Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Response Document

Response to the 2 August 2010 Request For Information Regarding the Type II Variation for Use of CONCERTA in Adults With ADHD Whose ADHD Diagnosis was Established Before the Age of 18 Years and Whose Symptoms Persist Into Adulthood (Mutual Recognition Procedure, UK/H/0544/002/II/056)

CONCERTA®
Prolonged-Release Tablets (18 mg, 27 mg, 36 mg, and 54 mg)
OROS Methylphenidate HCl

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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LIST OF ABBREVIATIONS

ADHD	attention-deficit/hyperactivity disorder
ADR	adverse drug reaction
AISRS	Adult ADHD Investigator Symptom Rating Scale
ANCOVA	analysis of covariance
ARCI	Addiction Research Center Inventory
AUC	area under the concentration-time curve
AUC_{0-2h}	area under the concentration-time curve over the time interval 0 to 2 hours
BMI	body mass index
C_{max}	peak plasma concentration
C-CASA	Columbia Classification Algorithm for Suicide Assessment
C-SSRS	Columbia-Suicide Severity Rating Scale
CAARS	Conners' Adult ADHD Rating Scale
CGI-I	Clinical Global Impression-Improvement
CMS	Concerned Member State
CSR	clinical study report
CVD	cardiovascular disease
DB	double-blind [used only as a study identifier, ie, 3002 DB]
DBP	diastolic blood pressure
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)
EU	European Union
IR	immediate release
ITT	intent-to-treat [analysis set]
kgs	kilograms
LOCF	last observation carried forward
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	mixed model repeated measures
NHANES III	[US] third National Health and Nutrition Examination Survey
OL	open-label [used only as a study identifier, ie, 3002 OL]
PCI	potentially clinically important
PIL	Patient Information Leaflet
P-RMS	PSUR Reference Member State
PSUR	Periodic Safety Update Report
RFI	Request for Further Information
RMP	Risk Management Plan
SBP	systolic blood pressure
SCS	Summary of Clinical Safety
SPC	Summary of Product Characteristics
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

This response document addresses the Medicines and Healthcare products Regulatory Agency (MHRA, serving as Reference Member State) Request for Further Information (RFI) regarding the Type II Variation for use of CONCERTA® XL prolonged-release tablets in adults with attention-deficit/hyperactivity disorder (ADHD) whose ADHD diagnosis was established before the age of 18 years and whose symptoms persist into adulthood (Mutual Recognition Procedure, UK/H/0544/002/II/056) dated 2 August 2010.

The Preliminary Assessment Report indicated that the data provided in the application were not sufficient to support an extension of the existing CONCERTA indication to treatment of adults with ADHD.

In an e-mail correspondence with the MHRA, Janssen, the Company, informed the MHRA that not all relevant information is available to respond to the request in a satisfactory manner at this time. Specifically, the additional data on long-term maintenance of efficacy in adults with ADHD cannot be provided. With reference to the conclusion on page 71 of the Preliminary Assessment Report that safety data from the adult studies should be added to the Summary of Product Characteristics (SPC) and Patient Information Leaflet (PIL) even if the indication is not approved, the Company agreed with the MHRA request to add adult safety data to the SPC. This seems reasonable especially since it is counterintuitive to withdraw a treatment that is effective and well tolerated from a patient who is still deriving benefit from it, because he/she has reached an arbitrary age cut-off (18 years). Therefore, the company proposes that the following amendments be made to the CONCERTA SPC under the current variation application:

- An additional table of adverse drug reactions (ADRs) identified on the basis of clinical trial data in adult subjects with ADHD that are either new or reported in a higher frequency category than in the pediatric population is added to Section 4.8 of CONCERTA SPC and reflected in the PIL.
- To further illustrate the relevance of the safety information in adults with ADHD to prescribers, additional guidance is provided regarding the continued use of CONCERTA into adulthood for those adolescents who benefit from treatment but whose symptoms of ADHD persist into adulthood. This could be similar to the guidance provided to prescribers in the SPC of Strattera® (atomoxetine HCL). Strattera is not currently authorized for use in adults with ADHD; however, Section 4.2 of the SPC includes the statement “In adolescents whose symptoms persist into adulthood and who have shown clear benefit from treatment, it may be appropriate to continue treatment into adulthood”. Furthermore, as in the

> Strattera SPC, Section 5.1 of the CONCERTA SPC could briefly describe the studies that have been conducted in adults with ADHD and include the sentence "Long term maintenance of effect in adults has not been demonstrated".

