last year used only pharmaceutical stimulants and a quarter had only ever used pharmaceuticals. As of 2002, there were approximately 303,000 individuals characterized as having physical dependency or addiction to amphetamine. The use of use of MPH has increased as noted in Figure 2.

Figure 5. U.S. Medical Consumption of Amphetamine and Methylphenidate.



Defined dosages: 10 mg amphetamine and 30 mg methylphenidate, anhydrous base.
Source: *American Journal of Public Health* 98.6 (2008): 974-985.

Reviewer note:

From a historical perspective, the increased prescriptive use of stimulants has led to increased abuse, physical dependency, addiction, and death. If history is used as a guide, the increased death rate, which invariably results from increased prescriptive use, will lead to increased awareness of the dangers of stimulants, renewed attempts to mitigate their risk, and a reduction of their use for ADHD. The increase in national consumption and increase in annual prescriptions of stimulant medications should make us vigilant to avoid a repeat of past episodes of abuse (Swanson and Volkow 2008).

4.6 Pediatric and Maternal Health

There is no pertinent new data in this Application regarding maternal health. Information on pediatric use is noted under the appropriate sections of this review.

5 Sources of Clinical Data

5.1 Table of Clinical Trials

Table 2. Clinical Studies Supporting NDA Submission

Study Number	Description	Population and Formulation
RP-BP-PK003	A single-dose, open-label, pharmacokinetic study	Aptensio XR in children 4 to less than 6 years of age with ADHD
RP-BP-EF003	A randomized, double-blind, placebo-controlled, flexible-dose titration study	Aptensio XR in children ages 4 to under 6 years with ADHD
RP-BP-EF004	A 12-month open label safety study	Aptensio XR in children ages 4 to under 6 years with ADHD

5.2 Review Strategy

The design of Study RP-BP-EF003 created significant issues for interpretation. The lead-in open-label phase was followed immediately by a relatively short double-blind phase with no washout period. This allowed children receiving placebo and withdrawing from methylphenidate to be compared with those who continued on their same dose and created the potential for symptoms of withdrawal from MPH to confound the comparison of placebo with Aptensio XR. Children whose condition became worse before the end of the double-blind phase were discontinued after less than 2 weeks of treatment. Also, if the drug caused adverse events in the open-label phase and these symptoms persisted, they were not counted as new drug-related adverse events in the double-blind phase.

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In light of the above considerations, the best data available for a safety review is derived from the two, 6-week periods leading up to the double-blind phase of Study RP-BP-EF003. Although not blinded, these two phases provide a comparison of adverse events on- and off-drug. I also reviewed the available literature on the efficacy and safety of MPH in this age group.

Another issue which complicated the review was that the double-blind portion of Study RP-BP-EF003 was designed so that any subject who became worse (based on investigator discretion and ≥50% worsening of symptoms on the ADHD-RS-IV and a CGI-I of 6 or 7) could be discontinued after 1 week. Of the 89 subjects randomized in the double-blind phase, 29 subjects were discontinued for this reason. Of these 29 subjects, 23 met the discontinuation criteria and 6 subjects were discontinued based on investigator discretion. The 60 subjects who completed 2 weeks of double-blind treatment to the endpoint visit included 4 who had met the discontinuation criteria but were not discontinued.

Reviewer Note:

The design issues of Study RP-BP-EF003 render the double-blind phase of this study ineffective for evaluating the efficacy and safety of Aptensio XR. At the planning stage of these studies, the agency did not agree to the proposed study design (refer to Written Request issued on May 11, 2016). DPP has since developed guidelines, "Attention Deficit Hyperactivity Disorder: Developing Stimulant Drugs for Treatment Guidance for Industry"[2], which make a number of applicable recommendations. Significantly, the guidelines note that an Applicant should evaluate the onset and duration of the clinical effect in an adequate and well-controlled trial conducted in a laboratory classroom setting. The guidelines also note that factors to be considered regarding the extrapolation of safety and efficacy between age groups include the PK profile of the active moiety in different age groups, a clearly defined dose for specific age groups, and products with a period of action of less than 12 hours.

For the 29 subjects who were discontinued from the double-blind phase of Study RP-BP-EF003, the study sites were requested by the Applicant to delete data from Visit 14 and record the Visit 14 data as a "Visit 15." Therefore, for these 29 subjects, the data obtained at the first post-baseline visit (Visit 14) were recorded as "Visit 15" in the CDISC SDTM data and in the analysis datasets. This highly non-standard way of constructing a database obfuscated the effect of Aptensio XR in this Application and complicated the review.

[2] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/attention-deficit-hyperactivity-disorder-developing-stimulant-drugs-treatment-guidance-industry

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6 Review of Efficacy

Efficacy Summary

Efficacy Summary

I conclude that the efficacy data of Study RP-EF-003 is not useful to describe the efficacy of Aptensio XR (b) (4).

The primary efficacy objective of Study RP-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 Aptensio XR responders, those 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).

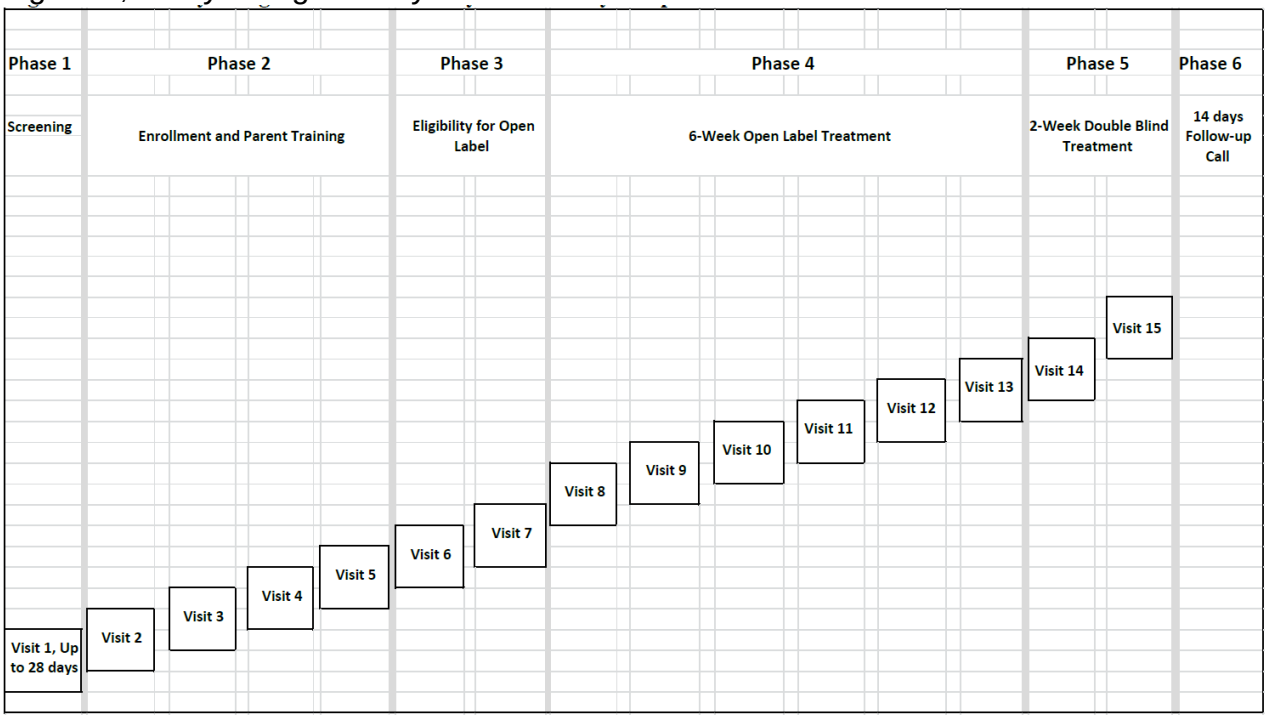
The Applicant's efficacy analysis deviated from the pre-specified primary efficacy. The FDA's statistical reviewer points out in his review that the ADHD-RS-IV total score data of the Applicant's primary efficacy analysis contained many intermediate visit (Week 1) measurements. Specifically, more than 30% of the randomized subjects were discontinued before the primary efficacy endpoint visit; they did not have a Week 2 measurement but only an intermediate visit (Week 1) measurement, and the Applicant used this is Week 1 measurement in their primary analysis. Utilizing subjects with endpoints at both Week 2 and Week 1, the Applicant reported the primary efficacy estimate of 11.2 points in favor of Aptensio XR, based on an ANOVA-based analysis of the change from baseline score in the ADHD-RS-IV total score. However, the inclusion by the Applicant of the discontinued subjects in the primary efficacy evaluation leads to a much larger effect estimate in contrast to the raw mean difference between Aptensio XR and placebo obtained from the Week 2 measurements. In contrast, the FDA statistical reviewer found that the mean difference in the change from baseline score of ADHD-RS-IV total score at the Week 2 endpoint between Aptensio XR and Placebo was only 7.3 points in favor of Aptensio XR (59 subjects had their Week 2 measurement). Given that a great majority of discontinuations were due to the protocol-defined Discontinuation Eligibility Assessment, and the fact that randomization was not conducted on responders as planned in the protocol but on almost all open-label completers, the ADHD-RS-IV total score efficacy data is difficult to interpret.

6.1 Methods

Study RP-BP-EF003

Efficacy was determined from Study RP-BP-EF003. The primary efficacy objective of Study RP-BP-EF003 was to compare Aptensio with placebo at 2-weeks on the ADHD-RS-IV total score. Subjects were male and female children ages 4 and 5 years old who had a diagnosis of ADHD for > 6 months. The diagnosis of ADHD was based on Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) criteria determined using the Kiddie-SADS (Schedule for Affective Disorders and Schizophrenia) - Present and Lifetime Version (K-SADS-PL). All subjects had adjusted ratings of ≥ 90th percentile Total Score on the ADHD Rating Scale (ADHD-RS-IV) Preschool Version. The ADHD-RS-IV consists of 18 items designed to reflect current symptomatology of ADHD based on DSM-5 criteria. Each item is scored from a range of zero (reflecting no symptoms) to 3 (reflecting severe symptoms) with total scores ranging from 0 to 54. In addition, subjects were required to have a score of < 65 on the Child Global Assessment Scale (CGAS), a Clinical Global Impression of Severity (CGI-S) score of ≥ 4, and an IQ ≥ 80. The study consisted of six phases: (1) screening / washout; (2) enrollment and parent training; (3) eligibility determination; (4) 6-week open-label dose titration; (5) a double-blind phase for responders; and (6) a 2-week follow-up call. See Figure 6.

Figure 6, Study Design: Study RP-BP-EF003



The enrollment and parent training phase was employed to assess the efficacy of non-pharmacological intervention and included behavior management techniques and ADHD education occurring during 90-minute visits (Visits 2-5).

Open Label Phase (OL), Study RP-BP-EF003

Eligibility for the open label phase occurred if participants had severe symptoms or if parent training did yielded < 30% improvement in ADHD-RS-IV and CGI-I score of >3. The ADHD-RS-IV was scored by the investigator during an interview with the parent. At visit 7, the 10mg Aptensio XR was administered in the morning, and could be raised to 15, 20, 30, or 40 mg, as guided by the ADHD-RS-IV rating scale to reach an optimal dose. An optimal dose was a dose producing a reduction from Visit 7 of ADHD symptoms of at least 30% and a CGI-I compared to Visit 7 of “much improved” or “very much improved” with tolerable side effects.

Double Blind Phase

Subjects who had ≥30% response on the ADHD-RS-IV and a CGI of “much” or “very much improved” at the end of Visit 13 were eligible for randomization to receive their optimal dose of Aptensio XR or placebo during the double-blind phase. (Note: This criterion was not uniformly applied as noted in Section 3.1). Blinded study drug was dispensed at Visit 13 and begun on the morning after Visit 13. Subjects who had a ≥50% worsening of symptoms on the ADHD-RS-IV at Visit 14 (compared to Visit 13, 1 week into the Double-Blind Phase) and a CGI-I of “much worse” or “very much worse” compared to Visit 13 could be discontinued from the Double-Blind Phase after completing end-of-study (Visit 15) procedures. These procedures included the ADHD-RS-IV, CGI-S, CGI-I, adverse event collection and a physical exam and ECG (see Table 3). The primary efficacy measure was change from baseline in ADHD-RS-IV Total Score from Visit 13 to Visit 15. Subjects who were discontinued because of deteriorating symptoms could enter the Open-Label Extension Study.

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Figure 7 ADHD Rating Scale (ADHD-RS-IV) Preschool Version

Circle the number that **best describes** the child's behavior over the past 6 months.

	never or rarely	sometimes	often	very often
1. Fails to give close attention to details (i.e. rushes through activities, makes careless mistakes)	0	1	2	3
2. Fidgets with hands or feet or squirms in seat (taps hands or feet)	0	1	2	3
3. Has difficulty sustaining attention in tasks or play activities	0	1	2	3
4. Leaves seat in classroom, during meals, or in other situations in which remaining seated is expected	0	1	2	3
5. Does not seem to listen when spoken to directly (tunes you out)	0	1	2	3
6. Runs about or climbs excessively in situations in which it is inappropriate	0	1	2	3
7. Does not follow through on instructions and fails to finish tasks (i.e. "go upstairs, get your shoes, and socks;" has difficulty with transitions)	0	1	2	3
8. Has difficulty playing quietly (alone or in groups)	0	1	2	3
9. Has difficulty organizing tasks and activities (i.e., choosing an activity, getting materials, doing steps, in order)	0	1	2	3
10. Is "on the go" or acts as if "driven by a motor"	0	1	2	3
11. Avoids tasks that require sustained mental effort (i.e., puzzles, learning ABC's, writing name)	0	1	2	3
12. Talks excessively	0	1	2	3
13. Loses things necessary for tasks or activities (mittens, shoes, backpack)	0	1	2	3
14. Blurts out answers before questions have been completed	0	1	2	3
15. Is easily distracted	0	1	2	3
16. Has difficulty awaiting turn	0	1	2	3
17. Is forgetful in daily activities(forgets papers, forgets directions)	0	1	2	3
18. Interrupts or intrudes on others	0	1	2	3

Secondary endpoints relative to baseline were:

- ADHD-RS-IV hyperactivity/impulsivity and inattention subscales (Composed of the even-numbered items from the ADHD Rating Scale (ADHD-RS-IV) Preschool Version)
- Clinical Global Impression Scale—Severity (CGI-S)
- Clinical Global Impression Scale—Improvement (CGI-I)
- Conners Early Childhood Behavior—Parent Short form (Conners EC BEHP[S])

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Table 3, Study RP-BP-PK003 Assessments

	Screening (Phase 1)	Wash-out Call	Enrollment & Parent Training (Phase 2)				Eligibility for 0pen-Label (Phase 3)		Open-Label Treatment (Phase 4)						Double-Blind Treatment (Phase 5)		14 Day Follow up (Phase 6)
Visit (Visit window is)	1	No	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Study Day	Up to -28	-7 to -3	0	7	14	21	28	42	49	56	63	70	77	84	91	98	112
Study Week	Up to -4	-1	0	1	2	3	4	6	7	8	9	10	11	12	13	14	16
KSADS-PL Structured Interview	X																
KBIT-2, CGAS	X																
ADHD-RS-IV Rating	X		X				X	X	X	X	X	X	X	X	X	X	
Conners EC BEH-	X							X						X		X	
CSHQ	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X
Demographics	X																
Physical exam, EKG	X															X	
Inclusion /Exclusion	X	X	X														
Body Weight	X		X				X	X	X	X	X	X	X	X	X	X	
Height	X						X									X	
Sitting Vital Signs	X		X				X	X	X	X	X	X	X	X	X	X	
Parent Training			X	X	X	X											
Urinalysis, Drug Test Hematology,							X										
CGI-S	X		X				X	X						X		X	
CGI-I							X		X	X	X	X	X	X	X	X	
C-SSRS	X		X				X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Open-Label								X	X	X	X	X	X				
Randomization														X			
Dispense Double-Blind														X	X		
Dose Assessment									X	X	X	X	X				

Kiddie-SADS-Present and Lifetime Version (KSADS-PL Structured Interview) ; Kaufman Brief Intelligence Test, Second Edition (KBIT-2); Children's Global Assessment Scale (CGAS); Attention Deficit Hyperactivity Disorder Rating Scale-IV Preschool Version (ADHD-RS-IV Rating Scale); The Conners Early Childhood Behavior—Parent Short (Conners EC BEH-P[S]); Children's Sleep Habits Questionnaire (CSHQ) Columbia Suicide Severity Rating Scale (C-SSRS)

Statistical methods for Primary Efficacy Analysis:

The protocol/statistical analysis plan defines the primary endpoint as 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 last visit of the Randomized 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.

The Applicant planned a discontinuation eligibility assessment based on efficacy data obtained at Visit 14, ADHD-RS-IV total score and CGI-Improvement. This created the potential to have missing efficacy data of the primary efficacy endpoint (Visit 15). The

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statistical team asked the Applicant to specify a method to handle the missing data issue. The Applicant did not clarify the concern and the final statistical analysis plan (SAP) does not specify a method to handle this missing data issue. During the study, 29 randomized subjects, about 34% of the randomized subjects, discontinued due to worsened symptoms and had missing efficacy data from the primary endpoint (Visit 15). Because the Applicant did not have agreement with the agency on the method of handling the missing data, evaluation of the primary efficacy became a matter of review.

Study RP-BP-EF004

Study RP-BP-EF004 was a long-term safety study of Aptensio XR in children ages 4 to 5 years diagnosed with ADHD. Subjects entered the12-month maintenance phase by two pathways: after participation in Study RP-BP-EF003 or after Study RP-BP-PK003. Subjects were male or female children with a diagnosis of ADHD (combined, inattentive, or hyperactive/impulsive type) based on DSM-5 criteria, who were 4 to less than 6 years of age at time of consent for their participation. Subjects completed the Screening/Baseline assessments the same day as the end of study visit for the prior study in which they participated. They began Aptensio XR treatment at their previously determined optimal dose. Study visits were scheduled for every 4 weeks for 12 months. A total of 90 ongoing subjects were enrolled from the two prior studies, 9 from RP-BP-PK003 and 81 from RP-BP-EF003.

Reviewer Note:

The population of Study RP-BP-EF-003 was an enriched (responder) population. There was no washout period before the placebo-controlled study creating a potential for confounding effects. A randomized, double-blind, placebo-controlled, parallel-group design trial conducted with a non-enriched population, which employed a simulated classroom direct-observation study would have provided more clinically meaningful results.

It is noted that almost all subjects who completed the OL phase were randomized and that 13 of the 90 randomized subjects did not meet the randomization criteria.

Subjects who had a ≥50% worsening of symptoms on the ADHD-RS-IV at Visit 14 (one week into the Double-Blind Phase) and a CGI-I of "much worse" or "very much worse" compared to Visit 13 could complete the end-of-study (Visit 15) procedures and discontinue the study after only 1 week of double-blind therapy. This led to a significant review issue with the missing primary efficacy endpoint data. The designed (planned) removal of randomized subjects based on individual efficacy data before the primary endpoint visit may make it difficult to interpret the pre-specified primary analysis results, because the defined primary analysis data may not represent the target study population.

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It is significant that Study RP-BP-EF004 has relatively few subjects who completed the year-long period of observation.

The protocol stipulates that each subject is evaluated for the presence of other psychiatric disorders, but the potential exists for children with PTSD to be misdiagnosed with ADHD, based on the overlap of symptoms as noted in the literature (Thomas 1995). This possibility was not noted in the protocol and there exists the possibility that some of the children had PTSD rather than ADHD (Brown, Brown et al. 2017). The ADHDRS- IV *Rating scale has been used often for evaluation of medication effects on ADHD, but of the 18 items on the scale, perhaps 2/3 of them are characteristic of childhood PTSD symptoms. Without careful exclusion of children PTSD, the ADHDRS-IV may not be fit-for-use as an endpoint in a study such as this. A proper evaluation of children with presumed ADHD should include careful exclusion of those with PTSD.*

6.2 Subject Disposition

Study: RP-BP-EF003

The study report summarizes the subject disposition of Study RP-EF-003 (see Table 4 and Figure 8). The Study screened 194 subjects, of whom 132 entered the enrollment and parent training phase. Of the 132 enrolled subjects, 128 were eligible for open-label treatment, 119 entered open-label treatment, and 90 open-label completers were randomized to double-blind treatment. 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 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. It should be noted that because one subject was lost to follow-up and was not assigned a treatment group, the efficacy evaluation may be performed on the 89 treated randomized subjects.

For the evaluation of the primary efficacy, the Applicant's summary may be misleading, because 23 subjects who were found to have met Discontinuation Eligibility Criteria were discontinued at the first post baseline visit; of the 89 treated randomized subjects, 30 subjects in total did not have their second post-baseline visit (primary endpoint) efficacy assessment and 59 subjects had the first and second post-baseline assessments in the DB phase. It is noted that we found there were 29 subjects who met

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the Discontinuation Eligibility Criteria, and thus 6 subjects (29 minus 23) who met the criteria were not discontinued as the protocol specifies.

Table 4, Subject Disposition from the Applicants Study Report

	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.)

Note: 29 subjects were discontinued before the completion of the two-week double bind period based on investigator discretion and ≥50% worsening of symptoms on the ADHD-RS-IV from Visit 13 and a CGI-I of 6 or 7 at Visit 14. Therefore, the total number (%) of Subjects Discontinued from the Study After Randomization was 33 (20.9). Source: Table 8 of the study report (page 63-64)

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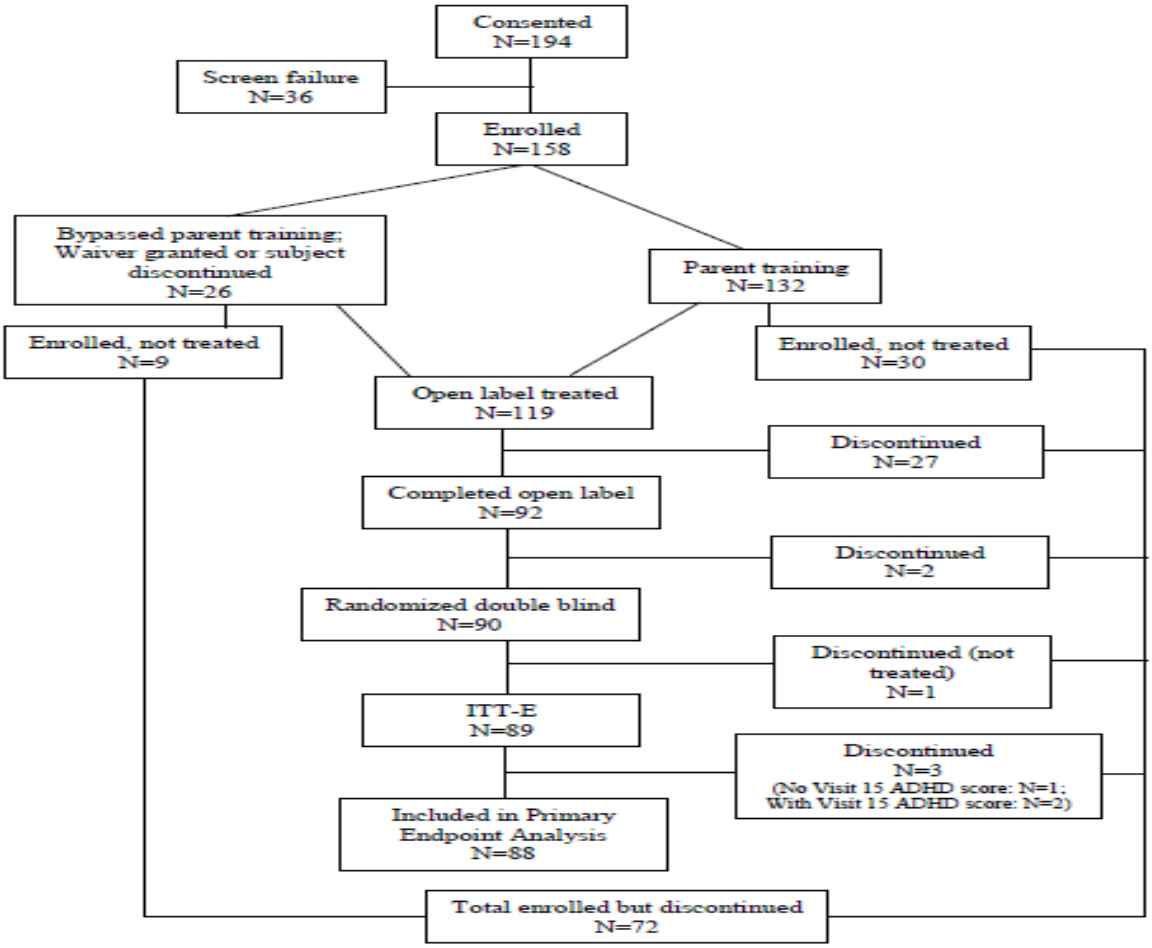
Figure 8, Study RP-BP-EF003 Subject Disposition (Constructed by Applicant)



The above figure was constructed by the Applicant; not indicated in Figure 8 is the fact that during the 2-week double-blind phase, 30 subjects were discontinued after 1 week of double bind therapy. These 30 subjects were included in the Primary Endpoint Analysis by the Applicant although they did not have the primary endpoint efficacy assessment from the 2-week end point of the double-blind phase; the Applicant described them as a "completer."

Study: RP-BP-EF004 – Interim Analysis

All subjects in Study RP-BP-EF004 were enrolled from either RP-BP-PK003 or RP-BP-EF003. Forty-four (44) subjects (48.8%) discontinued from the study either during or after the maintenance phase. At the time of the interim analysis data cut, a total of 31 subjects had completed the study (see Figure 10 and Table 5).

Table 5, Subject Enrollment (Consented Population)

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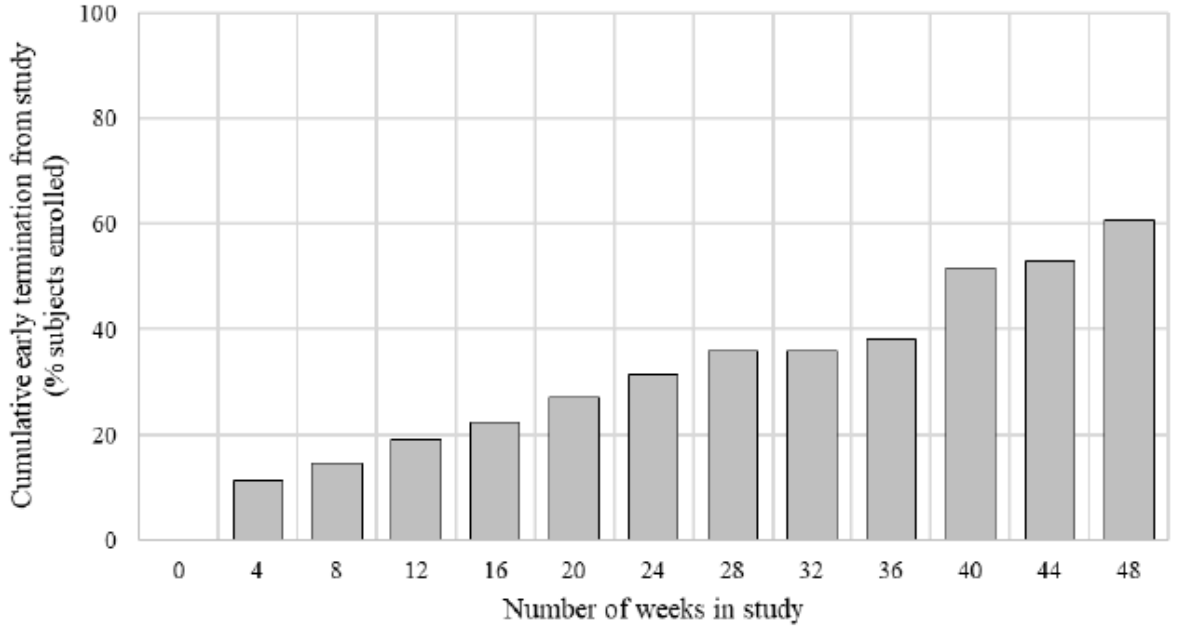
	New Subjects	Ongoing	Overall
Number of Subjects Screened	0	92	92
Number of Subjects in Dose Optimization Phase	0	0	0
Number of subjects who were a screen failure	0	2	2
Number of enrolled subjects	0	90 (100)	90 (100)
Number (%) of Subjects Discontinued from the Study Before Maintenance Phase	0	1 (1.1)	1 (1.1)
Number (%) of Subjects in Maintenance Phase	0	89 (98.9)	89 (98.9)
Number (%) of Subjects Who Completed the Study at the Time of the Interim Analysis Data Cut	0	31 (34.4)	31 (34.4)
Number (%) of Subjects Discontinued from the Study During/After Maintenance Phase	0	44 (48.8)	44 (48.8)

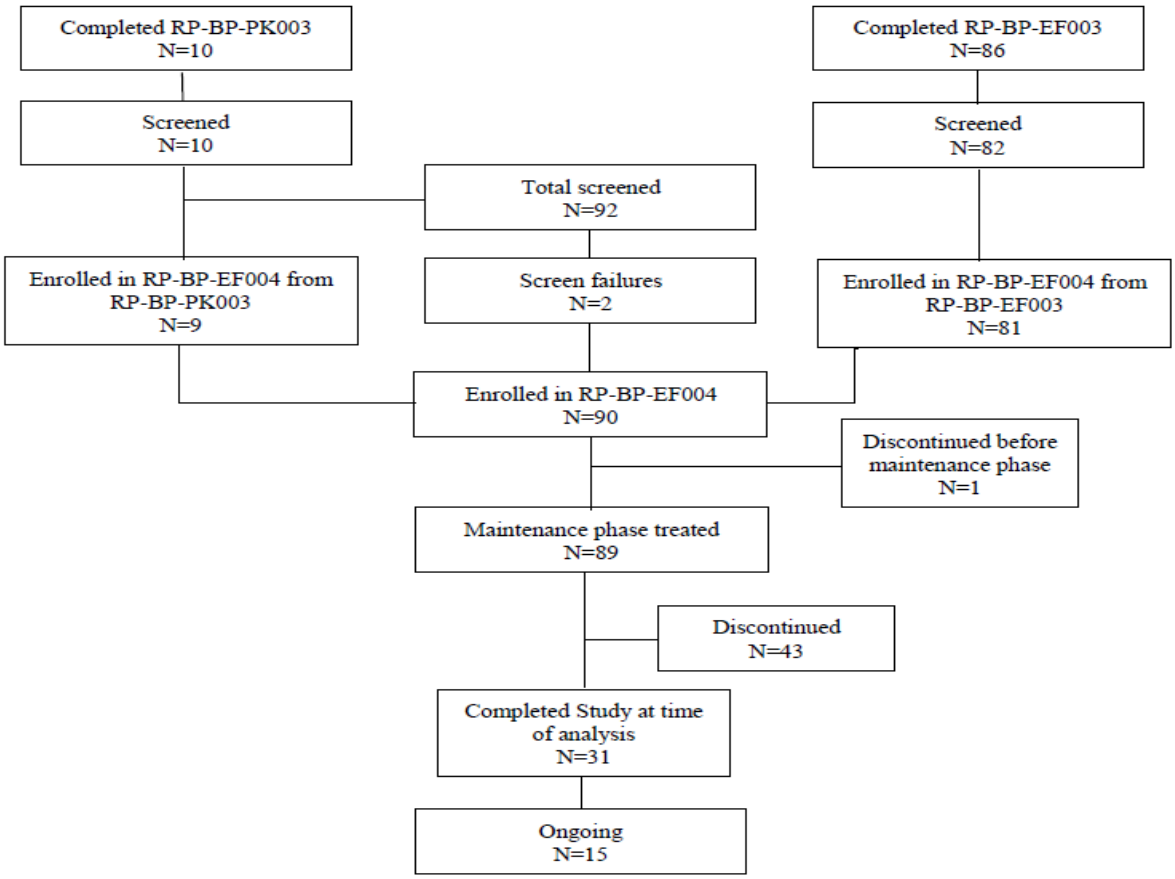
Source: Listing 16.2.1.1

Figure 9, Cumulative Early Withdrawal from Study as a Percentage of Enrolled Subjects.



The above figure was constructed by the Applicant and displayed in the Clinical study report.

Figure 10, Study RP-BP-EF004 Subject Disposition



The above figure was constructed by the Applicant.

6.3 Analysis of Primary Endpoints

Applicant's Primary Efficacy Analysis and Evaluation, RP-BP-EF003

As stated in the Protocol concerning the 2-week long double-bind phase, "the primary efficacy measure is the comparison of the two treatment groups (optimized dose vs placebo) using the change in ADHD-RS-IV Total Score during the double-blind phase, i.e., the change from end-of-open-label phase to end-of-double-blind phase." However, the Applicant's primary analysis was based on 59 subjects who completed the 2-week double-blind phase and 30 subjects who were discontinued before having ADHD-RS-IV total score assessment at the primary efficacy endpoint visit. As described in the previous section, 23 subjects who were found to have met the Discontinuation Eligibility criteria were discontinued and 7 subjects discontinued for some other reason.

The Applicant's primary analysis showed a LS Mean Estimate (ANOVA; N=89) difference of -11.2 (95% CI: -18.0, -4.4; p=0.002) for Aptensio XR compared to placebo. However, this analysis contains subjects other than the target study population

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(subjects who completed the 2-week double-blind randomized treatment) and this analysis result is difficult to interpret and may not provide a basis for drawing a conclusion on the efficacy the primary efficacy objective defines.

The Applicant also presented a re-submission analysis conducted using the smaller group of subjects meeting responder criteria as specified in the protocol. It was found after the initial submission that the Applicant did not randomize the responders as the protocol defines but all open-label subjects who completed the open-label phase. The result of this re-submitted analysis was similar (see details below).

The Applicant stated: "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." However, for the same reason as for the initial Applicant's primary analysis result, the re-submitted analysis result is difficult to interpret and may not provide a basis for drawing a conclusion on the efficacy the primary efficacy objective defines.

DPP Statistical Reviewer's Analysis of Primary Efficacy Endpoint, RP-BP-EF003

The DPP biometrics reviewer, Eiji Ishida, analyzed the data from the double-blind portion of the study.

The primary efficacy objective of Study EF-003 was to evaluate the efficacy of Aptensio in comparison with placebo at the endpoint of the randomized 2-week long double-blind period on responders (defined as subjects who meet Randomization Criteria). The randomization criteria were based on the efficacy assessments using ADHD-RS-IV total score and CGI-I score, over the 6-week open-label Aptensio exposure.

The study protocol defines the primary endpoint as change from baseline (Visit 13) to Visit 15 in ADHD-RS-IV total score. 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 is 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.

The details can be found in the biometrics review of this supplemental NDA.

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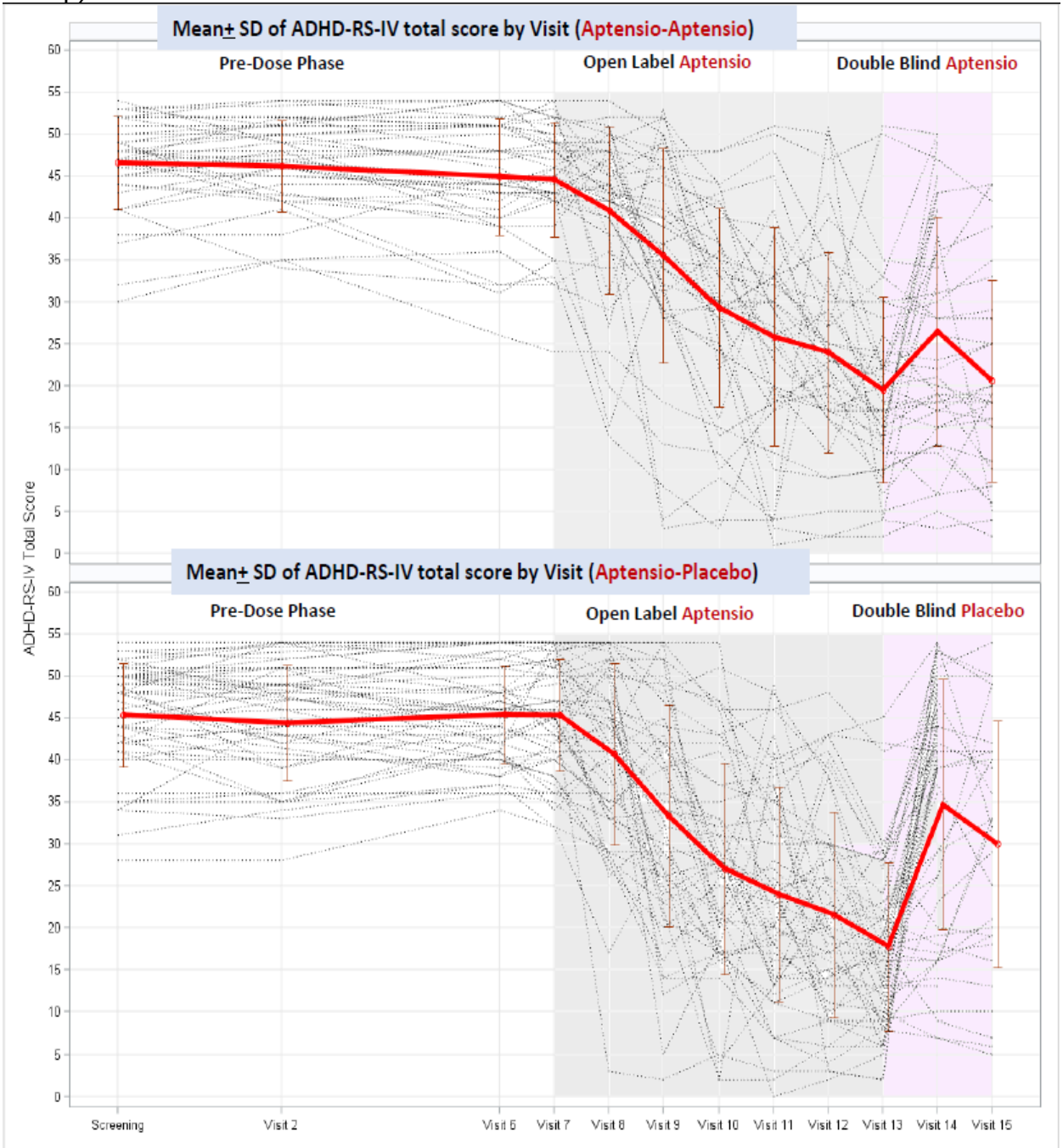
Figure 11, Efficacy Profile in Pre-Dose/Open-Label/Randomized Double-Blind Phases of Study EF-003 (Individual/Mean ADHD-RS-IV Total Score by Randomized Treatment Group)



The above figure was constructed by the DPP statistical reviewer.

Reviewer note:

The issues which the Agency biometrics reviewer identified in Study EF-003 are considerable (b) (4) *because the primary efficacy data consists of an enriched patient population (i.e., non-discontinued subjects) and the double-blind duration was only 2 weeks. In addition, not all analyses were conducted according to protocol.*

The study design of RP-BP-EF003 does not include a wash-out period. This complicates interpretation as withdrawal is commonly associated with rebound nervousness and irritability, behaviors which potentially could appear as ADHD symptoms and confound the results obtained by the ADHS-RS-IV scale (McCubbin and Cohen 1999). This fact has the potential to make the placebo patients look worse during the early part of the 2-week double-blind phase of the study. The study design allowed for removal of children who were worse after only 1 week; however, if such children had remained in the study, any withdrawal symptoms they were experiencing at 1 week may have resolved by the end of the 2-week study period. This design issue has the potential to exaggerate the benefit of remaining on Aptensio XR vs placebo.

An unusual and confusing feature of RP-BP-EF003 was that 30 subjects whose symptoms became worse after 1 week of the 2-week double-blind treatment period were discontinued, considered as "completers" and included in the Applicants primary efficacy analysis. This feature of the study design defeated the purpose of evaluating the effect of 2-week Aptensio exposure in comparison with 2-week placebo administration, because it allowed a removal of randomized subjects. The removal of these 30 subjects for worsening of their symptoms had the effect of making the effect of Aptensio XR in the Applicant's primary analysis (quantified as the difference between Aptensio XR and Placebo) appear more robust.

Although the Applicant's analysis suggested that the Aptensio XR group exhibited a significant difference of ~10 point on the ADHD-RS-IV scores at endpoint, a difference of this magnitude is not clinically meaningful. Conclusions regarding significance based on p-values only may not accurately represent the clinical relevance of an intervention. In a literature report, which provides an extensive evaluation of the validity of this particular scale, a difference of ~10 points corresponds to a CGI-I score of 3 (minimally improved) (Goodman, Faraone et al. 2010). The Agency biometrics reviewer's analysis of the difference between subjects who actually completed the 2-week double-blind period was 7.6, an even smaller difference. Based on these analyses, the results of this study, even if statistically significant, are not considered a meaningful clinical response.

There is a striking nocebo or expectation effect noted in the double-blind phase; after randomization both groups became more symptomatic. One possible explanation of this finding is that the effect of parent expectation on the children is significant. At the

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end of the double-blind investigation both the placebo group and the Aptensio XR group were becoming more symptomatic and this instability of effect could be a confounding factor. A longer double-blind period would more clearly determine if the benefit of Aptensio XR over placebo would have persisted.

6.4 Analysis of Secondary Endpoints

Study RP-BP-EF003

The Applicant reports the following results from secondary analyses.

- On change from baseline in ADHD-RS-IV Hyperactivity / Impulsivity subscale score at Visit 15, the Aptensio XR group had a lower mean change from baseline compared to placebo (p = 0.005).
- The CGI-S results, in contrast, showed no difference between treatment; in both groups the CGI-S ratings became worse from baseline to Visit 15. Of note, both groups demonstrated an increase in the number of subjects that were rated as "Markedly ill" at Visit 15 with an increase of 9 (23%) subjects in the Aptensio XR group and an increase of 18 (36%) subjects in the placebo group.
- An ANOVA assessing change in *T*-scores in Conners EC BEH-P(S) at Visit 15 compared to baseline in the ITT-E population indicated no difference between treatment groups.
- CGI-I scores improved in the Aptensio XR group relative to the placebo group (*p* = 0.045). This difference could be related to the proportion of subjects who were characterized as "Much worse"; 15.4% in the Aptensio XR group and 32.0% in the placebo group, respectively.

Reviewer Note:

The failure of the Conners T-score analysis to show a benefit of Aptensio XR is an important negative result, as this scale is commonly used to quantify severity of ADHD. The change in CGI-S score is considered superior to the CGI-I because it avoids recall bias inherent in the CGI-I.

As might be expected for studies conducted in young children, the patient's perception of treatment was not evaluated. It is unknown if the benefit of treatment is functionally for the parents and care-givers/guardians. The literature contains minimal data on this topic, but was replete with reports questioning the ethics of stimulant use in childhood. (McCubbin and Cohen 1999, Breeding and Baughman Jr 2001, Breggin 2001, Kean 2004).

6.5 Other Relevant Endpoints

None

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6.6 Subpopulations

The Agency biometrics reviewer performed the primary analysis for each of the subgroups based on gender and race, and this analysis did not alter the conclusion of the study.

6.7 Clinical Information Relevant to Dosing Recommendations

Flexible dosing was employed in this study beginning with 10 mg, the smallest dose form of Aptensio XR commercially available. This is the same starting dose level labeled for use in older children and adults. By the end of the dose-optimization phase in Study RP-BP-EF003, approximately one fourth of subjects reached the maximum allowable dose of 40 mg. Of the 31 subjects who completed 52 weeks on study drug, 8 (26%) reached the maximum dose of 60 mg by the end of the study.

Reviewer note:

In contrast to the 10-mg minimum dose used in this study, as noted in the Section 2.6 above, the PATS study found that lower daily doses of an immediate release formulation, i.e., 2.5 mg t.i.d. (0.4 mg/kg/day) produced significant reductions on ADHD symptom scales in a similar aged population. The PK study noted that preschool children have greater MPH exposure with Aptensio XR when compared to older age groups.