On 12 October 2010, the MHRA Assessor, [redacted], informed the Company that a revised SPC could be submitted as part of the Company's response to the Preliminary Assessment Report. This response would be assessed as part of the current Type II Variation application and should address the requests provided in the Preliminary Assessment Report, except those that are only relevant for a full adult indication.

1.2. Overview of Proposed Changes to the SPC

The proposed SPC changes provide guidance regarding the continued use of CONCERTA from adolescence into adulthood for individual patients with ADHD at Sections 4.2 (Section 1.2.1) and 4.4 (Section 1.2.2), in addition to safety data pertaining to the adult population at Section 4.8 (Section 1.2.3). The rationale and supporting documentation for these changes are provided in Section 2; the rationale for the format of additional safety data in SPC Section 4.8 is provided in Section 1.2.3.1. Proposed SPC revisions at Section 5.1 related to information regarding studies in the adult population are provided in Section 1.2.3.3. Additions or modifications of the text in the SPC are <u>double underlined</u>, and deletions are ~~struck through~~. Unaltered text within the same paragraph is shown in regular font.

1.2.1. SPC Section 4.2

The following changes are proposed at SPC Section 4.2, Posology and method of administration, under the subheadings of Dose titration, Long-term (more than 12 months) use in children and adolescents, and Adults.

Dose titration
In some instances, it might be appropriate to continue CONCERTA XL treatment into adulthood.
[This is a new fourth paragraph under the subheading of Dose titration.]

Long-term (more than 12 months) use in children and adolescents
The safety and efficacy of long-term use of methylphenidate has not been systematically evaluated in controlled trials. Methylphenidate treatment should not and need not, be indefinite. Methylphenidate treatment is usually discontinued during or after puberty. In some instances, it might be appropriate to continue CONCERTA XL treatment into adulthood. The physician who elects to use methylphenidate for extended periods (over 12 months) in patients ~~children and adolescents~~ with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to assess the patient's ~~child's~~ condition (preferable during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Adults
In adolescents whose symptoms persist into adulthood and who have shown clear benefit from treatment, it may be appropriate to continue treatment into adulthood. However, start of treatment with CONCERTA XL in adults is not appropriate. ~~Methylphenidate is not licensed for use in adults in ADHD. Safety and efficacy have not been established in this age group.~~

1.2.2. SPC Section 4.4

The changes proposed for SPC Section 4.2 (provided in Section 1.2.1) under the subheading of Long-term (more than 12 months) use in children and adolescents and the subheading of Adults are also proposed under these same subheadings in SPC Section 4.4, Special warnings and precautions for use.

1.2.3. SPC Section 4.8

1.2.3.1. Rationale for Presentation of SPC Section 4.8

The MHRA, in the 12 October 2010 communication, requested that safety data be added to the main adverse event table (SPC, Section 4.8) with an asterisk (*) footnote denoting that the additional safety information is from adult data. The Company proposes to present newly identified ADRs or ADRs identified in a higher frequency category in adults with ADHD in a separate table in the SPC. The current ADR table in the SPC, Section 4.8, is based on the assessment by the 5 major European Union (EU) Marketing Authorization Holders (MAHs) of methylphenidate-containing products of their respective pediatric clinical databases and/or postmarketing pharmacovigilance information as part of the

Article 31 referral, which was concluded in January 2009. To ensure consistency and transparency of the current core SPC ADR table, the Company proposes the addition of a new table at Section 4.8 of the CONCERTA SPC to provide ADRs that were identified on the basis of adverse events reported in clinical studies of CONCERTA in adults with ADHD and are either not listed in the current core SPC ADR table or occur in a higher frequency category than in the current core SPC ADR table. The proposed presentation of ADRs (2 tables) is similar to what is provided in the Straterra SPC (Straterra SPC 2009). It is not the intention of the Company to position the newly identified ADRs as relevant for adults only. An introductory sentence to this additional ADR table is proposed: "The safety profile of CONCERTA XL in adult subjects with ADHD was generally similar to that seen in children and adolescents with ADHD. The following additional ADRs were identified either as new ADRs or in a higher frequency category than the pediatric population during clinical trials in adult subjects with ADHD. These ADRs may also be relevant in the pediatric population."