DPP draft guidelines suggest the evaluation of multiple fixed-dose levels to determine efficacy of the lowest dose of stimulants required for treatment in this population. This consideration is important as side effect levels may be less with lower doses; if a lower dose had been employed in this study, it is possible that such a dose would have shown effectiveness for some children. This lower dose might prevent adverse events occurring as some children may be effectively treated with fewer adverse events.

6.8 Persistence and Durability of Effect; Tolerance

Persistence and durability of effect was evaluated in Study RP-BP004. The primary index to assess efficacy was ADHD-RS-IV Total Score. This measure was obtained at each monthly visit for 12 months. Excluding subjects who discontinued the study, the ADHD-RS-IV Total Score was stable throughout the study. As seen in Table 6, the 31 subjects out of 89 who remained in the study maintained their improvement.

Table 6, ADHD-RS-IV Total Score, Maintenance Phase, Safety Population

	ADHD-RS-IV Total Score

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	Visit M1 Week 0 (Baseline)	Visit M14 Week 52 (Ongoing subjects)	Visit M14 Week 52 (Study completers)
n	89	68	31
Mean	20.7	27.5	19.2
SD	12.25	13.62	11.4
Minimum	2	2	2
Maximum	51	54	17

Source: RP-BP-EF004 CSR Table 14.2.1.2 and Listing 16.2.6.1.

However, for most subjects, the beneficial effect of Aptensio XR did not persist as seen in Table 6, where the mean ADHD-RS-IV score for ongoing subject is 27.5, a score that is roughly equivalent to that of subjects after receiving placebo for two weeks in the double blind portion of Study RP-BP-EF003. This data can be found in Module 5, Table 14.2.101. Evaluating the persistence of effect is complicated by number of subjects who discontinued the study, as seen in Figure 9, Cumulative Early Withdrawal from Study as a Percentage of Enrolled Subjects. The persistence of effect of the drug is unclear, as many discontinuations occurred because there was a loss of effect or an adverse event.

Additional measures of efficacy included the CGI-S score which was assessed at each monthly visit. These scores became worse over time, consistent with a general worsening of ADHD symptoms (see Figure 12). These CGI-S data were collected from all subjects who completed a visit M14, including those who terminated early from the study for reasons including lack of symptom control and adverse effects. This likely contributed to the worsening in CGI-S measurements.

Figure 12, CGI-S at Baseline (M1) and Each Subjects Last Study Visit, (M14), Safety Population

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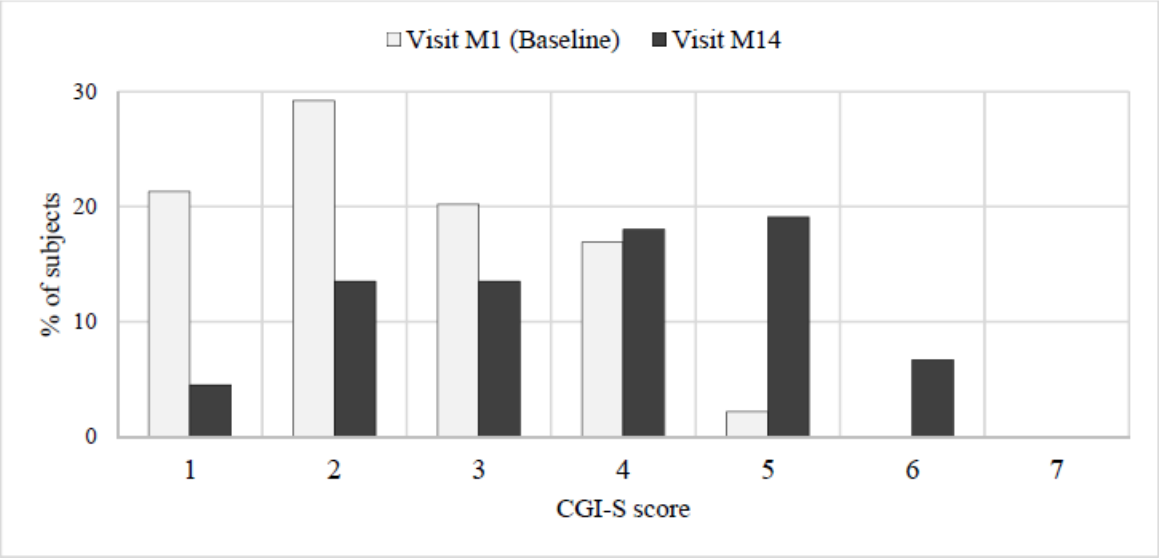

Source Table 14.2.107. All subjects were Ongoing Subjects (N=89); CGI-S score: 1=very much improved, 2=much improved, 3= minimally improved, 4= no change, 5= minimally worse, 6= much worse, 7= very much worse.

Reviewer note:

These data suggest that the beneficial effect of Aptensio XR may be maintained in some subjects who take it for 12 months. This interpretation assumes that these results were not confounded by drug seeking behavior of guardians or parents tasked with administering the drug. The CGI-S data suggest that initial beneficial effects of the drug on the overall clinical picture does not last over a 12-month period. As they are secondary measures, these results were not evaluated in the Agency biometrics reviewer's report and are not appropriate for labeling purposes.

Aptensio XR appears to have a persistent effect to reduce the symptoms of ADHD in some preschool children, but for the majority of children the improvement does not persist.

7 Review of Safety

Safety Summary

The studies submitted, RP-BP-EF003 and RP-BP-EF004, provide 6 weeks of open-label comparison to an off-drug lead in, ~2 weeks of double-blind treatment, and 31 subjects who were observed for 1 year. The short double-blind period did not reveal any safety signal, but, based on the design issues noted elsewhere, this was not unexpected. Although MPH is commonly used off label for children ages 4 to 5, these studies illustrate the potential for MPH to have adverse effects when administered at this age.

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AEs were prevalent at the lowest dose levels. During the 6-week off-drug period there were no reported psychiatric related AEs, such as anxiety, irritably, mood disorder, and affect lability. However, during the 6-weel open-label lead-in treatment phase, these psychiatric disorders occurred in two out of five treated subjects. The 34 discontinuations from Study RP-BP-EF003 included 14 withdrawals due to AEs, 10 of which were due to psychiatric AEs. The 43 discontinuations from Study RP-BP-EF004 included 14 withdrawals due to AEs, 7 of which were due to psychiatric related AEs. Weight loss and hypertension are also of significant concern; 35% of the children experienced weight loss during the 6-week open-label treatment phase, and 30% had hypertension. Over both studies, I found 10 subjects for whom there were questions about medication accounting; it is unknown if Aptensio XR was diverted for illicit use as this possibility did not appear to be actively addressed in the protocol.

7.1 Methods

7.1.1 Studies Used to Evaluate Safety

Three biopharmaceutic clinical studies were submitted with this application. Safety parameters included clinical laboratory evaluations, psychological instruments, vital signs, ECGs, and AE documentation and follow-up. Changes in sleep quality were evaluated with the Child Sleep Habits Questionnaire (CSHQ). The CSHQ total score is the sum of the scores for 33 items specified among the instrument's 48 items. Items are grouped into the following 8 subscales: Bedtime Resistance; Sleep Onset Delay; Sleep Duration; Sleep Anxiety; Night Wakings; Parasomnias; Sleep-disordered Breathing; and Daytime Sleepiness; the score for each subscale is the sum of the scores for items in each subscale. Each item is scored from a range of 0 to 3. A higher score indicates more sleep problems. The Clinical Global Impression Scale of Improvement (CGI-I) and the Clinical Global Impressions Scale of Severity (CGI-S) were administered to obtain an overall measure of the clinical situation. In addition, the Columbia Suicide Severity Rating Scale, (C-SSRS) was used to monitor for suicide risk.

7.1.2 Categorization of Adverse Events

Adverse Events were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0 and are presented for all treatment groups by both System Organ Class (SOC) and preferred term.

7.1.3 Pooling of Data across Studies to Estimate and Compare Incidence

Not Applicable

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7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Of the ten subjects who were enrolled in RP-BP-PK003 and received one dose of Aptensio XR, nine enrolled in RP-BP-EF004. Out of 119 subjects enrolled in RP-BP-EF003 who received a dose of Aptensio XR, 89 enrolled in Study RP-PB-EF004, the open-label maintenance phase, and received at least one dose of Aptensio XR (Figure 8, Figure 10). The maximum exposure time for any subject in this database was 60 weeks.

RP-BP-PK003

During study RP-BP-PK003, each subject received a single oral dose of Aptensio XR; five subjects received 10 mg, three received 15 mg, and two received 20 mg. The only AE (upper respiratory tract infection) that occurred during the study occurred before Aptensio XR administration. There were no clinically significant findings in laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), or physical examination data. No deaths, serious TEAEs, or other significant TEAEs occurred during the conduct of this study. As this study only involved the administration of one dose, it will not be discussed further.

RP-BP-EF003

The initial daily dose of Aptensio XR in study RP-BP-EF003 was 10 mg, which was titrated up to a maximum of 40 mg during the six-week open-label phase. Half of the randomized subjects received additional treatment with their optimized dose. This starting dose was not chosen based on the PK study or on the weight of the subjects. It is the lowest commercially-available dose of Aptensio XR.

RP-BP-EF004

Subjects in study RP-BP-EF004 were dosed at 10, 15, 20, 30, 40, 50, or 60 mg; the median dose was 40 mg. Eleven subjects received 10 mg throughout the course of the study and eighteen subjects received 60 mg at least once during this study. Study RP-PB-EF004 was terminated after 41 subjects had completed 1 year of open-label treatment in this study, however, only data on 31 subjects was submitted with this Application.

Table 7, Participant Demographics.

	RP-BP-PK003 (N = 10)	**RP-BP-EF003 (N = 119)**	**RP-BP-EF004**

				(N = 89; 31 completed 1 year)
Age, (months)	Mean	63.6	58.9	61.8
	(SD)	7.06	6.08	6.19
	Range	65-49	48-70	50 - 72
Female Sex, %		70	23.5	24.7
Female Sex, N		7	28	22
Race, % (N)	Asian, %	-	0.8	1.1
	Asian, N	-	1	1
	Black, %	60	41.2	37.1
	Black, N	6	49	33
	White, %	20	56.3	58.4
	White, N	2	67	52
	Other, %	20	1.7	3.3
	Other, N	2	[2]	3
Hispanic, %		30	9.2	12.4
Hispanic, N		3	11	11

Reviewer note:

The 31 subjects observed in RP-BP-EF-004 do not provide adequate exposure to detect serious adverse events in this vulnerable population and, based on ICH Guidelines, the study does not contain sufficient long-term safety data to warrant approval. Regarding the preschool age group, I am not aware that DPP has previously approved drugs for common disorders with so few subjects in the long-term safety database.

> *ICH guidelines for the number of subjects needed to adequately evaluate safety state:*
>
> *"The number of patients treated for 6 months at dosage levels intended for clinical use, should be adequate to characterize the pattern of ADEs over time. To achieve this objective the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g., in the general range of 0.5%-5%). Usually 300-600 patients should be adequate.*
>
> *There is concern that, although they are likely to be uncommon, some ADEs may increase in frequency or severity with time or that some serious ADEs may occur only after drug treatment for more than 6 months. Therefore, some patients should be treated with the drug for 12 months. In the absence of more information about the relationship of ADEs to treatment duration, selection of a*

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specific number of patients to be followed for 1 year is to a large extent a judgement based on the probability of detecting a given ADE frequency level and practical considerations. 100 patients exposed for a minimum of one-year is considered to be acceptable to include as part of the safety data base. The data should come from prospective studies appropriately designed to provide at least one-year exposure at dosage levels intended for clinical use.

When no serious ADE is observed in a one-year exposure period this number of patients can provide reasonable assurance that the true cumulative one-year incidence is no greater than 3%. Larger safety data bases may be needed to make risk/benefit decisions in situations where the benefit from the drug is either (1) small (e.g., symptomatic improvement in less serious medical conditions) or (2) will be experienced by only a fraction of the treated patients (e.g., certain preventive therapies administered to healthy populations) or (3) is of uncertain magnitude (e.g., efficacy determination on a surrogate endpoint)"(Guideline 1994).

Considering the ICH guidelines, the high prevalence of ADHD in preschool children, and the many years of MPH exposure these children are likely to receive, greater than 100 subjects exposed for longer than 1 year should be required to constitute an adequate long-term safety data base. This perspective is echoed by a recent literature review critical of the small numbers of child subjects typically studied in pharmacotherapeutic development programs leading to FDA approval. In this review, the authors cite the need to study sufficient subjects to detect rare or unexpected AEs (Bourgeois, Kim et al. 2014).

7.2.2 Explorations for Dose Response

Not provided

7.2.3 Special Animal and In Vitro Testing

None provided.

7.2.4 Routine Clinical Testing

Repeated clinical chemistry, hematology, and ECG results were evaluated as part of Study RP-BP-EF004. There were no significant mean changes noticed during this study and the Applicant reported that there were no instances where abnormal values were considered clinically relevant.

7.2.5 Metabolic, Clearance, and Interaction Workup

The studies conducted were intended to provide safety and efficacy information in children. No new information was presented on metabolic or drug interactions.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

To assess for ECG changes, increased blood pressure and pulse, investigators measured these at the beginning and end of RP-BP-EF004. Laboratory tests and physical exams were also collected at the beginning and end of Study RP-BP-EF004. Subjects were evaluated at regular intervals in the clinic in both Study RP-BP-EF003 and RP-BP-EF004 to monitor closely for AEs and obtain psychological scales, including an evaluation of sleep quality with the Child Sleep Habits Questionnaire (CSHQ).

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during the studies.

7.3.2 Nonfatal Serious Adverse Events

No serious adverse events (SAEs) occurred during Study RP-BP-PK003. Three subjects experienced SAEs during study RP-BP-EF003. Two SAEs occurred during the Off-Treatment period (Visits 2-7) and one occurred during the On-Treatment period (Visits 8-13) in a subject receiving 10 mg of Aptensio XR. The two SAEs during the Off-Treatment period were synovitis and hypoxia, while the SAE during the On-Treatment period was a campylobacter infection. One subject assigned to 30 mg of Aptensio XR was withdrawn from the study on the 10th day of the double-blind phase due to formication. One SAE (suicidal ideation) occurred during Study RP-BP-EF004.

7.3.3 Dropouts and Discontinuations

Study RP-BP-EF003

A total of 158 subjects were enrolled in Study RP-BP-EF003. Of the 132 subjects whose parents received parent training, 30 (23%) did not require or did not chose to receive Aptensio XR.

Of the 119 patients who received medication in Study RP-BP-EF003, 34 subjects discontinued. (This number does not include 29 subjects who were discontinued after 1 week of double-blind treatment and entered directly into Study RP-BP-EF004). Of the 34 subjects, 8 discontinued due to protocol violations, 7 were withdrawn by the parent

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or guardian, 5 were lost to follow up, 1 was lost to other reasons, and 13 were discontinued due to AEs. Most AEs resulting in discontinuation from the study (n=10; 77%), were psychiatric related. These AEs consisted of irritability/aggression (5), affect lability (3), emotional disorder (2), hypertension (2), insomnia (1). Eighty percent of these subjects were receiving 15 mg or less of Aptensio XR daily at the time of withdrawal. All the TEAEs leading to withdrawal were considered mild or moderate in severity except for one subject who had an emotional disorder considered severe by the Investigator. Most of these AEs were reported to have resolved.

Of the 119 subjects treated in with Aptensio XR in the open label phase of Study RP-BP-EF003, 88 were treated for at least 1 week of the Double-Blind Phase; 30 of these were entered into Study RP-BP-EF004 after only 1 week of double-blind therapy. One patient on Aptensio XR discontinued due to formication during the double-blind phase of this study (see Figure 8).

Study RP-BP-EF004

In Study RP-BP-EF004, 89 subjects received treatment in the Maintenance Phase (see Figure 10). Of these, the Application included data on 31 subjects who completed the 12-month open-label phase and have data available for this analysis (Table 8). The Applicant anticipated submitting data from an additional 13 subjects still participating in the study in a 120-day safety update. However, this data was not submitted until the PDUFA goal date and contributed to the extension of the goal date. No new subjects were enrolled into Study RP-BP-EF004, although this entry into the study was included in the protocol to ensure that adequate numbers of subjects could be evaluated for the long-term effects of Aptensio XR.

Of the 89 subjects who received medication in the 52-week maintenance phase (Study RP-BP-EF004), 48% (43 subjects) of enrolled subjects discontinued after receiving Aptensio XR. Of these, 3 discontinued due to protocol violations, 13 were withdrawn by the parent or guardian, 7 were lost to follow up, 5 were lost to other reasons, and 14 were discontinued due to AEs. Most AEs resulting in discontinuation from the study (n=7; 50%), were psychiatric related. Among the reasons for discontinuation, weight loss was noted in 4 cases.

Table 8, Discontinuation of Subjects Who Received Aptensio XR in Studies RP-BP-EF003 and RP-BP-EF004

Study	Patient number	Disposition	Discontinuation Reason Details
	(b) (6)	Adverse event	Emotional behavior and Increased sleep difficulties, resolved
		Adverse event	Irritability and mood swings; resolved 3 days after stopping medication

Study RP-BP-EF003 Safety Population	(b) (6)	Lost to follow-up	No AEs reported.
		Adverse event	The patient had the following AEs which resolved after leaving the study: decreased appetite, short-fused, severe emotional dysregulation. Patient had increased talkativeness which did not resolve.
		Adverse event	Hypertension which was unresolved at 1 week after disconnection
		Withdrawal by parent or guardian	According to mother, patient refuses to take medication. Therefore, patient is no longer compliant with drug resulting in early termination.
		Protocol violation	The patient had an episode of otitis media with fever in the study. Terminated early due to ineligibility to continue due to not meeting ADHD severity criteria (ADHD RS-IV score of >= 30% decrease and CGI-I score of 1 or 2. The sponsor requested a protocol deviation to be submitted saying the subject did not meet the inclusion criteria as being too old at time of consent; the subject was 68 months and 28 days.
		Withdrawal by parent or guardian	Mother reports medication was not working
		Adverse Event. (Applicant coded as withdrawal by parent or guardian)	The patient had irritability which resolved after discontinuing the drug. Mother no longer wanted to participate due to insufficient response to IP
		Adverse Event. (Applicant coded as withdrawal by parent or guardian)	The patient had the following AEs, which resolved before leaving the study: vomiting, aggressive behavior, stomach ache. On the date the subject withdrew, the chart notes: “the systolic and/or diastolic blood pressure is between 95th - 99th percentile for the subjects age, gender and height. For pi/sub-i review, an adverse event is expected”.

	(b) (6)	Withdrawal by parent or guardian	Mother wanted to stop IP and try therapy. The patient had the following AEs, which resolved 5 days before leaving the study: headaches, emotional behavior
		Adverse event	Emotional behavior, resolved
		Adverse event	Crying episodes, increased aggression, which resolved 6 days after stopping medication
		Withdrawal by parent or guardian	Prehypertension, mood liability noted; parent did not keep appointments
		Other	Patient refused to take IP repeatedly
		Protocol violation	Drug dispensing/accountability*
		Adverse event	Mood lability, resolved
		Lost to follow-up	Prior to leaving the study, patient had AEs of URI and being socially withdrawn
		Adverse event	Headaches, Insomnia
		Protocol violation	The adverse event of hypertension was still ongoing at the time of discontinuation. Subject was dispensed medication, but compliance was not confirmed*
		Protocol Violation	The clinical study report says the patient discontinued due to an AE of nausea, however, the Case Report Form indicates that the patient was terminated due to medication non-compliance*
		Withdrawal by parent or guardian	Patient's mom had to have emergency surgery, unable to bring patient to clinic for study visits.
		Lost to follow-up	Prior to leaving the study in phase 4, patient had AEs of a cold and increased appetite
		Lost to follow-up	Prior to leaving the study in Phase 4, patient had reported suicidal ideation at visit 1, but had no known AEs. No further information
		Withdrawal by parent or guardian	Unable to comply with scheduled visits
		Protocol violation	Pt ran out of medication due to missing v9
		Adverse event	Irritability resolved after two days off medication

	(b) (6)		
		Withdrawal by parent or guardian	Mother would like child to come off study to allow her child to heal prior to initiating ADHD treatment again. The patient had a number of AEs prior to stopping the study; respiratory syncytial virus, allergic reaction to mosquito bite mosquito bite, allergy burn, campylobacter infection, neck pain, headache, nausea, vomiting, abdominal pain, decreased appetite, intermittent fever, ear infection, dehydration, diarrhea.
		Adverse event	Emotional outbursts
		Adverse event	Discontinued for insomnia and irritability.
		Lost to follow-up	Prior to leaving the study in Phase 5, patient had AEs of crying episodes and calf pain
		Protocol violation	Compliance could not be calculated*
		Protocol violation	Subject did not qualify for double blind. Deviation was noted for not following protocol.
		Protocol violation	Non-compliant with protocol and drug administration*
Protocol RP-BP-EF004 Interim analysis		Withdrawal by parent/guardian	Parent decided study drug no longer effective.
		Adverse event	Suicidal ideation
		Adverse event	Increased irritability
		Withdrawal by parent or guardian	Vomiting occurred a month before leaving the study. Study drug intolerance
		Withdrawal by parent or guardian	AEs of headaches irritability occurred. No further information
		Lost to follow-up	
		Withdrawal by parent or guardian	Parental perception of lack of efficacy
		Lost to follow-up	
		Withdrawal by parent or guardian	Subject moving out of state

	(b) (6)		
		Withdrawal by parent or guardian	Early termination due to patient moving Out of state
		Adverse event	Mood lability
		Lost to follow-up 1	
		Adverse Event (Listed by Applicant as Withdrawal by parent or guardian)	The MD noted mild weight loss, and felt that it was safe to continue but subject terminated
		Adverse Event (listed by Applicant as Withdrawal by parent or guardian)	The MD felt patient safe to continue after mild weight loss. Mother requested early termination
		Physician decision	Pi concern regarding subject compliance with study drug administration*
		Lost to follow-up	
		Adverse event	Hallucinations
		Adverse event	Tic (simple) blinking both eyes
		Withdrawal by parent or guardian	Mother wanted to try alternate medication
		Withdrawal by parent or guardian	Mother perceived that medication was not working
		Adverse Event (listed by Applicant as Withdrawal by parent or guardian)	Patient had tachycardia, and mother terminated at the time this occurred
		Withdrawal by parent or guardian	Mother stated IP was no longer effective
		Withdrawal by parent or guardian	Mother withdrew consent- mom stated the IP wasn't working

	(b) (6)		
		Withdrawal by parent or guardian	Mom stated IP lost effectiveness over time
		Withdrawal by parent or guardian	No further information
		Withdrawal by parent or guardian	Mom reported IP was no longer effective
		Protocol deviation	IP was never returned to site by parent*
		Lost to follow-up	No further information
		Other	Treatment no longer effective
		Lost to follow-up	No further information
		Adverse event	Formication
		Lost to follow-up	No further information
		Protocol deviation	Subject was not compliant with study drug administration*
		Other	ET at Applicant request due to IP compliance*.
		Other	Visit was 16 days out of window.
		Adverse event	Decreased social interaction
		Other	Noncompliance with ip*; noncompliance with visits- subject out of visit window and without study drug for 15 days
		Protocol deviation	Poor compliance - off study drug for 10 days
		Adverse event	Aggression
		Adverse event	Emotionally withdrawn
		Adverse event	Decreased height and weight (i.e., height velocity)
		Other	Decreased efficacy
		Adverse event	Decreased weight

*Indicates 10 protocol violations related to medication compliance; none of these cases provide sufficient detail to rule out the possibility that the investigator had suspicion the MPH was diverted for illicit use.
Note 1: Not indicated in the table are 30 subjects discontinued after one week of double bind therapy and entered into study RP-BP-EF004.
Note 2: Based on information in the case report forms, I changed the Applicants description of a subject's reason for being discontinued for five subjects, and they are noted as such in the table.
Note 3: The accounting of study discontinuations shows minor discrepancies which can be understood by considering subjects discontinued immediately preceding the drug administration.

Reviewer Note:

The occurrence of dropouts without information on the cause may be due to unreported adverse events. The Applicant was asked to provide additional information on the cause of dropouts and discontinuations, but no new significant information was contained in the response dated February 8, 2019. Many subjects who were described as withdrawn at the parent's request actually had adverse effects noted in the case report forms, but these were not coded as AEs causing withdrawal (i.e., (b) (6)).

There is a lack of detailed information regarding the reasons that subjects were withdrawn for protocol violations. Case report descriptions that some subjects left the study because of "compliance" with medication issues raises the possibility that the young child's stimulant dose was diverted for illicit use. The parents of these children may be drug-seeking either to support their own addiction or as a way to supplement their income. Considering that 4 and 5-year-old preschool children are a vulnerable population, and stimulants such as Aptensio XR have considerable street value in the underground economy, the possibility exists that the results of the study were confounded by parents who were drug-seeking rather than acting in their child's best interests. Such parents may exaggerate their child's symptoms in order for the physician to increase the dose of stimulants given to the child. Such parents could potentially create or exaggerate a child's ADHD symptoms, falsify data or they even induce symptoms. A controlled trial design employing a classroom study day as an endpoint may reduce this potential confounding issue. To reduce this possibility in future studies of stimulants in children, it may be possible to include an evaluation of the potential for guardians and subjects to use or abuse scheduled drugs. Urine drug testing of the children could ensure that these children were actually receiving Aptensio XR themselves.

Emotional-disorder-related problems and weight loss are prominent among the reasons given for withdrawal from the study, reinforcing the importance of this safety signal.

7. 3.4 Significant Adverse Events

A subject in Study RP-BP-EF004 stated at Visit M14 that he wished he was dead; this was reported as a serious AE. No deaths, serious AEs, or other significant AEs occurred during the conduct of Study RP-BP-EF003.

7.3.5 Submission-Specific Primary Safety Concerns

(b) (6)

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Reviewer Note:

The risks and benefits of approval of Aptensio XR for 4- and 5-year old children should include consideration about the possible changes in prescribing practices that could result. (b) (6) may increase the potential for prescribers to use this drug off-label for children who are 3 and younger. (b) (6) *may promote less use of potentially more dangerous psychotropic medications (such as atypical antipsychotics). There is a lack of data available which provides useful information about these issues.*

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Summary

The most common reported AE observed in the Aptensio XR development program for children ages 4 and 5 were subsumed under the System Organ Class (SOC) of Psychiatric disorders, which includes affect lability, aggression, irritability, and emotional disorder as well as insomnia. Other prominent AEs include weight loss and loss of appetite and hypertension.

During the 6-week open-label treatment phase of Study RP-BP-EF003, adverse reactions occurring in > 5% of patients (and at a rate greater than in the 6-week pretreatment phase) included: insomnia (23%), decreased appetite (20%), decreased weight (35%), irritability (including aggression, anger, and negativism) 19%, hypertension (30%), affect lability (10%), abdominal pain (9%), emotional disorder (11%), headache (8%), pyrexia (5%), and vomiting (5%).

Because of the trial design (a 6-week open-label active treatment phase followed by a 2-week, randomized, double-blind, placebo-controlled withdrawal), the adverse reaction rates described in the double-blind phase are lower than expected in clinical practice.

Study: RP-BP-PK003 PK Evaluation

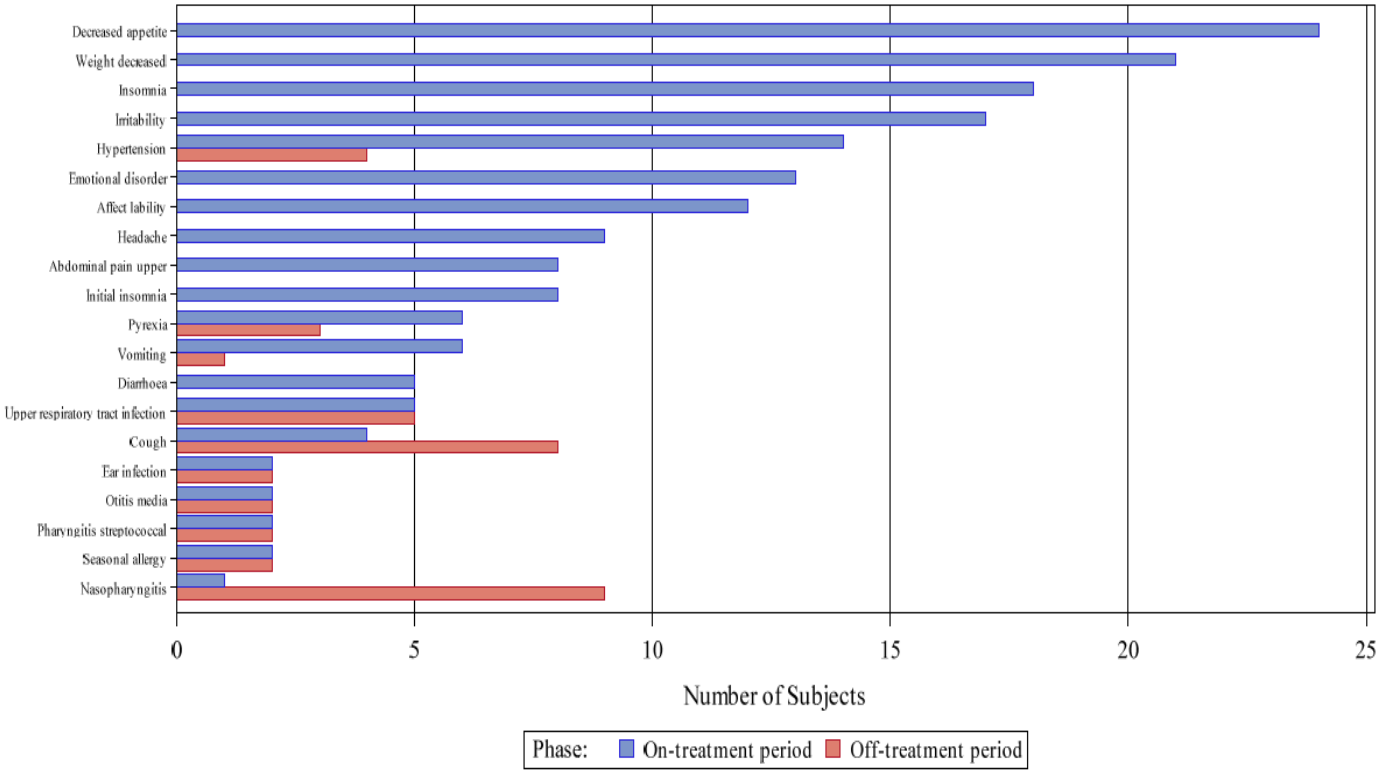
There were no AEs that were severe or serious in severity or that lead to discontinuation in Study RP-BP-PK003. There was only one AE (Upper respiratory tract infection) during the study, and as this was not temporally related to Aptensio XR, this review will not make further reference to Study RP-BP-PK003 in regard to safety.

Study: RP-BP-EF003 Off-label VS. On-label Data

Subjects had AE data collected for a 6-week period during Visits 2 to 7 (i.e., Off-treatment Period) followed by a 6-week period, Visits 8 to 13, (i.e., On-treatment Period) when they received Aptensio XR; these subjects served as their own controls for AEs. The comparison of these two groups was intended to evaluate the safety profile of Aptensio XR in this age group.

As noted below in Figure 13, the AE profile during the off-treatment period (Visits 2 to 7) vs. the on-treatment period, (Visits 8 to 13), evaluating the enrolled population (N=102) indicates that Aptensio XR administration was associated with AEs including decreased appetite, decreased weight, and insomnia. If psychiatric related AEs, such as irritability, affect lability, and emotional disorder are considered one group, they would constitute the most common AE. Of note, these AEs (irritability, affect lability, and emotional disorder) did not occur during the off-treatment period. The AE of 'Hypertension' adverse event is defined in Protocol RP-BP-EF003 as a systolic and/or diastolic BP that is ≥95th percentile (for gender, age, and height) on ≥ 3 occasions. Height was extrapolated.

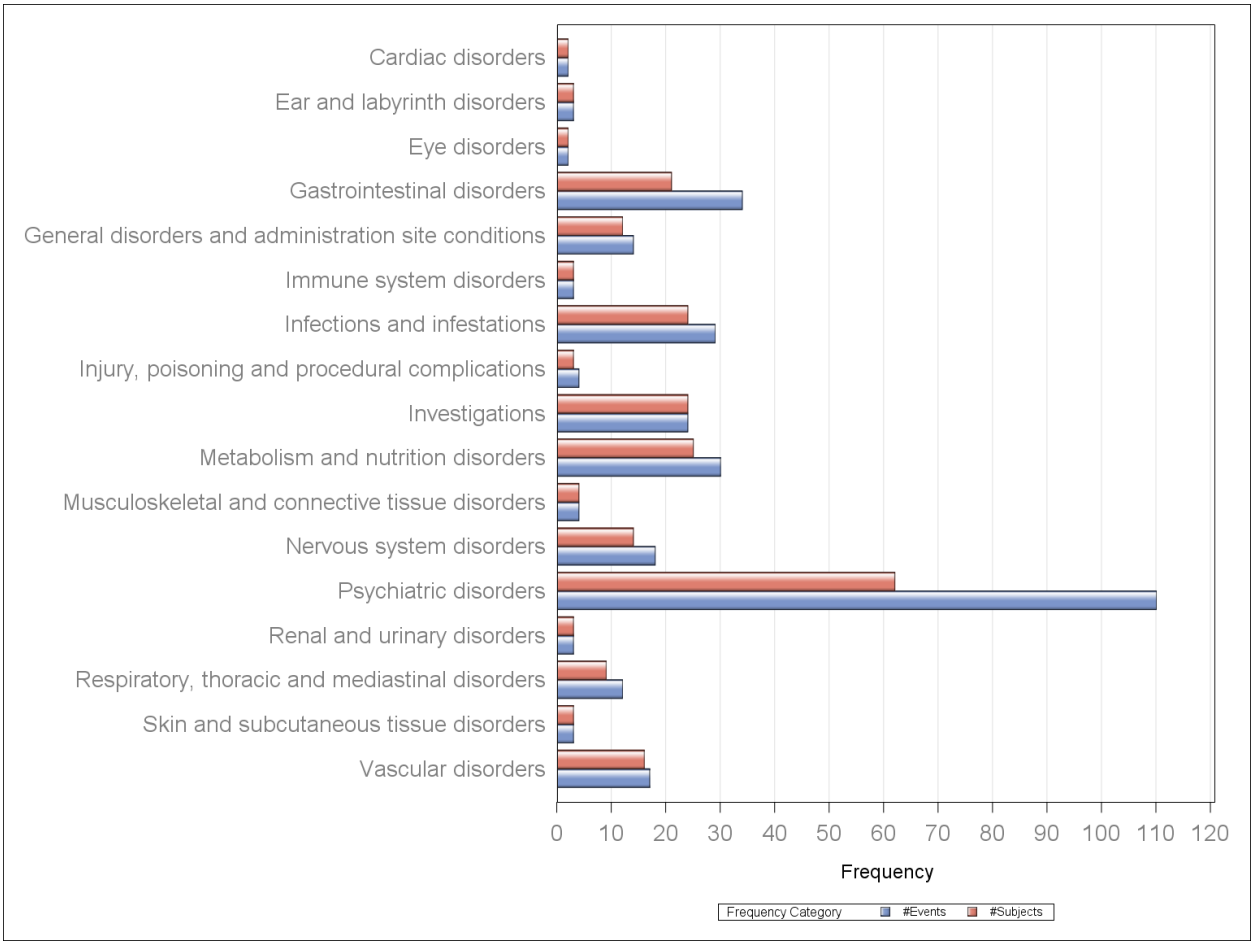
Figure 13, Study RP-BP-EF003, Adverse Event Profile Off Treatment (Visits 2-7) vs. On Treatment (Visits 8-13), Enrolled Population (N=102).



Note; This figure was prepared by the Applicant and was based on the Applicants analysis of AEs. The true incidence of hypertension and weigh loss are greater than indicated here.

The prominence of psychiatric disorders induced by Aptensio XR in this age group can be seen when looking at AEs grouped by System Organ Class (SOC), which groups insomnia with other neuropsychiatric issues. This is illustrated in Figure 14. This figure illustrates events and subjects for all reported SOC who had any post-OL exposure AE.

Figure 14, Study RP-BP-EF003, Numbers of Events and Subjects for All Reported SOC Who Had Any Post-OL Exposure AE.



Note: This figure was prepared by the Applicant and was based on the Applicant's analysis of AEs and does not reflect the data provided in the Major Amendment. The true incidence of hypertension and weight loss are greater than indicated here.

The breakdown of more specific types of psychiatric AEs is seen in

Figure 15, which illustrates that the most common AEs in the psychiatric SOC are insomnia, irritability, emotional disorder, and affect lability.

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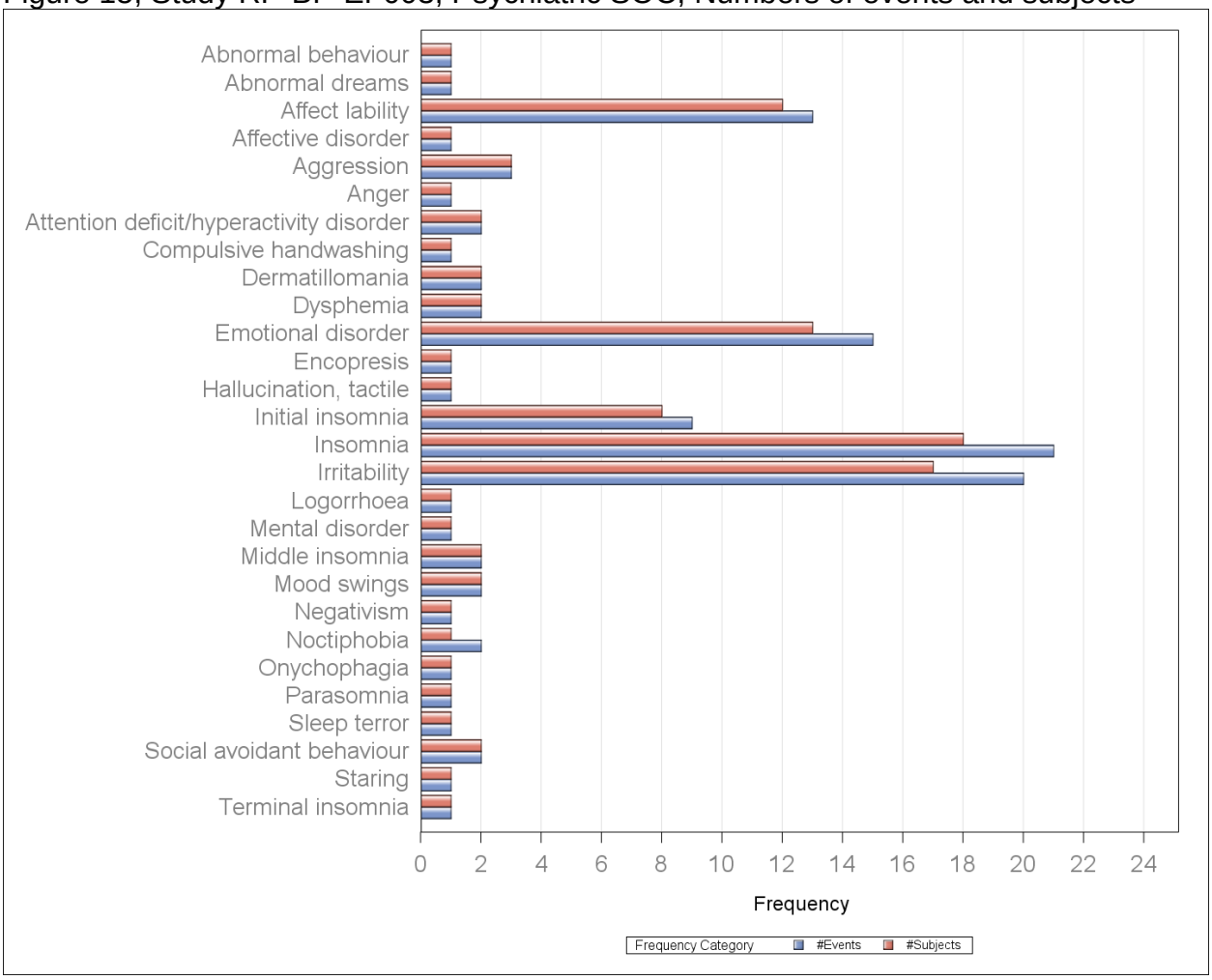
Figure 15, Study RP-BP-EF003, Psychiatric SOC, Numbers of events and subjects



Note: This figure was prepared by the Applicant and was based on the Applicant's analysis of AEs.

Study RP-BP-EF003 Double Blind Period

Adverse events which were incident in the open-label phase and continued into the double-blind phase do not appear as occurring in the Double-Blind Phase in Table 11 as they did not first manifest in the double-blind phase. The most common AEs which were incident during the Double-blind Phase were hypertension, and pollakiuria/urinary incontinence. As the placebo group and the Aptensio XR group were not balanced (i.e., subjects could be discontinued after 1 week if their symptoms became worse), the design does not permit a valid comparison between the two groups. Also, the fact that the lead-in open-label phase occurred immediately prior to the relatively short double-blind phase (i.e., there was no washout period before the double-blind phase) created a situation where children receiving placebo and withdrawing from methylphenidate were compared with those who continued on Aptensio XR without interruption. Therefore,

symptoms of withdrawal could confound the comparison of placebo with Aptensio XR (Cho and Melega 2002). Also, if the drug caused adverse events in the open-label phase and these symptoms persisted, they were not counted as drug-related adverse events in the double-blind phase. For these reasons, AEs have been combined in Table 9, below.

Study RP-BP-EF004

Overall, a total of 283 AEs were reported in 65 (73.0%) subjects during the extension maintenance phase. One serious TEAE of suicidal ideation occurred. There were no clinically significant ECG changes or in hematology and urinalysis, and no deaths. Thirty-one of 89 enrolled subjects completed 52 weeks and had data for analysis.

Table 9, Adverse Events Incident in Safety and Efficacy Studies, # Subjects (%)

Applicant's Adverse Event Reports

Number of Subjects (% in 119 OL enrolled subjects) with the AE.
Note: Not all of 119 OL participants continued to DB phase and to RP-BP- EF004 Extension. All Extension subjects included in the table participated in Study RP-BP-EF003 (The reported percentages are not presented as a risk estimate).

Primary System Organ Class	Dictionary-Derived Term	Study RP-BP-EF003				Study EF004 Extension (N=80) [PK subjects not included]	EF003 (OL/DB) or RP-BP-EF004 (N=119)
		Pre-OL phase (N=119) [subjects who participated in OL phase]	OL phase (N=119)	DB phase (N=89)			
				Aptensio (N=39)	Placebo (N=50)		
Blood and lymphatic system disorders		0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Lymphadenitis	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
Cardiac disorders		0 (0)	2 (1.7)	1 (0.8)	0 (0)	3 (2.5)	5 (4.2)
	Sinus tachycardia	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Tachycardia	0 (0)	2 (1.7)	1 (0.8)	0 (0)	2 (1.7)	4 (3.4)
Ear and labyrinth disorders		2 (1.7)	3 (2.5)	0 (0)	0 (0)	3 (2.5)	5 (4.2)
	Ear pain	2 (1.7)	1 (0.8)	0 (0)	0 (0)	2 (1.7)	3 (2.5)
	Hypoacusis	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Otorrhoea	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Tympanic membrane perforation	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
Eye disorders		0 (0)	2 (1.7)	0 (0)	0 (0)	0 (0)	2 (1.7)
	Dry eye	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Eye allergy	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)

Applicant's Adverse Event Reports

Number of Subjects (% in 119 OL enrolled subjects) with the AE.

Note: Not all of 119 OL participants continued to DB phase and to RP-BP- EF004 Extension. All Extension subjects included in the table participated in Study RP-BP-EF003 (The reported percentages are not presented as a risk estimate).