1.2.3.2. Proposed Changes to SPC Section 4.8

The following changes are proposed for SPC Section 4.8, Undesirable effects.

The following changes are proposed for the introductory paragraph:

> The table below shows all adverse drug reactions (ADRs) observed during clinical trials <u>in children and adolescents with ADHD</u> and post-market spontaneous reports <u>in both paediatric and adult patients</u> with CONCERTA XL and those, which have been reported with other methylphenidate hydrochloride formulations. If the ADRs with CONCERTA XL and the methylphenidate formulation frequencies were different, the highest frequency of both databases was used.

The following additional table and introductory paragraph are proposed for the presentation of adult ADR information:

> <u>The safety profile of CONCERTA XL in adult subjects with ADHD was generally similar to that seen in children and adolescents with ADHD. The following additional ADRs were identified either as new ADRs or in a higher frequency category than the paediatric population during clinical trials in adult subjects with ADHD. These ADRs may also be relevant in the paediatric population.</u>

System Organ Class	Adverse Drug Reaction Frequency				
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
Infections and infestations		Upper respiratory tract infection, Sinusitis			
Blood and lymphatic system disorders			Leucopenia	Anaemia	
Metabolism and nutrition disorders*	Decreased appetite				
Psychiatric disorders*	Anxiety*	Initial insomnia, Restlessness, Depressed mood, Libido decreased, Tension*, Bruxism, Panic attack	Confusional state, Mania*, Apathy, Delusion*	Suicide attempt*	
Nervous system disorders		Tremor, Migraine, Paresthesia, Tension headache	Lethargy	Cerebrovascular accident*	
Eye disorders		Blurred vision	Dry eye, Accommodation disorder		
Ear and labyrinth disorders		Vertigo			
Cardiac disorders*				Extrasystoles, Ventricular extrasystoles	
Vascular disorders*			Hot flush, Peripheral coldness		
Respiratory, thoracic and mediastinal disorders		Dyspnoea			
Gastrointestinal disorders	Dry mouth, Nausea	Dyspepsia, Constipation			
Skin and subcutaneous tissue disorders		Hyperhidrosis			
Musculoskeletal, connective tissue and bone disorders		Muscle tightness, Myalgia, Muscle spasms			

System Organ Class	Adverse Drug Reaction Frequency				
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
Reproductive system and breast disorders		Erectile dysfunction			
General disorders and administration site conditions		Irritability, Feeling jittery, Asthenia, Chest discomfort, Thirst			
Investigations		Alanine aminotransferase increased	Blood bilirubin increased		

*see Section 4.4

1.2.3.3. SPC Section 5.1

The following changes are proposed for SPC Section 5.1, Pharmacodynamic properties.

Section 5.1 Pharmacodynamic properties

In the pivotal clinical studies <u>in children with ADHD</u>, CONCERTA XL was assessed in 321 patients already stabilised with immediate release preparations (IR) of methylphenidate and in 95 patients not previously treated with IR preparations of methylphenidate.

Clinical studies <u>in children with ADHD</u> showed that the effects of CONCERTA XL were maintained until 12 hours after dosing when the product was taken once daily in the morning.

<u>Eight hundred ninety-nine (899) adults with ADHD aged 18 to 65 years were evaluated in three double-blind, placebo-controlled studies of 5 to 13 weeks duration. Generally, efficacy of CONCERTA XL was demonstrated in a dose range of 18 to 72 mg/day. The maintenance of effect of CONCERTA XL during long-term use in adults with ADHD has not been shown.</u>

2. REQUESTS FOR FURTHER INFORMATION FROM THE REFERENCE MEMBER STATE

2.1. Request 1: Major Objection - Efficacy in the Proposed Indication

Request:

Efficacy for the proposed indication has not been clearly demonstrated as follows:

- A robust and clinically relevant estimate of short term efficacy for the indicated population has not been demonstrated. Further analyses are requested (see other efficacy concerns).
- The relevance of the data derived from the population who were diagnosed after the age of 18 to the indicated population is unclear. Clear detail of how the study populations were assessed to have met DSM IV criteria for adult ADHD for the study populations in general and for the subgroup analysis population diagnosed <18 years of age should be provided.
- Long term efficacy. The withdrawal study failed to demonstrate efficacy. The published paper by Rosler lacks the required detail for an efficacy assessment. Data from that study should be submitted if the MAH wishes to use these as the primary supportive evidence.