Primary System Organ Class	Dictionary-Derived Term	Study RP-BP-EF003				Study EF004 Extension (N=80) [PK subjects not included]	EF003 (OL/DB) or RP-BP-EF004 (N=119)
		Pre-OL phase (N=119) [subjects who participated in OL phase]	OL phase (N=119)	DB phase (N=89)			
				Aptensio (N=39)	Placebo (N=50)		
Gastrointestinal disorders		4 (3.4)	21 (17.6)	1 (0.8)	1 (0.8)	9 (7.6)	26 (21.8)
	Abdominal pain	0 (0)	3 (2.5)	0 (0)	0 (0)	0 (0)	3 (2.5)
	Abdominal pain upper	0 (0)	8 (6.7)	0 (0)	0 (0)	5 (4.2)	11 (9.2)
	Chapped lips	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Constipation	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Dental caries	2 (1.7)	1 (0.8)	0 (0)	0 (0)	1 (0.8)	2 (1.7)
	Diarrhoea	1 (0.8)	5 (4.2)	0 (0)	0 (0)	2 (1.7)	7 (5.9)
	Dry mouth	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Flatulence	0 (0)	2 (1.7)	0 (0)	0 (0)	0 (0)	2 (1.7)
	Frequent bowel movements	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Gastritis	0 (0)	1 (0.8)	1 (0.8)	0 (0)	0 (0)	2 (1.7)
	Nausea	0 (0)	3 (2.5)	0 (0)	0 (0)	0 (0)	3 (2.5)
	Toothache	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Vomiting	1 (0.8)	6 (5)	0 (0)	1 (0.8)	3 (2.5)	9 (7.6)
General disorders and administration site conditions		4 (3.4)	12 (10.1)	2 (1.7)	1 (0.8)	4 (3.4)	18 (15.1)
	Adverse event	0 (0)	0 (0)	1 (0.8)	0 (0)	0 (0)	1 (0.8)
	Asthenia	0 (0)	0 (0)	1 (0.8)	0 (0)	0 (0)	1 (0.8)
	Crying	0 (0)	3 (2.5)	0 (0)	0 (0)	0 (0)	3 (2.5)
	Fatigue	0 (0)	1 (0.8)	0 (0)	0 (0)	1 (0.8)	2 (1.7)
	Feeling abnormal	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Injection site pain	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Pain	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Pyrexia	3 (2.5)	6 (5)	0 (0)	1 (0.8)	2 (1.7)	9 (7.6)
	Thirst	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
		3 (2.5)	3 (2.5)	0 (0)	0 (0)	1 (0.8)	3 (2.5)

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Primary System Organ Class	Dictionary-Derived Term	Study RP-BP-EF003				Study EF004 Extension (N=80) [PK subjects not included]	EF003 (OL/DB) or RP-BP-EF004 (N=119)
		Pre-OL phase (N=119) [subjects who participated in OL phase]	OL phase (N=119)	DB phase (N=89)			
				Aptensio (N=39)	Placebo (N=50)		
Immune system disorders	Allergy to arthropod bite	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Hypersensitivity	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Seasonal allergy	2 (1.7)	2 (1.7)	0 (0)	0 (0)	1 (0.8)	3 (2.5)
Infections and infestations		22 (18.5)	24 (20.2)	2 (1.7)	1 (0.8)	33 (27.7)	46 (38.7)
	Body tinea	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Campylobacter infection	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Cellulitis	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)	2 (1.7)
	Conjunctivitis	2 (1.7)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Croup infectious	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Ear infection	2 (1.7)	2 (1.7)	0 (0)	0 (0)	4 (3.4)	6 (5)
	Enterobiasis	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Gastroenteritis	0 (0)	1 (0.8)	0 (0)	0 (0)	3 (2.5)	4 (3.4)
	Gastroenteritis viral	0 (0)	3 (2.5)	0 (0)	0 (0)	4 (3.4)	7 (5.9)
	Gastrointestinal infection	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Hordeolum	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Influenza	1 (0.8)	1 (0.8)	0 (0)	0 (0)	4 (3.4)	5 (4.2)
	Localised infection	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Nasopharyngitis	8 (6.7)	1 (0.8)	0 (0)	0 (0)	10 (8.4)	11 (9.2)
	Oral herpes	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Otitis media	1 (0.8)	2 (1.7)	0 (0)	0 (0)	5 (4.2)	6 (5)
	Otitis media acute	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Pharyngitis	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Pharyngitis streptococcal	1 (0.8)	2 (1.7)	0 (0)	0 (0)	7 (5.9)	7 (5.9)
	Pneumonia	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)

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Primary System Organ Class	Dictionary-Derived Term	Study RP-BP-EF003				Study EF004 Extension (N=80) [PK subjects not included]	EF003 (OL/DB) or RP-BP-EF004 (N=119)
		Pre-OL phase (N=119) [subjects who participated in OL phase]	OL phase (N=119)	DB phase (N=89)			
				Aptensio (N=39)	Placebo (N=50)		
	Respiratory syncytial virus infection	1 (0.8)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Respiratory tract infection viral	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Sinusitis	1 (0.8)	0 (0)	0 (0)	1 (0.8)	0 (0)	1 (0.8)
	Streptococcal infection	0 (0)	2 (1.7)	0 (0)	0 (0)	0 (0)	2 (1.7)
	Tinea capitis	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Tonsillitis	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Tooth abscess	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.7)	2 (1.7)
	Upper respiratory tract infection	5 (4.2)	5 (4.2)	2 (1.7)	0 (0)	7 (5.9)	12 (10.1)
	Viraemia	0 (0)	1 (0.8)	0 (0)	0 (0)	1 (0.8)	2 (1.7)
	Viral infection	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Viral rash	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
Injury, poisoning and procedural complications		6 (5)	3 (2.5)	0 (0)	1 (0.8)	3 (2.5)	7 (5.9)
	Arthropod bite	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Arthropod sting	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Burns first degree	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Chemical burn of skin	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Chemical injury	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Concussion	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Contusion	1 (0.8)	1 (0.8)	0 (0)	0 (0)	1 (0.8)	2 (1.7)
	Exposure via direct contact	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Head injury	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Injury corneal	0 (0)	0 (0)	0 (0)	1 (0.8)	0 (0)	1 (0.8)
	Laceration	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.7)	2 (1.7)

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		Pre-OL phase (N=119) [subjects who participated in OL phase]	OL phase (N=119)	DB phase (N=89)			
				Aptensio (N=39)	Placebo (N=50)		
	Procedural pain	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Skin abrasion	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Thermal burn	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Upper limb fracture	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
Investigations		2 (1.7)	23 (19.3)	1 (0.8)	1 (0.8)	18 (15.1)	32 (26.9)
	Aspiration joint	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Blood pressure diastolic increased	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Blood triglycerides	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Body height decreased	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Heart rate increased	0 (0)	2 (1.7)	0 (0)	0 (0)	1 (0.8)	3 (2.5)
	Hypertension**	9 (6.8)	36 (30.3)			36 (40.0)	60 (50.4)
	Hypertension***	1 (0.8)	19 (16.0)			15 (16.9)	25 (21.0)
	Influenza A virus test positive	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Weight decreased****	-	42 (35)	-	-	-	-
	Weight decreased*****	0 (0)	20 (16.8)	1 (0.8)	1 (0.8)	16 (13.4)	29 (24.4)
	Weight increased	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Metabolism and nutrition disorders		2 (1.7)	24 (20.2)	1 (0.8)	0 (0)	16 (13.4)	32 (26.9)
	Decreased appetite	0 (0)	24 (20.2)	1 (0.8)	0 (0)	16 (13.4)	31 (26.1)
	Dehydration	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Hypertriglyceridaemia	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Hyponatraemia	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Increased appetite	1 (0.8)	0 (0)	0 (0)	0 (0)	2 (1.7)	3 (2.5)
		1 (0.8)	4 (3.4)	0 (0)	1 (0.8)	3 (2.5)	7 (5.9)
	Muscle spasms	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)

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Primary System Organ Class	Dictionary-Derived Term	Study RP-BP-EF003				Study EF004 Extension (N=80) [PK subjects not included]	EF003 (OL/DB) or RP-BP-EF004 (N=119)
		Pre-OL phase (N=119) [subjects who participated in OL phase]	OL phase (N=119)	DB phase (N=89)			
				Aptensio (N=39)	Placebo (N=50)		
Musculoskeletal and connective tissue disorders	Neck pain	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Pain in extremity	0 (0)	2 (1.7)	0 (0)	1 (0.8)	2 (1.7)	5 (4.2)
	Synovitis	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Trigger finger	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
Nervous system disorders		0 (0)	14 (11.8)	0 (0)	0 (0)	10 (8.4)	21 (17.6)
	Disturbance in attention	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Formication	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Headache	0 (0)	9 (7.6)	0 (0)	0 (0)	4 (3.4)	12 (10.1)
	Hypersomnia	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Hypoaesthesia	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Lethargy	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Myoclonus	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Somnolence	0 (0)	2 (1.7)	0 (0)	0 (0)	2 (1.7)	4 (3.4)
	Speech disorder	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
Psychiatric disorders		4 (3.4)	62 (52.1)	2 (1.7)	1 (0.8)	31 (26.1)	70 (58.8)
	Abnormal behaviour	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Abnormal dreams	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Affect lability	0 (0)	12 (10.1)	0 (0)	0 (0)	5 (4.2)	14 (11.8)
	Affective disorder	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Aggression	0 (0)	3 (2.5)	0 (0)	0 (0)	4 (3.4)	7 (5.9)
	Anger	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Anxiety	0 (0)	0 (0)	0 (0)	0 (0)	3 (2.5)	3 (2.5)
	Attention deficit/hyperactivity disorder	0 (0)	2 (1.7)	0 (0)	0 (0)	0 (0)	2 (1.7)
	Blunted affect	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)

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		Pre-OL phase (N=119) [subjects who participated in OL phase]	OL phase (N=119)	DB phase (N=89)			
				Aptensio (N=39)	Placebo (N=50)		
	Change in sustained attention	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Compulsive handwashing	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Compulsive lip biting	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Dermatillomania	0 (0)	2 (1.7)	0 (0)	0 (0)	2 (1.7)	4 (3.4)
	Dysphemia	0 (0)	2 (1.7)	0 (0)	0 (0)	0 (0)	2 (1.7)
	Emotional disorder	0 (0)	13 (10.9)	0 (0)	1 (0.8)	2 (1.7)	15 (12.6)
	Emotional distress	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Emotional poverty	0 (0)	0 (0)	1 (0.8)	0 (0)	0 (0)	1 (0.8)
	Encopresis	1 (0.8)	1 (0.8)	0 (0)	0 (0)	1 (0.8)	2 (1.7)
	Flat affect	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Hallucination	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Hallucination, tactile	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Initial insomnia	0 (0)	8 (6.7)	0 (0)	0 (0)	1 (0.8)	8 (6.7)
	Insomnia	2 (1.7)	19 (16)	0 (0)	0 (0)	8 (6.7)	23 (19.3)
	Irritability	0 (0)	17 (14.3)	0 (0)	0 (0)	6 (5)	19 (16)
	Logorrhoea	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Mental disorder	1 (0.8)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Middle insomnia	0 (0)	2 (1.7)	0 (0)	0 (0)	0 (0)	2 (1.7)
	Mood swings	0 (0)	2 (1.7)	0 (0)	0 (0)	1 (0.8)	3 (2.5)
	Mutism	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Nail picking	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Negativism	0 (0)	1 (0.8)	1 (0.8)	0 (0)	2 (1.7)	3 (2.5)
	Nightmare	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Noctiphobia	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)

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		Pre-OL phase (N=119) [subjects who participated in OL phase]	OL phase (N=119)	DB phase (N=89)			
				Aptensio (N=39)	Placebo (N=50)		
	Nocturnal fear	0 (0)	1 (0.8)	0 (0)	0 (0)	1 (0.8)	2 (1.7)
	Onychophagia	0 (0)	1 (0.8)	1 (0.8)	0 (0)	3 (2.5)	5 (4.2)
	Parasomnia	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Personality disorder	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Poverty of speech	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Self-injurious ideation	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Sleep terror	0 (0)	1 (0.8)	0 (0)	0 (0)	1 (0.8)	2 (1.7)
	Social avoidant behaviour	0 (0)	2 (1.7)	0 (0)	0 (0)	2 (1.7)	4 (3.4)
	Staring	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Suicidal ideation	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Terminal insomnia	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Tic	0 (0)	0 (0)	0 (0)	0 (0)	3 (2.5)	3 (2.5)
Renal and urinary disorders		1 (0.8)	3 (2.5)	2 (1.7)	0 (0)	2 (1.7)	6 (5)
	Dysuria	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Enuresis	1 (0.8)	2 (1.7)	0 (0)	0 (0)	1 (0.8)	3 (2.5)
	Pollakiuria	0 (0)	0 (0)	1 (0.8)	0 (0)	0 (0)	1 (0.8)
	Urinary incontinence	0 (0)	1 (0.8)	1 (0.8)	0 (0)	0 (0)	1 (0.8)
Respiratory, thoracic and mediastinal disorders		10 (8.4)	9 (7.6)	0 (0)	0 (0)	9 (7.6)	16 (13.4)
	Asphyxia	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Asthma	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Cough	7 (5.9)	4 (3.4)	0 (0)	0 (0)	7 (5.9)	10 (8.4)
	Epistaxis	0 (0)	3 (2.5)	0 (0)	0 (0)	2 (1.7)	5 (4.2)
	Hypoxia	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Nasal congestion	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Oropharyngeal pain	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)

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Primary System Organ Class	Dictionary-Derived Term	Study RP-BP-EF003				Study EF004 Extension (N=80) [PK subjects not included]	EF003 (OL/DB) or RP-BP-EF004 (N=119)
		Pre-OL phase (N=119) [subjects who participated in OL phase]	OL phase (N=119)	DB phase (N=89)			
				Aptensio (N=39)	Placebo (N=50)		
	Respiratory tract congestion	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Rhinitis allergic	1 (0.8)	1 (0.8)	0 (0)	0 (0)	1 (0.8)	2 (1.7)
	Rhinorrhoea	1 (0.8)	2 (1.7)	0 (0)	0 (0)	1 (0.8)	3 (2.5)
	Throat irritation	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
Skin and subcutaneous tissue disorders		2 (1.7)	3 (2.5)	0 (0)	1 (0.8)	3 (2.5)	7 (5.9)
	Hyperhidrosis	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Pruritus	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Rash	2 (1.7)	1 (0.8)	0 (0)	1 (0.8)	2 (1.7)	4 (3.4)
	Urticaria	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
Surgical and medical procedures		1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Tonsillectomy	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
	Tooth extraction	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vascular disorders		8 (6.7)	16 (13.4)	3 (2.5)	0 (0)	8 (6.7)	25 (21)
	Diastolic hypertension	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Flushing	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)
	Prehypertension	1 (0.8)	0 (0)	0 (0)	0 (0)	3 (2.5)	3 (2.5)
	Systolic hypertension	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.8)

* indicates one Placebo subject had the listed AE in DB phase. 25 adverse events (with 18 subjects) were observed in DB phase. Of 18 subjects, 6 were on Placebo and 12 were on Aptensio in the DB phase.
**Hypertension AE calculated by this reviewer is defined as a systolic and/or diastolic BP that is ≥95th percentile (for gender, age, and height) on ≥ 3 occasions. These data are based on the data submitted with the major amendment, i.e. the listing 16.200.1 from Studies RP-BP-PK003 and RP-BP-PK004. These data reflect the Applicants categorization of each BP value as being above the 95th percentile. but were not summited to permit the aggregation of data.
*** Hypertension AE calculated by this reviewer using more stringent criteria is defined as above but stipulating that BP elevations must occur over three consecutive visits, scheduled weekly or monthly in Studies RP-BP-EF003 and RP-BP-EF004, respectively.
Weight Decreased**** These values were derived from the data base weights by Dr. Bernie Fischer, based on weight from the visit before starting MPH and after 6 weeks of medication.

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Weight Decreased ***** These values are those provide by the Applicant: A 'weight decreased' adverse event was defined as a ≥5% reduction in body weight.
Note 1: In the pre-OL (Open Label), off drug period, 11 subjects did not have any adverse events.
Note 2: RP-BP-PK003 subjects are not included in the table.
Note 3: There were 119 and 89 subjects who received Aptensio XR in Study RP-BP-EF003 and RP-BP-EF004, respectively, but 80 of the 89 RP-BP-EF004 subjects were from Study RP-BP-EF003. This means that many of them had an AE previously in Study RP-BP-PK003. Therefore, the most representative way to look at the relative frequency of AE's is to look at the combined or far left column.
Note 4: This table was constructed in collaboration with Dr. Eiji Ishida.

Reviewer Note:

The data indicate that children 4 to 5 years of age have many AEs while taking Aptensio XR, and many of these are emotional dysregulation related AEs. As noted in this application, and in comparison to the data reported in the Aptensio XR label, this is a relatively high frequency of adverse events.

It is instructive to compare results from older children and adolescents (6 to 17 years) with ADHD, Study RP-BP-EF002, (n = 221) noted in the original Aptensio XR NDA. This study included an 11-week open-label phase, which can be compared to the 7-week open-label phase of Study RP-BP-EF003. Adverse events in the older children included decreased appetite (19.0%), headache (17.6%), insomnia (11.8%), upper abdominal pain (10.9%), upper respiratory tract infection (6.3%), irritability (5.4%), and fatigue (5.0%). In contrast, the younger 4- and 5-year-old children in Study RP-BP-EF003 had adverse reactions of: insomnia (23%), decreased appetite (20%), decreased weight (35%), irritability (including aggression, anger, and negativism) (19%), hypertension (30%), affect lability (10%), abdominal pain (9%), emotional disorder (11%), headache (8%), pyrexia (5%), and vomiting (5%).

Neuropsychiatric symptoms induced by MPH appear to be less common in studies of children older than 6 years of age (Greenhill, Posner et al. 2008). This is illustrated in the above paragraph where the only common neuropsychiatric symptoms induced by MPH in older children was irritability noted in just 5.4%. The observation that preschool children have excessive neuropsychiatric symptoms is also supported by literature studies, which compare preschool children with older children and find that the younger children experience more adverse effects from stimulants, including irritability and anxiety (Firestone, Musten et al. 1998, Ghuman, Ginsburg et al. 2001).

The observation that preschool children experience more adverse effects than older children is also seen in a large national outpatient and emergency department dataset where the incidence of adverse events seen per 1,000 persons was nearly twice as great in children less than age 5 than in those aged 5 to 17 years (Safer 2011).

The relative increase in adverse events when MPH is given to preschool children is noted in the literature; according to the PATS study authors (Greenhill, Posner et al.

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2008), the safety findings in pre-school children differ from those in older, school-age children in two respects:

1. *First, preschoolers exposed to MPH in PATS have a higher rate of discontinuation due to AEs (11%) compared to a rate of <1% in school-age children.*
2. *Second, the profile of AEs that are reported for preschoolers have a different pattern from those identified in school-age children. In school-age children, decreased appetite, delay of sleep onset, headaches, and stomachaches are prominent whereas in pre-school children in the PATS study, the CNS related AEs, i.e., crabby/irritable, emotional outbursts, difficulty falling asleep, repetitive behaviors and thoughts, and decreased appetite were prominent.*

Weight loss, potentially related to reduced appetite, is commonly observed and this adverse event has the potential to be especially problematic when stimulant therapy is started at age 4. The long-term impact of this weight loss is unknown but has the potential to be significant (McCarthy, Neubert et al. 2018). There was no data presented in the Application indicating that preschool children can catch up with their normal growth curve.

Hypertension is a significant issue, and there is a significant occurrence in subjects exposed to Aptensio XR, regardless of how hypertension is defined. The more stringent definition, requiring that hypertension occur over three consecutive visits, makes the most striking comparison between 6-week on- and off-treatment periods of study RP-BP-EF003. In this comparison, there was one instance in the off-treatment period compared with 19 during the on-treatment period. This data was not presented as clearly in the initial submission as it was in the major amendment.

The pattern of psychiatric adverse events noted by the preschool children is concerning. As noted in section 4.4, pre-clinical studies from the literature indicate that MPH has an adverse effect on rat brain tissue, causing neuroinflammation, and on the blood brain barrier, promoting increased permeability. Considering that these animal studies are designed to mirror the MPH exposure of human children, neuroinflammation may also be occurring in the preschool children given Aptensio XR. In adult humans, diverse manifestations of psychopathology are associated with neuroinflammation and increased blood brain barrier permeability and it is reasonable to assume that the same occurs in children. Of particular concern is the potential for the brain to be permanently damaged by neuroinflammation. This potential for lifelong psychological disability is a critical consideration for the risk benefit analysis. Please see section 4.4 for a discussion of the animal literature on this topic.

The predominance of psychiatric AEs (as well as hypertension, weight loss, etc.) noted in this study may be related to excessive levels and doses of MPH in children who experienced high circulating levels of MPH as noted in the PK study. Alternately, this pattern of AEs may be due the immature state of metabolic pathways and the central

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nervous system in these younger children. Recent investigators report that preschool aged exhibit high rates of somatic concerns, irritability and moodiness, and decrements in growth; Children with more complicated clinical pictures, e.g. multiple comorbid conditions, become worse while on methylphenidate compared to those with fewer comorbid conditions (Charach, Carson et al. 2013).

The study design of RP-BP-EF003 limits the safety information which can be obtained from the double-blind phase. During this study period, the observed incidence of adverse events is confounded by the lack of a wash-out, as subjects were either continued on their optimized dose or were given placebo. In addition, 29 subjects were discontinued after 1 week and did not complete 2 weeks, creating an imbalance in the two groups. This creates several problematic issues for interpretation:

- *Subjects on placebo may have been experiencing adverse effects from the withdrawal of MPH, and these symptoms, which can mimic ADHD symptoms, have the potential to manifest in the double-blind phase.*

- *The true incidence of adverse events is obscured by the study design. Side effects, which had begun in the open label phase continued into the double-blind phase and were not counted as being incident.*

- *The potential for exposure to MPH was not matched in the two groups because subjects could be discharged from open-label treatment if their condition became worse.*

- *As the sample of subjects entering the double-blind phase was enriched with patients who could tolerate Aptensio XR over a 6-week dose optimization phase, the adverse reaction rates described in the double-blind phase are lower than expected in clinical practice.*

As noted above, rates of adverse events from the double-blind study should not be reported in the label as design related issues of interpretation will create the misleading impression that the drug is safer than it is in reality.

7.4.2 Laboratory Findings

Subjects were evaluated for changes in serum chemistry values and hematocrit in study RP-BP-EF004. There were no significant mean changes in any of these values during this study. The applicant reported that there were no significant changes noted by the Applicant over the 52-week observation period. The following parameters were evaluated at the beginning and end of study:
Clinical Chemistry and Electrolytes: albumin, alkaline phosphatase, alanine aminotransferase (ALT or SGPT), aspartate aminotransferase (AST or SGOT), gamma-glutamyl transferase (GGT), creatine phosphokinase, lactic acid dehydrogenase (LDH),

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total bilirubin, creatinine, blood urea nitrogen, uric acid, cholesterol, triglycerides, total protein, calcium, glucose, potassium, sodium, chloride, bicarbonate
Hematology: hematocrit, hemoglobin, platelet count, white blood cells
Urinalysis: specific gravity, glucose, protein, white blood cells, red blood cells

7.4.3 Vital Signs

Per protocol, vital sign data (height, weight, blood pressure, heart and respiratory rate) were acquired at screening and subsequently throughout Studies RP-BP-EF003 and RP-BP-EF004. Blood pressure was obtained over the course of the 6-week off-drug period and compared to the 6-week open-label on-drug period in RP-BP-EF003. The AE of hypertension was described in Protocol RP-BP-EF003, 6.1.1 Vital sign assessments as follows: "A 'Hypertension' adverse event is defined as a systolic and/or diastolic BP that is ≥95th percentile (for gender, age, and height) on ≥ 3 occasions." Height was extrapolated. Adverse effects on BP which were noted as AEs were further defined by the Applicant as noted here:

> According to standard procedures available at the time of the study, blood pressure measurements ≥95th percentile for age, gender, and height on three successive visits were defined as an adverse event ('hypertension') that was deemed to have started on the date that elevated blood pressure was first determined. Midway through the study, the criteria used for hypertension was clarified for the sites based on the available American Academy of Pediatrics (AAP) Guidelines of 2004 and reanalyzed using the 2017 AAP Guidelines. An important difference between the 2004 Guidelines and the 2017 Guideline is that when a blood pressure ≥90 percentile for adjusted for height, age and gender is detected, two further blood pressure determinations need to be made at that visit and the values averaged to confirm the finding. This was not advised in the AAP 2004 Guidelines.

As noted in section 3.1, there were irregularities noted in AE reporting related to hypertension. To respond to FDA concerns, on March 14, 2019, the Applicant submitted additional BP data in a major amendment specifying which BP readings were elevated (based on published criteria) for each child based on their age, weight, and height. Applying the above definition to Listing 16.200.1, (Blood Pressure greater than or equal to 95th percentile) for Protocol RP-BP-EF003 and RP-BP-EF004, which was included in the major amendment, this AE occurred in 9 (6.8%) of those in the 6 -week off drug period, 36 (30.3%) in the 6-week open label period, and in 36 (40.0%) of those in the extension study.

Applying an alternative, more stringent, definition to Listing 16.200.1 (Blood Pressure greater than or equal to 95th percentile) for Protocol RP-BP-EF003 stipulating that BP elevations must occur over three consecutive weekly visits for an AE to have occurred determined that this AE occurred in 1 (0.8%) patient in the 6 -week off drug period and 19 (16%) patients in the 6-week open-label period. Using this more stringent definition

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to listing 16.200.1, blood pressure greater than or equal to 95th percentile, for Protocol RP-BP-EF004 (stipulating that BP elevations must occur over three consecutive monthly visits for an AE to have occurred) determined that this AE occurred in 15 (16.9%) of subjects during the year-long open-label period. The Applicant reported fewer hypertensive AEs than this reviewer determined by either method described above.

To further evaluate elevations in blood pressure due to Aptensio XR, each elevation in the on-drug period were calculated by Eiji Ishida, biometrics reviewer, and compared to the off-drug periods. The results for blood pressure are displayed below in Table 10.

Table 10, Hypertension based on Blood Pressure data (Pre-dose vs On-dose)

Numbers of Male Subjects Experiencing a Blood Pressure >95% for age and weight and height comparing 6 weeks off-drug to 6 weeks open label Aptensio X, Study RP-BP-EF003			
Male subjects	**#Hypertension/#Subjects**		
	Hypertension based on		
	SBP	**DBP**	**Either SBP or DBP**
Pre-dose (Open Label)	24/90 (26.7%)	41/90 (45.6%)	48/90 (53.3%)
On-dose (Open Label)	37/87 (42.5%)	50/87 (57.5%)	58/87 (66.7%)
Numbers of Female Subjects Experiencing a Blood Pressure >95% for age and weight, and height comparing 6 weeks off drug to 6 weeks open label Aptensio X, Study RP-BP EF003			
Female subjects	**#Hypertension/#Subjects**		
	Hypertension based on		
	SBP	**DBP**	**Either SBP or DBP**
Pre-dose (Open Label)	3/27 (11.1%)	11/27 (40.7%)	12/27 (44.4%)
On-dose (Open Label)	6/25 (24.0%)	7/25 (28.0%)	8/25 (32.0%)

Note 1: Pre-dose BP measurements were those taken (over 6 weeks) before the first dose in Open Label phase of Study RP-BP-EF003. On-dose BP measurements were those taken after the OL first dose (the next morning of Visit 7 of Study RP-BP-EF003) till the end of the Open Label phase of Study RP-BP-EF003 (Visit 13).
Note 2: Table 4 of "Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents" (American Academy of Pediatrics) was used for the Hypertension criteria.
Note 3: Missing height measurements are imputed by linearly interpolating observed measurements. Age is based on the time of measurements.

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Reviewer note:

Regardless of the method used to access BP elevation, these results indicate that the use of Aptensio XR by preschool children is associated with hypertension. The risk of hypertension beginning in this age group is unknown but has the potential to result in a shortened life due to adverse cardiovascular effects through the lifespan.

Weight

See section 7.6.3 Pediatrics and Assessment of Effects on Growth

7.4.4 Electrocardiograms (EKGs)

No significant changes were noted over the time of the extension study.

7.4.5 Special Safety Studies/Clinical Trials

The effect of Aptensio XR on suicidality was assessed using the Columbia Suicide Scale Score. At baseline (Visit 1), one subject (12-336) provided an affirmative answer for at least one question concerning suicidal ideation and two subjects (11-306 and 14-306) provided an affirmative answer for at least one question concerning suicidal behavior. One subject indicated suicidal ideation at the last visit.

The effect of Aptensio XR on sleep quality was assessed using the Child Sleep Habits Questionnaire (CSHQ). In Study RP-BP-EF003, sleep quality improved during the time the children were in the study, either off or on Aptensio XR, as illustrated in Figure 16. A higher scone indicates more sleep problems. The mean CSHQ Total Score in study RP-BP-EF004 was 46.7 at baseline (Visit M1) and ranged from 43.8-46.7 over 14 visits.

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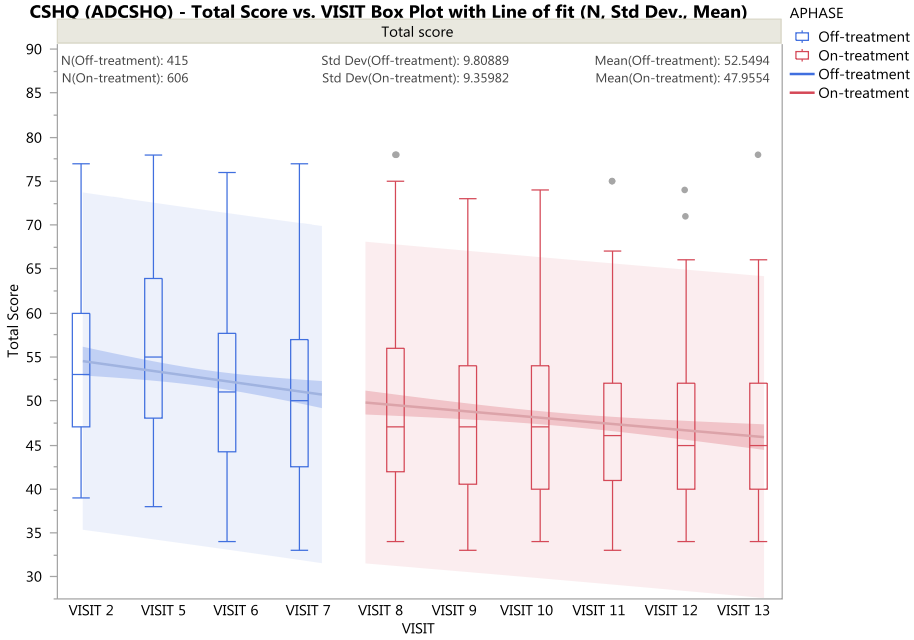
Figure 16, CSHQ Sleep Scale During the ON and Off Treatment Period (Visits 2 – 13)



Reviewer Note:

Aptensio XR appears unlikely to have a negative effect on suicidal ideation or behavior. The data obtained from the CSHQ suggests that Aptensio XR has no significant impact on sleep quality in these studies. The effect of sleep on children with ADHD exposed to MPH may require a longer period of study to detect (Solleveld, Schrantee et al. 2017).

7.4.6 Immunogenicity

No information submitted

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

With assistance from the Agency biometrics reviewer, Eiji Ishida, we evaluated the accumulated dose by estimating the dose amounts taken prior to experiencing an emotional disorder related AE. An estimate was made of the accumulated dose in the following manner. If a patient was compliant with all planned visits, i.e., Visits 7, 8, 9, 10, 11, 12, and 13, we assume that they started with taking 10 mg daily from the next morning following Visit 7 through the next drug dispense at Visit 8. From Visit 8, (for this example) through Visit 13, this patient took 15 mg daily. Then assuming this patient was totally in compliant with the drug administration schedule, the same amount of dose would have been taken daily. Therefore, for this example, the accumulated dose at Visit

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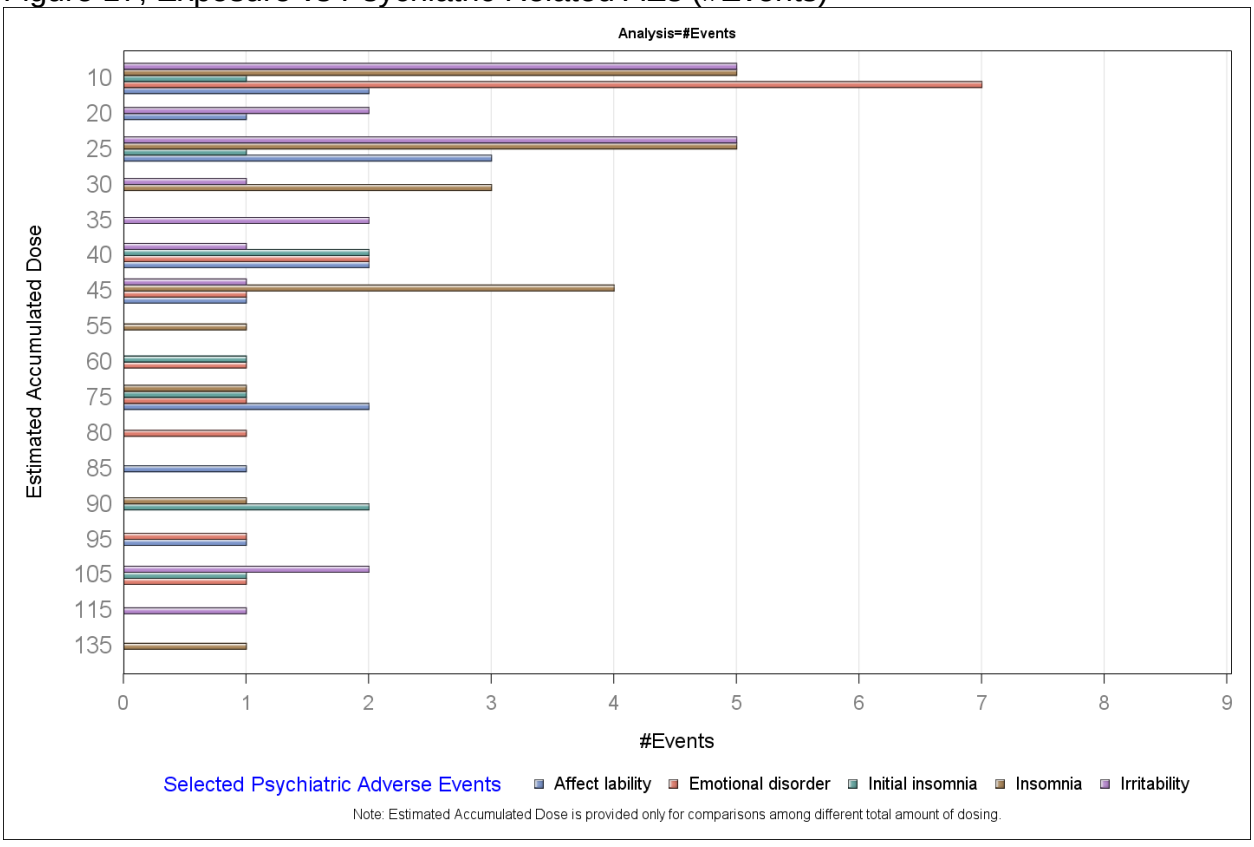
13 (following 6 weeks of exposure) is computed as 10+15+15+15+15+15=85. Similarly, we would estimate the accumulated dose at Visit 9 to be 10+15=25. If the investigator found at Visit 9 that a new AE occurred, the accumulated dose corresponding to the time when this AE occurred would be 25 mg. Also, for example, if the investigator found at Visit 8 that an AE occurred after 1 week of exposure to 10 mg, the accumulated dose for this AE would be 10. Proportionally, the accumulated dose computed this way permits us to make a fair comparison, based on recorded administration dose levels.

When exploring the accumulated dose at which the emotional disorder related AEs occurred, these AEs were noted to occur with any dose, and many occurred the first week, at the lowest dose administered.

Figure 17 shows that one 10 mg dose of Aptensio XR had adverse effects, especially emotional disorder, irritability, and insomnia.

Figure 17, Exposure vs Psychiatric Related AEs (#Events)



Reviewer note:

An increased incidence of adverse events with MPH is supported by literature reports describing an increased likelihood for preschool-age children with ADHD to experience medication related side effects. Psychiatric related side effects occur with the first dose,

and the incidence appears to increase with higher doses of methylphenidate (McGoey, Eckert et al. 2002).

7.5.2 Time Dependency for Adverse Events

Adverse events, particularly psychiatric related SOC AEs, occurred with the onset of Aptensio XR treatment. See the above analysis for accumulated dose.

7.5.3 Drug-Demographic Interactions

None were noted.

7.5.4 Drug-Disease Interactions

Not evaluated

7.5.5 Drug-Drug Interactions

Not evaluated

7.6 Additional Safety Evaluations

Not evaluated

7.6.1 Human Carcinogenicity

Not evaluated

7.6.2 Human Reproduction and Pregnancy Data

Not evaluated

7.6.3 Pediatrics and Assessment of Effects on Growth

In Study RP-BP-EF003, 35% of the patients experienced weight loss during the 6-week open-label treatment phase (N=119). The average weight loss in those patients was 0.68 kg. Eleven patients lost more than 1 kg over this 6-week period. 1 kg represents approximately 5% of the body weight of the average child's weight at baseline, 20.29 kg. The weight change over time for each subject as a function of their expected growth curve was evaluated by Eiji Ishida. These analyses suggest that many children fell off their normal growth trajectory as a result of receiving Aptensio XR. Please see the Appendix for the graphical depiction of this data.

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The principal investigator (PI) at each study site was responsible for assessing the severity of any weight loss of 5 to < 10% (compared to visit 7) to determine if it should be classified as an adverse event, ('weight loss'). Instances of weight loss ≥ 10% (compared to visit 7) were all to be recorded as an adverse event. These criteria for determining this AE characterized 24% of subjects who participated in either Study RP-BP-EF003 or RP-BP-EF003 as having decreased weight (see Figure 18).

Four children were withdrawn from study because of concerns about weight loss. On inspection of the Case Report Forms for two of these children, the notes indicated that the child's parents rather than the site investigator insisted on withdrawal for adverse effects on growth.

The related AE of Decreased Appetite was also prominent, occurring in 26% of subjects who participated in either Study RP-BP-EF003 or RP-BP-EF003 (see Figure 19).

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Figure 18, Weight Decreased Adverse Events

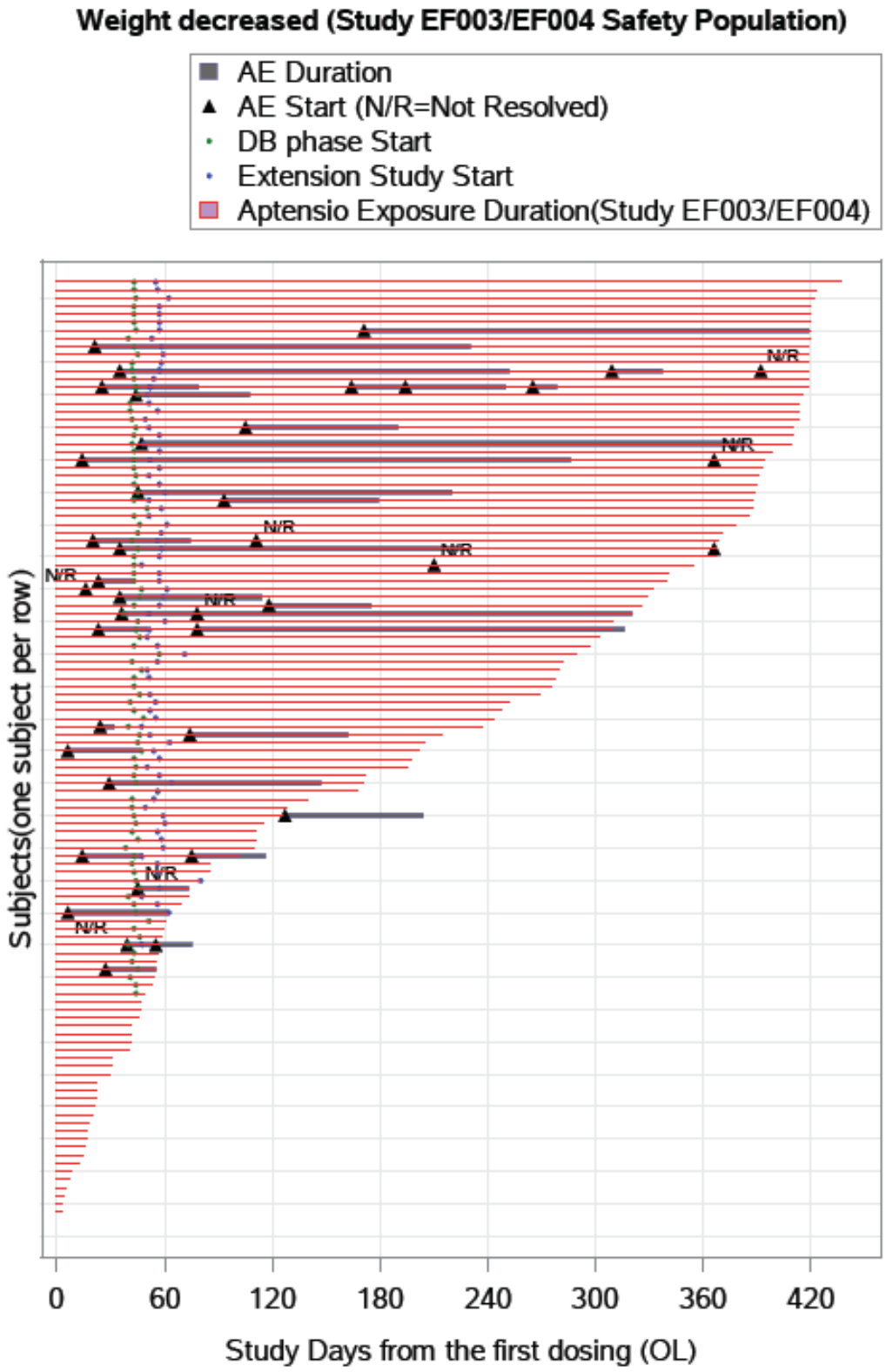

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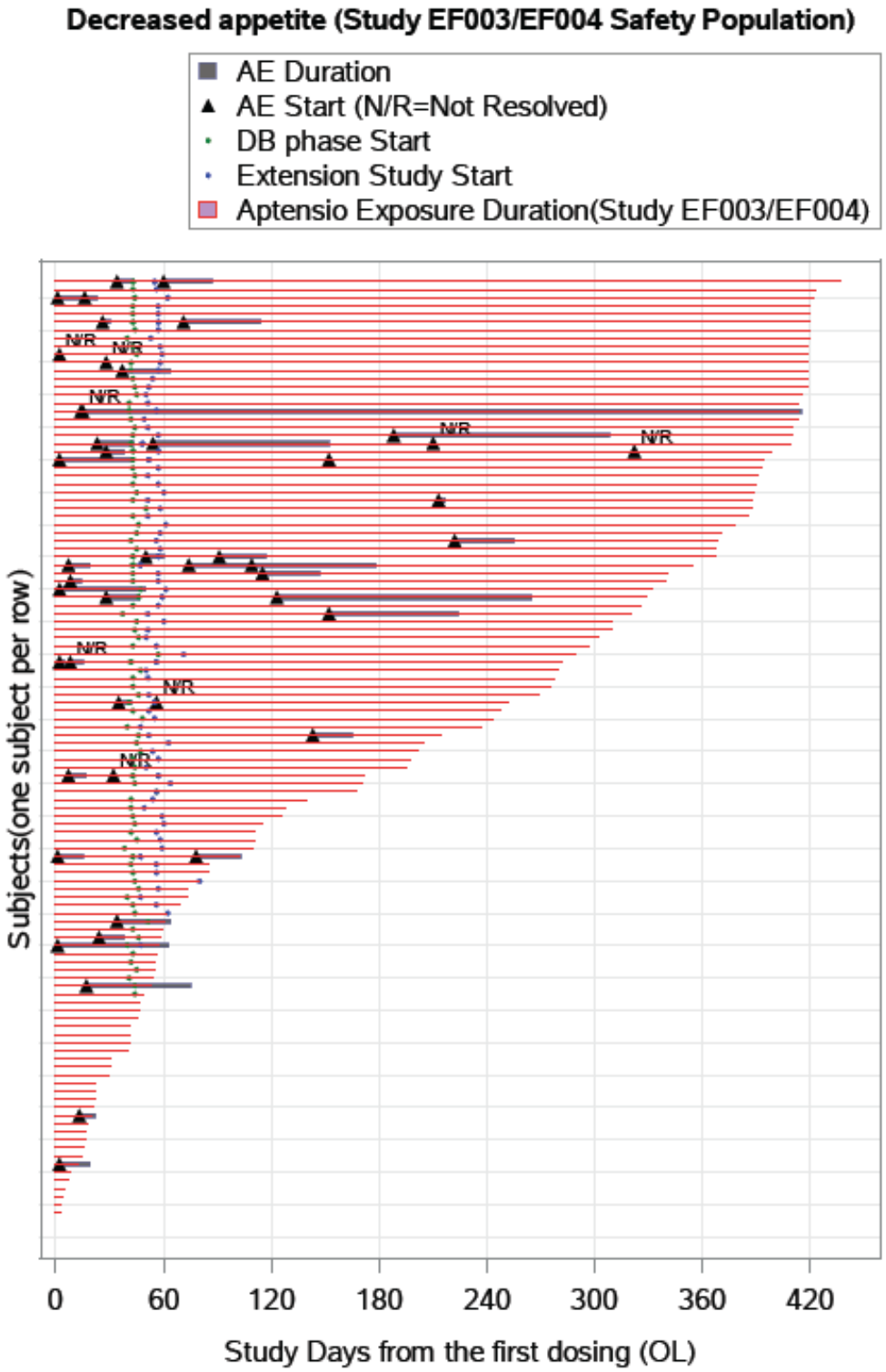
Figure 19, Figure 20, Decreased Appetite Adverse Events



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Reviewer note:

The weight loss noted in the open-label study is concerning. Combined with reports of reduced appetite, this may represent an inferior nutritional status. A significant reduction in growth was also noted in the long-term PATS study, which reported that preschoolers treated with methylphenidate experienced significant growth retardation (Swanson, Greenhill et al. 2006). Based on this data, the PATS study authors estimate that 1 year of continuous treatment with MPH may result in a reduction in growth rate by ~20% (1.38 cm/year) for height and ~55% (1.32 kg/year) for weight.