Response:

Additional analyses are provided to support the short-term efficacy of CONCERTA in the 3 pivotal short-term efficacy studies: Study 42603ATT3002 (hereafter referred to as Study 3002), Study 02-159, and Study 42603ATT3013 (hereafter referred to as Study 3013). Detailed information regarding these analyses is provided in the following sections: additional responder analyses for the pivotal studies (Section 2.3), tally of subjects who discontinued early and who were considered responders in the original analyses for the pivotal studies (Section 2.4), proportion of subjects who initially responded to study drug and who were no longer considered responders at the Final Visit by dose of initial clinical response for Study 02-159 (Section 2.5), additional primary analysis for Studies 3002 (without gender in model) and 3013 (without age in model) (Section 2.6), and an evaluation of a possible interaction between age of diagnosis of ADHD (distinct from age of first occurrence of ADHD symptoms) and age at enrollment in the study for the pivotal studies (Section 2.7).

The Company no longer proposes an extension of the CONCERTA indication to include adult patients with ADHD whose ADHD diagnosis was established before the age of 18 years and whose symptoms persist into adulthood. Therefore, responses to the concerns regarding relevance of the clinical trial data for the originally proposed target population and long-term efficacy (bullets 2 and 3, respectively) are not provided.

2.2. Request 2: Major Objection - Safety in the Proposed Indication

Request:

The safety of Concerta in the proposed indication has not been adequately described particularly:

- Cardiovascular risk
- Psychiatric adverse events
- Dependence and abuse risks
  (see safety concerns below)

Response:

Additional analyses are provided to more fully describe the cardiovascular risks and psychiatric adverse events in the population evaluated in clinical trials. Detailed information regarding these analyses is provided in the following sections: cardiovascular safety including a discussion regarding the level of vital sign increases that pose a risk to adults and a presentation of clinical trial data related to vital sign increases (Section 2.8), presentation and discussion of clinical data related to the psychiatric adverse events of suicidality and aggression (Section 2.9), additional presentation and discussion of clinical data related to weight loss (Section 2.10), additional discussion of clinical data regarding drug dependence and abuse (Section 2.11), update on the ongoing safety evaluation for pregnancy outcomes (Section 2.12), and additional discussion of clinical data for subjects who experienced important adverse events that resolved with residual effects or did not resolve by the end of the study (Section 2.25). The Company considers that the results of these additional presentations of clinical data support the safety profile described in the submission: the safety profile of CONCERTA in adults with ADHD who received CONCERTA in double-blind and open-label clinical studies was similar to that in children and adolescents and, likewise, the safety profile was similar to that of other methylphenidate-containing products in adults with ADHD.

2.3. Request 3: Other Efficacy Concern – Responder Analyses

Request:

> It is unclear how the applicant has defined whether a patient is a responder when the data is missing. For each of the 3 pivotal short term efficacy studies, the applicant should clarify how this has been done. For each trial, if this analysis has not already presented, an analysis including missing data as failures should be presented, including point estimates, p-values and confidence intervals, adjusted using Dunnett's procedure for controlling the Type I error.

Response:

An additional responder analysis was conducted for each of the 3 pivotal short-term efficacy studies, treating subjects with missing data at the final study visit as non-responders. Using this more conservative definition of responder, a smaller percentage of subjects were considered responders at the final efficacy visit across treatment groups compared with the original responder analysis for each of the pivotal studies. The new responder analyses still support the clinical relevance of the findings for the primary endpoint in each of the studies (except for CONCERTA 54-mg dose in Study 3013). (The additional analyses for Studies 3002 and 3013 were adjusted for multiple comparisons between placebo and active treatment groups using Sidak's procedure.) Detailed information for each new responder analysis is provided in following paragraphs.