The long-term effect of stimulants on growth in pediatric patients ages 4 to less than 6 is unknown. Stimulants have an established effect to lessen growth velocity in weight and height in youth with ADHD, and this effect is relatively more prominent in preschoolers (Ahmann, Theye et al. 2001, Safer 2011). As the duration of medication treatment increases in youth, the decrement in height and weight percentile growth velocity tends to increase and has not been show to rebound after therapy stops (Swanson, Elliott et al. 2007).

As the use of MPH in children may continue on a chronic basis, and this potentiates the potential for life-long nutritional related adverse effects. Although the most obvious effect is for the children to have short stature as adults, other organ systems, including the brain, may be affected as well.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The study report contains no data on the illicit abuse of Aptensio XR. Although not described in detail in case report forms, as many as 10 subjects appeared to have been terminated from the study for reasons related to medication compliance, and this may or may not indicate that Aptensio XR was diverted by the parents for illicit sale or use. Considering the potential for illicit use of Aptensio XR, the investigators on site may have had concerns about careful accounting of this controlled substance but there is no evidence for this presented in the application (see Table 8).

Reviewer note:

The Integrated Summary of Safety (2.7.4.8.11) mentions that: "There was no evidence of study drug abuse noted. Aptensio XR was administered to the subject by his or her parent." This statement does not evidence comprehension that it is the parent, not the 4- or 5-year-old child, who would be most likely to abuse this stimulant (Fulton and Yates 1988). However, the following except concerning patient (b) (6) from Table 8, although not explicitly mentioning diversion, seems to create the potential for this to have occurred:

Patient number	Disposition	Discontinuation Reason Details
(b) (6)	Physician decision	Pi concern regarding subject compliance with study drug administration*

It is noteworthy that the possibility of parental diversion was apparently not addressed in the protocol. Considering that a considerable proportion of all prescription stimulants are diverted for non-medical use, this omission is significant. Parental diversion has the potential to cause significant confounding effects which, if present, could invalidate a study.

MPH has a great potential to cause harm as a result of illicit use and the investigators should be aware of this possibility and confront the issue directly. A study involving children should carefully evaluate signs of illicit drug use and diversion by the parents or guardians who may be drug seeking. For example, a careful family history may alert physicians to be particularly vigilant that these addictive drugs were being diverted from their patients for a caregiver's personal use. The potential diversion of stimulants for illicit use is a critical aspect to consider as a component of the risk:benefit profile of Aptensio XR and all stimulants.

There is also the potential that administering MPH to this vulnerable population will promote their future addiction to stimulants. Although poorly understood, the scope of this potential problem is great because of the large population of children at risk. This is a critical unknown risk of Aptensio XR and other stimulants.

7.7 Additional Safety Issue

None

8 Postmarket Experience

The Label from Aptensio XR includes the following description of post-marketing experience.

> The following adverse reactions have been identified during post approval use of methylphenidate products. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are as follows:
>
> > *Blood and Lymphatic System Disorders*: Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura
> >
> > *Cardiac Disorders*: Angina pectoris, Bradycardia, Extrasystole, Supraventricular tachycardia, Ventricular extrasystole

Eye Disorders: Diplopia, Mydriasis, Visual impairment
General Disorders: Chest pain, Chest discomfort, Hyperpyrexia

Immune System Disorders: Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus NEC, Rashes, Eruptions, and Exanthemas, NEC

Investigations: Alkaline phosphatase increased, Bilirubin increased, Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal, severe hepatic injury

Musculoskeletal, Connective Tissue and Bone Disorders: Arthralgia, Myalgia, Muscle twitching, Rhabdomyolysis

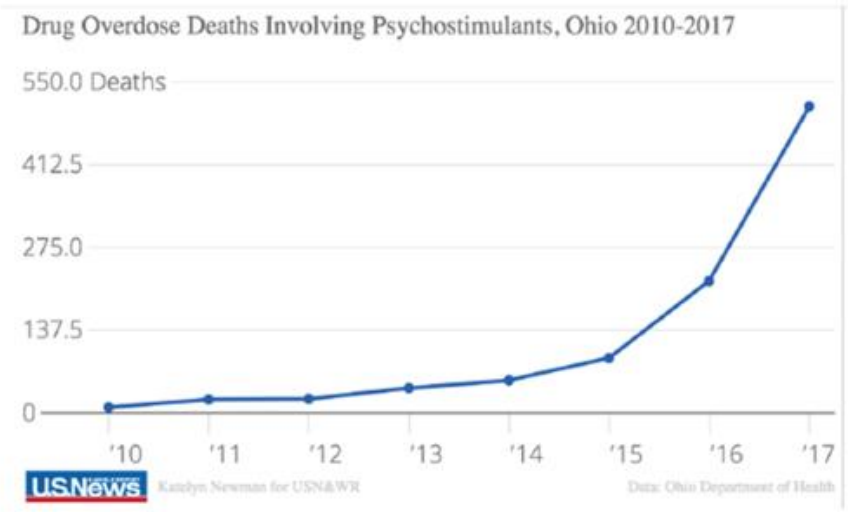
Nervous System: Convulsion, Grand mal convulsion, Dyskinesia, serotonin syndrome in combination with serotonergic drugs

Psychiatric Disorders: Disorientation, Libido changes

Skin and Subcutaneous Tissue Disorders: Alopecia, Erythema

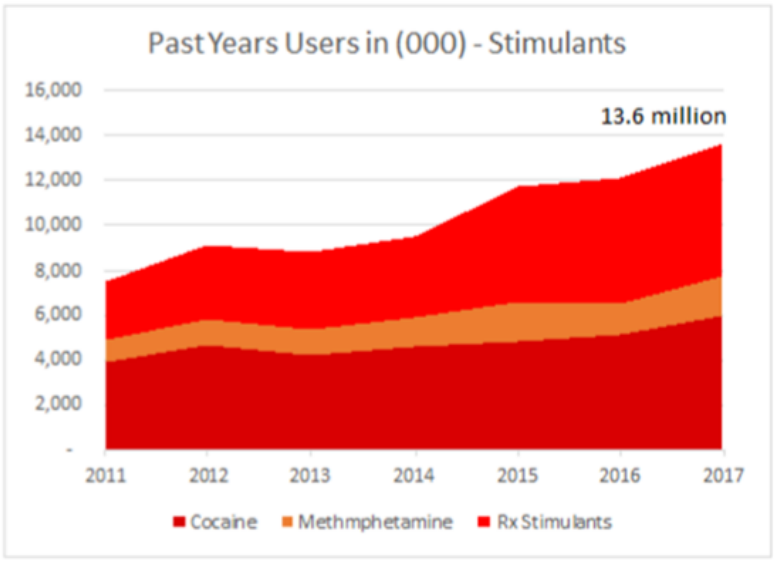
Surveillance of the illicit use of psychostimulants such as MPH indicate that abuse is a growing problem. The rate of overdose deaths involving psychostimulants increased by 33.3% from 2016 (Newman 2018) and this is even more pronounced in some areas of the country, as noted in Figure 21.

Figure 21, The Rate of Overdose From Stimulants is Increasing



Although stimulants available by prescription such as MPH are not the only stimulants abused, their use is significant, as noted in Figure 22 (Eadie).

Figure 22, Non-Medical Use of Stimulant in the Past Year



9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

The proposed labeling for Aptensio XR is based on the current Aptensio XR label. (b) (6) , the label should include the safety results of study RP-BP-EF003

which describe 6 weeks of the adverse effects noted during the off-treatment lead-in and the open-label period. A summary of AEs off- and on-treatment, occurring Study RP-BP-EF003 should be included.

I do not recommend that the label include data regarding adverse events from the double-blind study period. I consider that the issues of interpretation note above in 7.4.1 are so serious that they will create a misunderstanding about the likelihood of AEs to occur with Aptensio XR in this vulnerable population.

9.3 Advisory Committee Meeting

There is no advisory committee meeting planned. However, based on my evaluation of the potential risks and benefits of Aptensio XR for the treatment of ADHD presented in this application, I am concerned about the safety of all stimulant use in children 4 to under 6 years of age. Considering the history of intense public interest in the safe use of stimulants in this vulnerable population, I recommend that an advisory committee meeting should be held before any new stimulant products are approved for preschool aged children. The purpose would be to ensure the safety of the continued use of stimulant drugs in preschool children.

The potential for psychiatric sequalae, as noted in animals exposed to MPH, has the potential to be of great public health significance. Other common adverse events in this age group, particularly weight loss and hypertension, also have the potential to cause life-long disability.

Reviewer Note:

My review has revealed uncertainty about the safe use of MPH in preschool children. The safety concerns raised in the review extend to the use of any stimulant in these young children, despite the fact that some are approved for use in children as young as 3.

I found no data or literature references in this application indicating that children derive an actual benefit from ADHD symptom reduction unless they are old enough to attend school. I found no data or literature references showing a benefit to preschool children who receive stimulant treatment for ADHD beyond an effect to temporarily reduce ADHD criteria. Thus, improvement in ADHD criteria, the purported benefit of stimulant use, may not reflect any actual benefit to the preschool children. The primary benefit of treating preschool children with ADHD appears to be for the benefit for the caregivers, yet even this potential benefit has little empirical support.

An advisory committee could evaluate these issues. Stimulant use in preschool children is considered by some as a form of chemical restraint in a vulnerable population and as such, requires careful ethical and scientific consideration.

Reference ID: 4445893

9.4 Safety Explorations Conducted but Not Included Above

Adverse Event Data

Adverse events occurring during the Double-blind phase were confounded by the study design, as noted above. However, for the sake of completeness, AE information as provided by the Applicant in the submitted database is presented below.

Table 11, Study RP-BP-EF003, Adverse Reactions Incident in ≥ 2% of Pediatric Patients (4 to Under 6 Years of age) with ADHD Taking APTENSIO XR and at a Rate

System Organ Class Preferred Term	**Aptensio XR (n= 40)**	**Placebo (n=50)**
Gastrointestinal		
Gastritis	3%	0%
Metabolism and Nutritional		
Decreased appetite	3%	0%
Psychiatric		
Formication	3%	0%
Emotional poverty	3%	0%
Negativism	3%	0%
Onychophagia	3%	0%
Renal and Urinary		
Pollakiuria/Urinary incontinence	5%	0%
Vascular		
Hypertension	8%	0%
Tachycardia	3%	0%

Greater than Placebo

Reference ID: 4445893

Adverse Event Incidence Considered by Body Mass Index

The data suggest that normal subjects had a higher proportion in weight decrease and decreased appetite, as might be expected. Normal weight subjects had a numerically greater reduction in appetite.

The data suggest that hypertension is also more likely to occur in the overweight children (17%), than it does in the normal weight children (9%). This parallels the increase in blood pressure that is noted in overweight individuals.

Table 12, Adverse Events as a function of BMI based Weight Class, Exposed Subjects from All Studies

Primary System Organ Class	Dictionary-Derived Term	Weight status based on Baseline BMI			
		Underweight (N=12)	Normal (N=121)	At Risk of Overweight (N=33)	Overweight (N=51)
Blood and lymphatic system disorders	Lymphadenitis		1 (0.8)		
Cardiac disorders	Sinus tachycardia				1 (2)
	Tachycardia	1 (8.3)	3 (2.5)		
Ear and labyrinth disorders	Ear pain	1 (8.3)	1 (0.8)		1 (2)
	Hypoacusis				1 (2)
	Otorrhoea		1 (0.8)		
	Tympanic membrane perforation				1 (2)
Eye disorders	Dry eye				1 (2)
	Eye allergy				1 (2)
Gastrointestinal disorders	Abdominal pain		3 (2.5)		
	Abdominal pain upper		6 (5)	3 (9.1)	2 (3.9)
	Chapped lips		1 (0.8)		
	Dental caries		2 (1.7)		
	Diarrhoea		4 (3.3)	1 (3)	2 (3.9)
	Dry mouth		1 (0.8)		
	Flatulence		2 (1.7)		
	Frequent bowel movements			1 (3)	
	Gastritis		2 (1.7)		

Primary System Organ Class	Dictionary-Derived Term	Weight status based on Baseline BMI			
		Underweight (N=12)	Normal (N=121)	At Risk of Overweight (N=33)	Overweight (N=51)
	Nausea	1 (8.3)	1 (0.8)		1 (2)
	Toothache		1 (0.8)		
	Vomiting		5 (4.1)		4 (7.8)
General disorders and administration site conditions	Adverse event				1 (2)
	Asthenia		1 (0.8)		
	Crying		2 (1.7)	1 (3)	
	Fatigue		2 (1.7)		
	Feeling abnormal		1 (0.8)		
	Injection site pain		1 (0.8)		
	Pain				1 (2)
	Pyrexia	1 (8.3)	7 (5.8)		1 (2)
	Thirst		1 (0.8)		
Immune system disorders	Hypersensitivity		1 (0.8)		
	Seasonal allergy		3 (2.5)		
Infections and infestations	Body tinea			1 (3)	
	Campylobacter infection		1 (0.8)		
	Cellulitis		2 (1.7)		
	Conjunctivitis		1 (0.8)		
	Croup infectious		1 (0.8)		
	Ear infection		4 (3.3)		2 (3.9)
	Enterobiasis		1 (0.8)		
	Gastroenteritis		4 (3.3)		
	Gastroenteritis viral		5 (4.1)		2 (3.9)
	Gastrointestinal infection		1 (0.8)		
	Influenza		5 (4.1)		
	Localised infection			1 (3)	
	Nasopharyngitis		9 (7.4)		2 (3.9)
	Otitis media		4 (3.3)	1 (3)	1 (2)
	Pharyngitis streptococcal		6 (5)		1 (2)

Primary System Organ Class	Dictionary-Derived Term	Weight status based on Baseline BMI			
		Underweight (N=12)	Normal (N=121)	At Risk of Overweight (N=33)	Overweight (N=51)
	Pneumonia		1 (0.8)		
	Respiratory syncytial virus infection		1 (0.8)		
	Respiratory tract infection viral		1 (0.8)		
	Sinusitis		1 (0.8)		
	Streptococcal infection		1 (0.8)	1 (3)	
	Tinea capitis			1 (3)	
	Tonsillitis		1 (0.8)		
	Tooth abscess		2 (1.7)		
	Upper respiratory tract infection		9 (7.4)	1 (3)	2 (3.9)
	Viraemia		2 (1.7)		
	Viral infection		1 (0.8)		
	Viral rash		1 (0.8)		
Injury, poisoning and procedural complications	Arthropod bite		1 (0.8)		
	Chemical burn of skin		1 (0.8)		
	Concussion		1 (0.8)		
	Contusion		2 (1.7)		
	Injury corneal			1 (3)	
	Laceration		2 (1.7)		
	Procedural pain		1 (0.8)		
	Upper limb fracture				1 (2)
Investigations	Blood pressure diastolic increased			1 (3)	
	Blood triglycerides		1 (0.8)		
	Body height decreased		1 (0.8)		
	Heart rate increased	1 (8.3)	1 (0.8)		1 (2)
	Influenza A virus test positive			1 (3)	
	Weight decreased	1 (8.3)	20 (16.5)	3 (9.1)	5 (9.8)

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Primary System Organ Class	Dictionary-Derived Term	Weight status based on Baseline BMI			
		Underweight (N=12)	Normal (N=121)	At Risk of Overweight (N=33)	Overweight (N=51)
Metabolism and nutrition disorders	Decreased appetite	1 (8.3)	21 (17.4)	3 (9.1)	6 (11.8)
	Dehydration		1 (0.8)		
	Hypertriglyceridaemia		1 (0.8)		
	Increased appetite		3 (2.5)		
Musculoskeletal and connective tissue disorders	Muscle spasms		1 (0.8)		
	Neck pain		1 (0.8)		
	Pain in extremity		4 (3.3)		1 (2)
	Trigger finger				1 (2)
Nervous system disorders	Disturbance in attention				1 (2)
	Formication				1 (2)
	Headache		9 (7.4)		3 (5.9)
	Hypersomnia			1 (3)	
	Hypoaesthesia		1 (0.8)		
	Lethargy		1 (0.8)		
	Myoclonus		1 (0.8)		
	Somnolence		4 (3.3)		
	Speech disorder		1 (0.8)		
Psychiatric disorders	Abnormal behaviour			1 (3)	
	Abnormal dreams				1 (2)
	Affect lability		10 (8.3)	1 (3)	3 (5.9)
	Affective disorder			1 (3)	
	Aggression		5 (4.1)	1 (3)	1 (2)
	Anger			1 (3)	
	Anxiety		3 (2.5)		
	Attention deficit/hyperactivity disorder		1 (0.8)		1 (2)
	Blunted affect		1 (0.8)		
	Change in sustained attention		1 (0.8)		

Primary System Organ Class	Dictionary-Derived Term	Weight status based on Baseline BMI			
		Underweight (N=12)	Normal (N=121)	At Risk of Overweight (N=33)	Overweight (N=51)
	Compulsive handwashing			1 (3)	
	Compulsive lip biting		1 (0.8)		
	Dermatillomania		3 (2.5)		1 (2)
	Dysphemia		2 (1.7)		
	Emotional disorder		11 (9.1)	1 (3)	3 (5.9)
	Emotional distress		1 (0.8)		
	Emotional poverty		1 (0.8)		
	Encopresis		2 (1.7)		
	Flat affect			1 (3)	
	Hallucination		1 (0.8)		
	Hallucination, tactile		1 (0.8)		
	Initial insomnia	1 (8.3)	5 (4.1)		2 (3.9)
	Insomnia	2 (16.7)	14 (11.6)	1 (3)	6 (11.8)
	Irritability	2 (16.7)	13 (10.7)	1 (3)	3 (5.9)
	Logorrhoea			1 (3)	
	Mental disorder				1 (2)
	Middle insomnia		2 (1.7)		
	Mood swings		3 (2.5)		
	Mutism				1 (2)
	Nail picking		1 (0.8)		
	Negativism		3 (2.5)		
	Nightmare		1 (0.8)		
	Noctiphobia		1 (0.8)		
	Nocturnal fear		2 (1.7)		
	Onychophagia		4 (3.3)		1 (2)
	Parasomnia			1 (3)	
	Personality disorder		1 (0.8)		
	Poverty of speech		1 (0.8)		
	Sleep terror		1 (0.8)		1 (2)

Primary System Organ Class	Dictionary-Derived Term	Weight status based on Baseline BMI			
		Underweight (N=12)	Normal (N=121)	At Risk of Overweight (N=33)	Overweight (N=51)
	Social avoidant behaviour		3 (2.5)	1 (3)	
	Staring				1 (2)
	Suicidal ideation	1 (8.3)			
	Terminal insomnia		1 (0.8)		
	Tic		3 (2.5)		
Renal and urinary disorders	Dysuria		1 (0.8)		
	Enuresis		3 (2.5)		
	Pollakiuria		1 (0.8)		
	Urinary incontinence		1 (0.8)		
Respiratory, thoracic and mediastinal disorders	Asphyxia		1 (0.8)		
	Cough		5 (4.1)	2 (6.1)	3 (5.9)
	Epistaxis		4 (3.3)	1 (3)	
	Nasal congestion				1 (2)
	Oropharyngeal pain		1 (0.8)		
	Respiratory tract congestion				1 (2)
	Rhinitis allergic		1 (0.8)		1 (2)
	Rhinorrhoea		1 (0.8)		2 (3.9)
	Throat irritation		1 (0.8)		
Skin and subcutaneous tissue disorders	Hyperhidrosis		1 (0.8)		
	Pruritus				1 (2)
	Rash		3 (2.5)	1 (3)	
	Urticaria		1 (0.8)		
Surgical and medical procedures	Tonsillectomy				1 (2)
Vascular disorders	Flushing		1 (0.8)		
	Hypertension		11 (9.1)	1 (3)	9 (17.6)
	Prehypertension	1 (8.3)	1 (0.8)		1 (2)
	Systolic hypertension		1 (0.8)		

Blood Pressure Data

Blood pressure figures here are presented for completeness, to indicated that this information was evaluated, but should not be considered as completely valid because of the issues with the double-blind phase of study noted in the review above. The following figures on blood pressure were constructed using the SDTM data and have the caveat that they do not represent properly randomized groups. Some of the data noted as "Week 15" is from 1 week of double-blind treatment and some is from 2 weeks of double-blind treatment. The trend for an increase in blood pressure to occur with Aptensio XR is noted for both systolic and diastolic blood pressure.

Figure 23, Study RP-BP-EF003 Double Blind Period: Systolic Blood Pressure

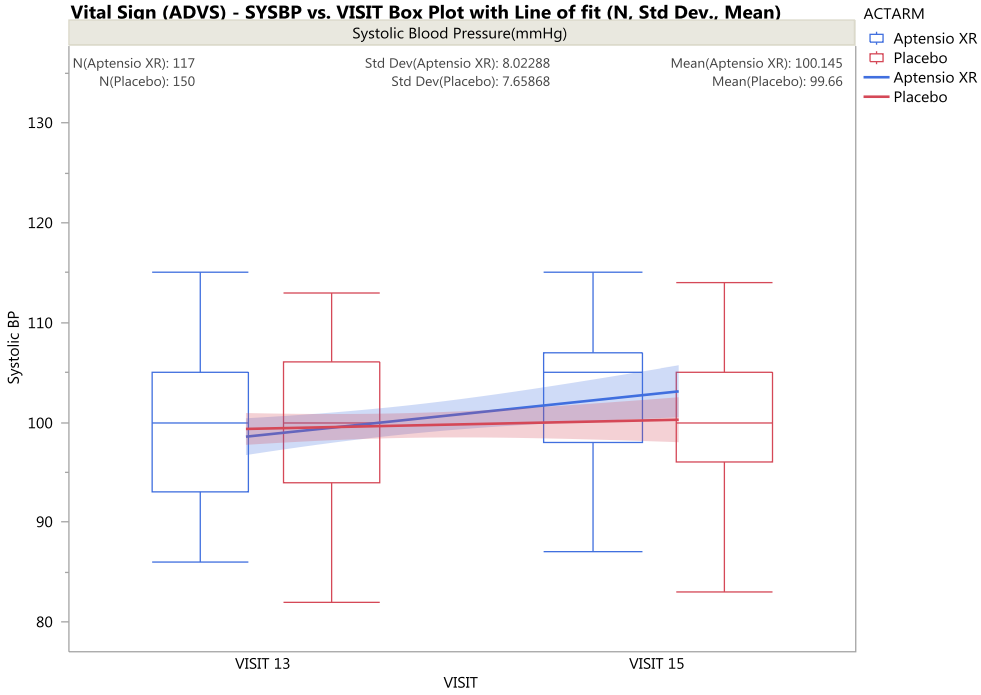
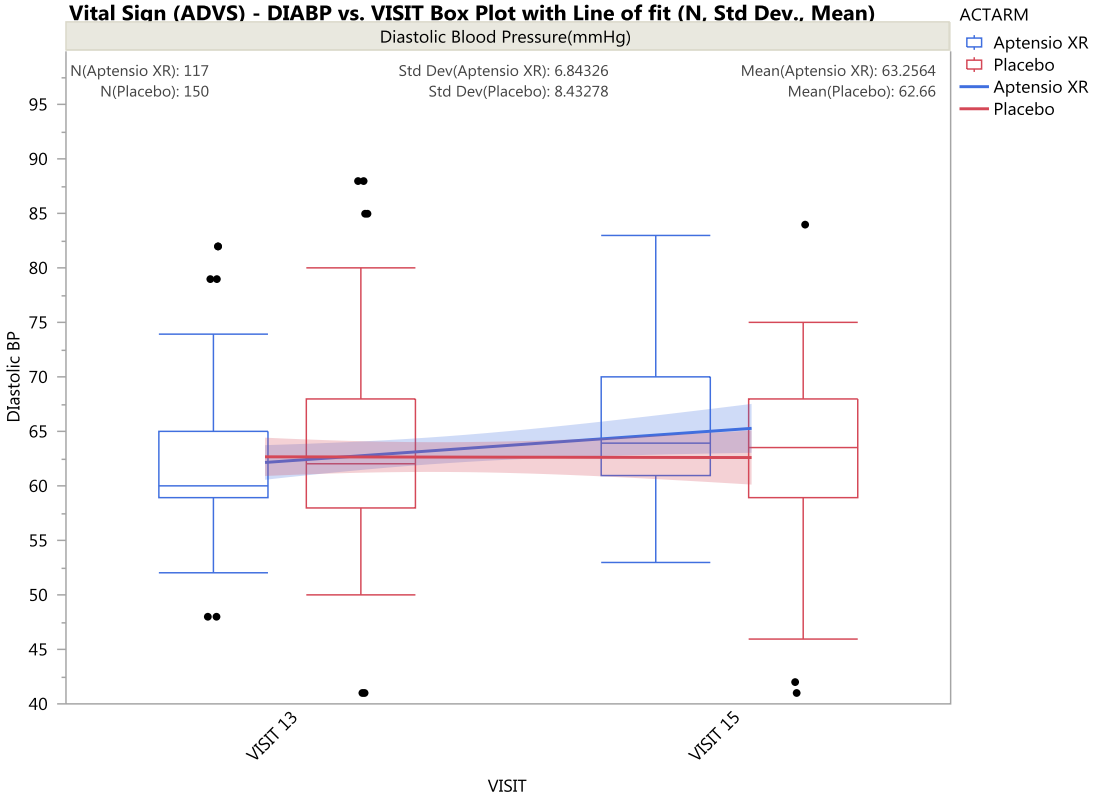


Figure 24, Study RP-BP-EF003 Double Blind Period: Diastolic Blood Pressure



Weight Data from Studies RP-EF-003 and RP-EF-004

Age-matched weight percentile profiles of subjects participated in Studies RP-EF-003 and RP-EF-004 (Figure 25, Figure 26, Figure 27, and Figure 28) suggest that positive weight growth did not occur to many subjects during their participation in the study, with respect to the CDS growth chart during the study participations.

Reference ID: 4445893

Figure 25: Age-matched weight percentile of Female Subjects referenced to CDS weight-age growth chart

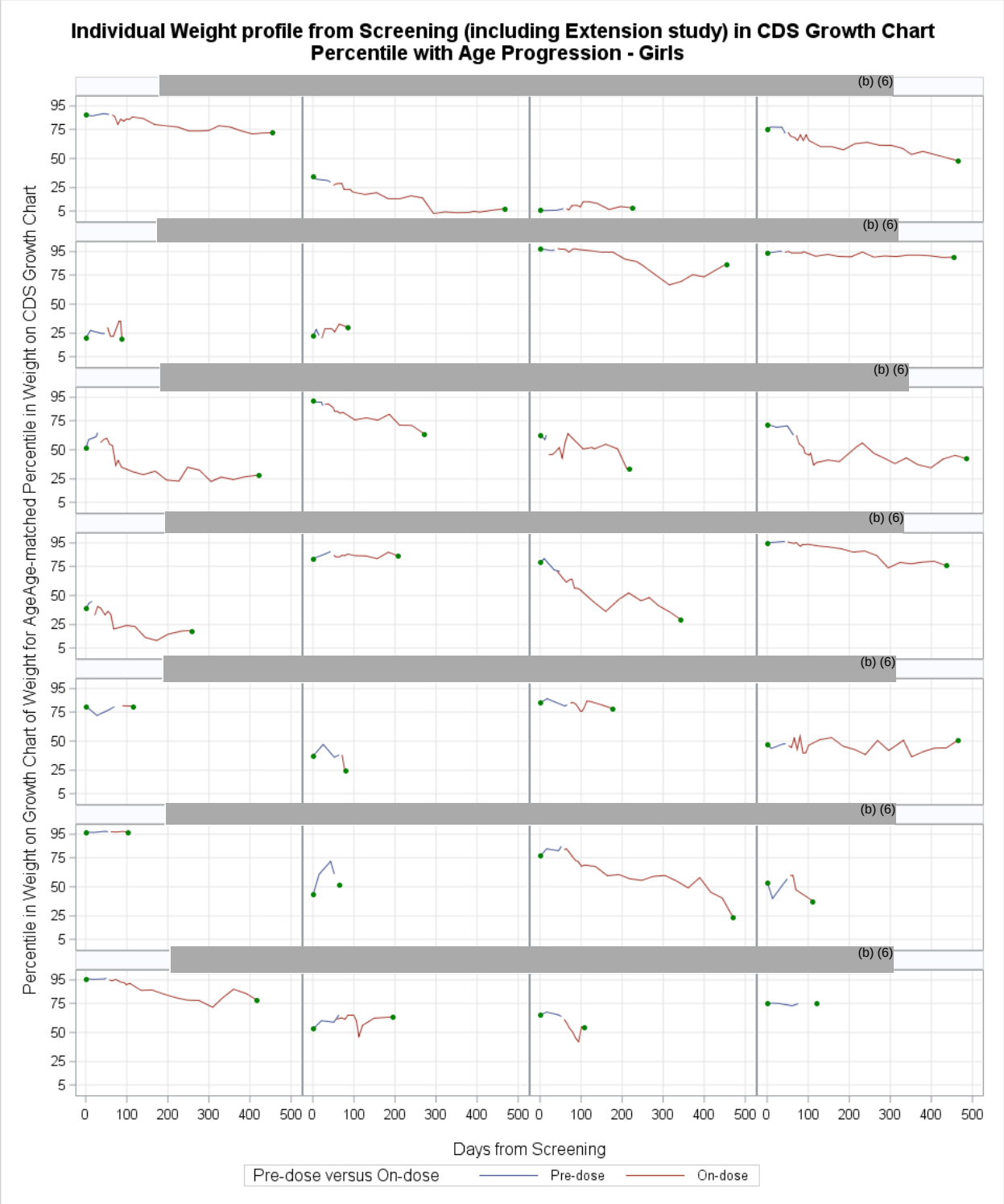


Figure 26: Age-matched weight percentile of Male Subjects referenced to CDS weight-

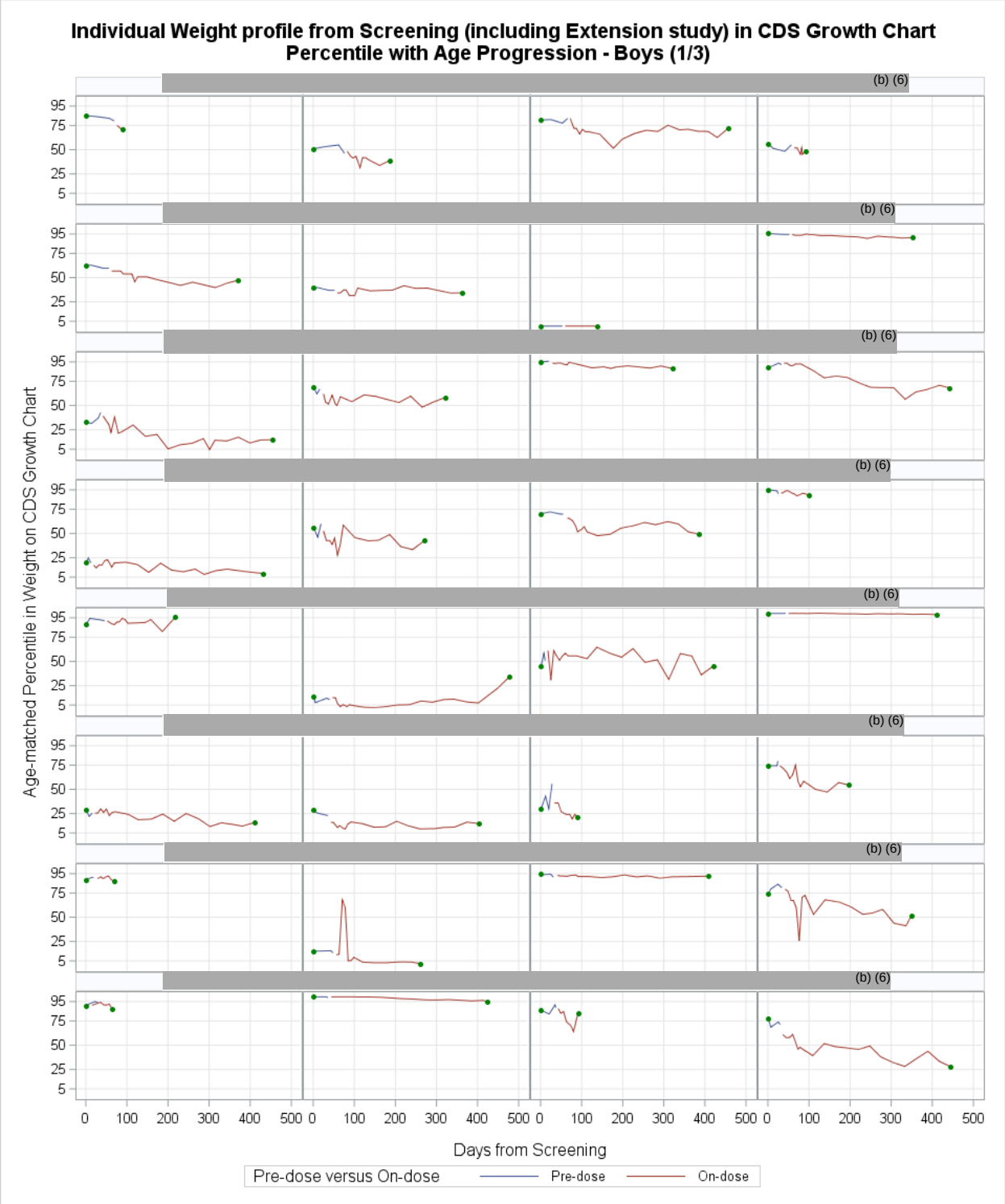


Figure 27: Age-matched weight percentile of Male Subjects referenced to CDS weight-

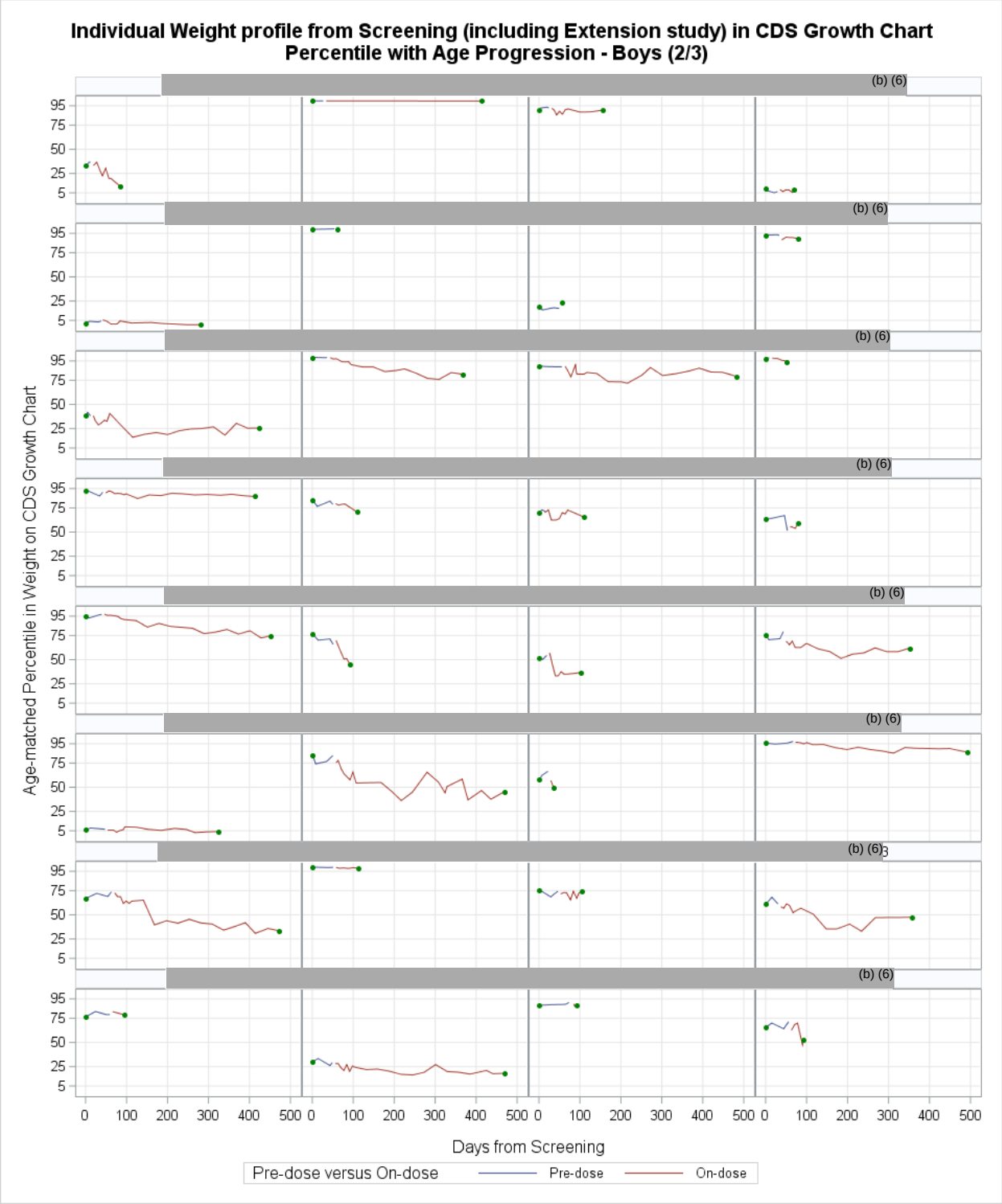
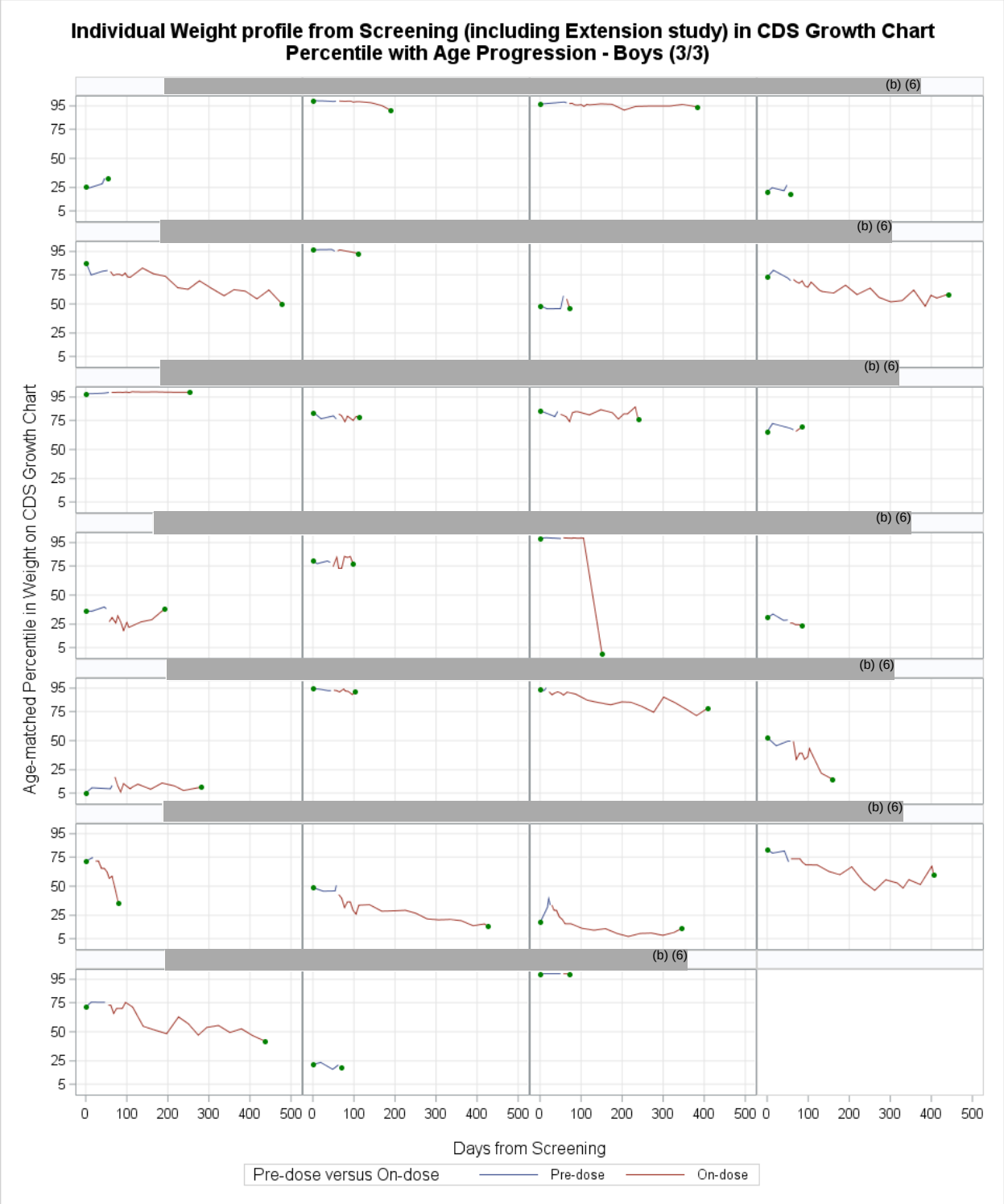


Figure 28: Age-matched weight percentile of Male Subjects referenced to CDS weight-



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BERNARD A FISCHER
06/11/2019 06:24:31 AM
Lead Medical Officer I have read and acknowledge Dr. Umhau's Review. Please see the Joint CDTL/DDSR for my review of this Supplement.