For Study 3002, a responder was defined as a subject with ≥30% reduction from baseline in Conners' Adult ADHD Rating Scale (CAARS) ADHD symptoms total score. The original responder analysis reported in the clinical study report (CSR) used the intent-to-treat (ITT) analysis set, which included subjects who received study drug and had at least 1 postbaseline efficacy assessment (Table 1). The original analysis also utilized last-observation-carried forward (LOCF). The additional responder analysis utilized the all subjects analysis set that included all subjects who received study drug (Table 2). Using the more conservative approach (ie, new definition of response – with missing CAARS ADHD symptoms total score at Week 5 considered as grounds for non-response – applied to the all subjects analysis set), a smaller percentage of subjects were considered responders at Week 5 compared with the original analysis: Placebo, 26.0% vs. 27.4%; CONCERTA 18 mg, 45.5% vs. 50.5%, 36 mg, 45.1% vs. 48.5%; and 72 mg, 50.0% vs. 59.6%. In the additional analysis, there were statistically significantly more responders in each CONCERTA dose group compared to the placebo group ($p \leq 0.0171$, Table 2). The difference between the denominators for the response rate in the original versus additional analysis is observed in the "No postbaseline CAARS data" row of Table 2. In addition to these subjects included in the all subjects analysis set who were not included in the ITT analysis set, non-responders

in the additional analysis included subjects who were missing data at the Week 5 visit as well as subjects who were truly non-responders (ie, data available at Week 5, but did not meet the criterion for response).

Table 1. Original Responder Analysis Study 3002: Number (%) of Responders at Week 5 End Point (LOCF) Based on Equal To or Greater Than 30% Reduction From Baseline in CAARS ADHD Symptoms Total Score
– Intent-to-Treat Analysis Set

	Placebo (N=95)	**CONCERTA 18 mg (N=99)**	**CONCERTA 36 mg (N=101)**	**CONCERTA 72 mg (N=99)**
Responder at Week 5: n (%)	26 (27.4)	50 (50.5)	49 (48.5)	59 (59.6)
Non-responder at Week 5: n (%)	69 (72.6)	49 (49.5)	52 (51.5)	40 (40.4)
p-value* (comparison versus placebo)		0.0020	0.0074	<0.0001

* CMH general association test controlling for country, comparing each dose group with placebo using a Sidak multiplicity correction
N=number of subjects with data; n=number of responders
Source: CSR 3002, Table 26.

Table 2. Additional Responder Analysis Study 3002: Number (%) of Responders at Week 5 Based on Equal To or Greater Than 30% Reduction From Baseline in CAARS ADHD Symptoms Total Score Including Subjects With Missing Data at Week 5 Treated as Non-Responders
– All Subjects Analysis Set

Time Point	**Placebo (N=96)**	**CONCERTA 18 mg (N=101)**	**CONCERTA 36 mg (N=102)**	**CONCERTA 72 mg (N=102)**
Week 5				
Responder at Week 5: n (%)	25 (26.0)	46 (45.5)	46 (45.1)	51 (50.0)
Non-responder at Week 5: n (%)	71 (74.0)	55 (54.5)	56 (54.9)	51 (50.0)
Missing responder data at Week 5	7 (7.3)	7 (6.9)	13 (12.7)	13 (12.7)
No postbaseline CAARS data	1 (1.0)	2 (2.0)	1 (1.0)	3 (2.9)
Non-responder at Week 5	63 (65.6)	46 (45.5)	42 (41.2)	35 (34.3)
Odds Ratio*		2.4	2.4	2.7
(95% CI)*		(1.27,4.39)	(1.28,4.40)	(1.48,5.07)
p-value** (comparison versus placebo)		0.0122	0.0171	0.0018

* Odds ratio and 95% CI of achieving response; adjusted for country but unadjusted for multiplicity
** CMH general association test controlling for country, comparing each dose group with placebo using a Sidak multiplicity correction
N=number of subjects with data; n=number of responders
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For Study 02-159, a responder was defined as a subject with ≥30% improvement in Adult ADHD Investigator Symptom Rating Scale (AISRS) total score and a Clinical Global Impression-Improvement (CGI-I) score of 1 or 2 (very much improved or much improved). In the original responder analysis reported in the CSR using LOCF, subjects with missing CGI-I were not included, as this is a postbaseline assessment only (there is no baseline measurement that can be carried forward) (Table 3). The additional responder analysis utilized the ITT analysis set including subjects without any CGI-I data and considering those subjects with

missing CGI-I or AISRS data at the 2-week efficacy visit as non-responders (Table 4). Using this more conservative approach a smaller percentage of subjects were considered responders at the 2-week efficacy visit (ie, 7 weeks after initiation of double-blind treatment) compared with the original analysis: Placebo, 19.0% vs. 24.4%; All CONCERTA, 30.0% vs. 44.6%. In the additional analysis, there were not statistically significantly more responders for the CONCERTA group compared to the placebo group (p=0.055, Table 4). The difference between the denominators for the responder rate in the original (LOCF) versus additional analysis (ie, subjects with at least one dose of study drug and at least one CGI-I assessment versus subjects with at least one dose of study drug) is observed in the "No CGI-I data" row of Table 4. Note that non-responders included subjects without any CGI-I data and subjects who were missing CGI-I or AISRS data from the 2-week efficacy visit (ie, no data at this time point), as well as subjects who were truly non-responders (ie, had data at the 2-week efficacy visit, but did not meet the criteria for response).

Table 3. Original Responder Analysis Study 02-159: Number (%) of Responders at the Final Visit (2-Week Efficacy Visit) Based on the AISRS Total Score and the CGI - Improvement Scale - Intent-to-Treat Analysis Set

Visit	All CONCERTA	Placebo	Odds Ratio[a]	95% CI	p-Value[b]
Responders:					
2-Week Efficacy Visit, n/N (%)	33/74 (44.6)	22/90 (24.4)	2.78	(1.36, 5.65)	0.003
Final Visit (LOCF), n/N (%)	38/103 (36.9)	24/115 (20.9)	2.16	(1.18, 3.95)	0.009

[a] The odds ratio of achieving response for All CONCERTA versus placebo, adjusted for pooled study site.
[b] p-value from Cochran-Mantel-Haenszel row mean score. A responder is a subject who had at least 30% improvement in the AISRS score and had a CGI-Improvement score of 1 or 2 (Very Much Improved or Much Improved). Nominal p-value with no adjustment for multiple testing.
Source: CSR 02-159, Table 9-11.

Table 4. Additional Responder Analysis Study 02-159: Number (%) of Responders at the Final Visit (2-Week Efficacy Visit) Based on the AISRS Total Score and the CGI - Improvement Scale Including Subjects With Missing Data at Final Visit (2-Week Efficacy Visit) Treated as Non-Responders
- Intent-to-Treat Analysis Set

Final Visit (2-Week Efficacy Visit)	All CONCERTA	Placebo	Odds Ratio	95% CI	p-value
Responders: n/n (%)	33/110 (30.0)	22/116 (19.0)	1.80	(0.96, 3.37)	0.055
Non-responders: n/n (%)	77/110 (70.0)	94/116 (81.0)			
No CGI-I data	7	1			
Missing responder data at final visit (2-week efficacy visit)	29	25			
Non-responder at final visit (2-week efficacy visit)	41	68			

Note: The odds ratio of achieving response for All CONCERTA versus placebo, adjusted for pooled study site.
Note: p-value from Cochran-Mantel-Haenszel row means score. A responder is a subject who had at least 30% improvement in the AISRS score and had a CGI-Improvement score of 1 or 2 (Very Much Improved or Much Improved). Nominal p-value with no adjustment for multiple testing.
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For Study 3013, a responder was defined as a subject with ≥30% reduction from baseline in CAARS ADHD symptoms total score. The original responder analysis reported in the CSR used the ITT analysis set, which included all subjects who were randomly assigned to treatment (including 1 subject who did not receive study drug) (Table 5). The original analysis also utilized LOCF. The additional responder analysis included subjects with missing data at Week 13 as non-responders, and also adjusted for multiplicity (Table 6). As the original analysis used the ITT analysis set that included all randomized subjects including 1 subject who did not receive study drug, the denominator for the response rate in the original analysis and the additional analysis remains unchanged. Using this definition of clinical response, a smaller percentage of subjects were considered responders at Week 13 compared with the original analysis: Placebo 35.1% vs. 45.4%; CONCERTA 54 mg, 46.7% vs. 55.6%; 72 mg, 48.9% vs. 64.1%. In the additional analysis, there were not statistically significantly more responders in either CONCERTA dose group compared to the placebo group ($p \geq 0.1977$, Table 6).

Table 5. Original Responder Analysis Study 3013: Number (%) of Responders at Week 13 End Point (LOCF) Based on a 30% or Greater Reduction From Baseline in the ADHD Symptoms Total Score of the Investigator-Rated CAARS - Intent-to-Treat Analysis Set

Time Point	Placebo (N=97)	CONCERTA 54mg (N=90)	CONCERTA 72mg (N=92)
Responder at Week 13: n (%)	44 (45.4)	50 (55.6)	59 (64.1)
Non-responder at Week 13: n (%)	53 (54.6)	40 (44.4)	33 (35.9)
p-value[a]		0.1679	0.0098

[a]Cochran-Mantel-Haenszel general association test on the ranks, comparing each dose group with placebo
N=number of subjects with data, n=number of responders
Source: CSR 3013, Table 24.

Table 6. Additional Responder Analysis Study 3013: Number (%) of Responders at Week 13 Based on a 30% or Greater Reduction From Baseline in the ADHD Symptoms Total Score of the Investigator-Rated CAARS Including Subjects With Missing Data at Week 13 Treated as Non-Responders - Intent-to-Treat Analysis Set

Time Point	Placebo (N=97)	CONCERTA 54mg (N=90)	CONCERTA 72mg (N=92)
Responder at Week 13: n (%)	34 (35.1)	42 (46.7)	45 (48.9)
Non-responder at Week 13: n (%)	63 (64.9)	48 (53.3)	47 (51.1)
Missing responder data at Week 13	29 (29.9)	32 (35.6)	34 (37.0)
No postbaseline CAARS data		2 (2.2)	
Non-responder at Week 13	34 (35.1)	14 (15.6)	13 (14.1)
Odds Ratio*		1.7	1.7
(95% CI)*		(0.89,3.05)	(0.91,3.10)
p-value** (comparison versus placebo)		0.2740	0.1977

* Odds ratio and 95% CI of achieving response; adjusted for country but unadjusted for multiplicity.
** CMH general association test on the ranks adjusted for country, comparing each dose group with placebo using a Sidak multiplicity correction.
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2.4. Request 4: Other Efficacy Concern – Drop Outs Considered Responders

Request:

> For all studies the applicant should provide details on how many patients who did drop out were considered responders. In particular, if this is much higher on treatment compared to placebo, a full discussion of why LOCF and MMRM are appropriately conservative methods for handling missing data should be provided.

Response:

A summary table providing the number and percentage of drop outs who were considered responders in the primary analysis is presented for each pivotal study. For Study 3002, a total of 9 subjects dropped out of the study who were considered responders in the primary analysis (placebo, n=1; CONCERTA, 18 mg, n=2; 36 mg, n=2; 72 mg, n=4) (Table 7). For Study 02-159, a total of 8 subjects dropped

out of the study who were considered responders in the primary analysis (placebo, n=2; CONCERTA, n=6) (Table 8). For Study 3013, a total of 33 subjects dropped out of the study who were considered responders in the primary analysis (placebo, n=10; CONCERTA, 54 mg, n=8; 72 mg, n=15) (Table 9). There was no consistent, directionally differential effect in the drop-out rate between subjects who responded to treatment with CONCERTA and placebo across studies. The differences between the placebo and CONCERTA treatment groups were not considered clinically relevant or likely to grossly violate the assumptions underlying the primary or supportive analyses presented in the clinical study reports. Thus, the use of LOCF and mixed model repeated measures (MMRM) is appropriate.

Table 7. Study 3002: Number (%) of Drop Outs Who Were Considered Responders in the Original Responder Analysis - Intent-to-Treat Analysis Set

Time Point		**CONCERTA**		
Double-Blind End Point	**Placebo**	**18 mg**	**36 mg**	**72 mg**
Drop Outs Who Were Responders: n/N (%)	1/26 (3.8)	2/50 (4.0)	2/49 (4.1)	4/59 (6.8)

Note: The denominator is the number of responders at double-blind end point.
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Table 8. Study 02-159: Number (%) of Drop Outs Who Were Considered Responders in the Original Responder Analysis - Intent-to-Treat Analysis Set

Tine Point	**All**	
Final Visit (Two Week Efficacy Visit), LOCF	**CONCERTA**	**Placebo**
Drop Outs who were responders: n/n (%)	6/38 (15.8)	2/24 (8.3)

Note: The denominator is the number of responders at the Final Visit (LOCF).
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Table 9. Study 3013: Number (%) of Drop Outs Who Were Considered Responders in the Original Responder Analysis - Intent-to-Treat Analysis Set

Time Point		**CONCERTA**	
Double-Blind End Point	**Placebo**	**54 mg/day**	**72 mg/day**
Drop Outs Who Were Responders: n/N (%)	10/44 (22.7)	8/50 (16.0)	15/59 (25.4)

Note: The denominator is the number of responders at end point.
DEFF24.rtf

2.5. Request 5: Other Efficacy Concern – Study 02-159 Responders

Request:

For Study 0159 the applicant should clarify how many patients initially responded (and at what dose) but were not considered to be responders by the end of the study.

Response:

For Study 02-159, the number of subjects who initially responded (ie, subjects who met criteria for clinical response for the first time during titration) at each dose and, of those who responded, the number (%) of subjects who were considered responders at the Final Visit is provided in Table 10. At each CONCERTA dose level (36 mg, 72 mg, 90 mg, 108 mg), approximately 20% of the subjects were noted to respond, with the exception of the 54 mg dose level at which a slightly lower percentage of subjects responded (14.1%). The majority (≥75%) of subjects who first responded at the 72 and 90 mg dose level and approximately half of the subjects who first responded at the 36 and 54 mg dose levels were considered responders at the final visit. Data for subjects assigned to placebo who initially responded at each of the corresponding dose levels are presented for comparison. However, the proportion of subjects who initially responded to placebo and met criteria for response at the final visit is difficult to interpret due to the small number of subjects in each equivalent dose group. For placebo, 1.4% to 10.7% of subjects initially responded at each dose level. Of the total number of initial placebo responders (n=30), 73 % maintained this response at end point.

Table 10. Study 02-159: Number of Responders at Each Dose and of These, Number (%) of Responders at the Final Visit - Intent-to-Treat Analysis Set

	---------- CONCERTA ----------			---------- Placebo ----------		
Dose Level (mg/day)	**No. Subjects Evaluated at This Dose**	**First Responded at This Dose N (%)**	**Of Those Who First Responded, Still Responder at Final Visit N (%)***	**No. Subjects Evaluated at This Dose**	**First Responded at This Dose N (%)**	**Of Those Who First Responded, Still Responder at Final Visit N (%)***
36	103	21 (20.4)	10 (47.6)	115	9 (7.8)	4 (44.4)
54	78	11 (14.1)	5 (45.5)	103	11 (10.7)	11 (100.0)
72	59	12 (20.3)	10 (83.3)	85	6 (7.1)	4 (66.7)
90	44	8 (18.2)	6 (75.0)	71	1 (1.4)	0
108	29	5 (17.2)	2 (40.0)	67	3 (4.5)	3 (100.0)

*: Denominator is based on those who first responded at the given dose.
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2.6. Request 6: Other Efficacy Concern – Primary Analysis for Studies 3002 (Without Gender in Model) and 3013 (Without Age in Model)

Request:

For Study 3002, the applicant should provide the results of the analysis for the primary endpoint without gender in the model. For study 3013, age should be removed from the model.

Response:

For Studies 3002 and 3013, the primary efficacy endpoint was defined as the change in the ADHD symptoms total score of the investigator-rated CAARS, from baseline to the end of the double-blind treatment, ie, end of 5 weeks (Study 3002), end of 13 weeks (Study 3013) or last assessment. Tables providing descriptive statistics for the actual scores at baseline and end point, and changes from baseline to end point (LOCF) in CAARS ADHD symptoms total score for Study 3002 without gender in the model and for Study 3013 without age in the model are presented; for comparison, the p values for these studies with gender and age in the models are provided in the tables, respectively. The removal of gender and age from the models of these studies resulted in only a small numerical change in the adjusted p values for some of the comparisons between the CONCERTA treatment groups and placebo for change from baseline to end point in total scores (Study 3002, 18 and 36 mg; Study 3013, 54 mg); the statistical significance for these comparisons remained unchanged from the analyses presented in the submission (Tables 11 and 12, respectively).

Table 11. Study 3002: CAARS Total Score: Actual Values and Change From Baseline to Double-Blind End Point (Additional Analysis Without Gender in the Model) - - Intent-to-Treat Analysis Set

		CONCERTA		
	Placebo	**18mg**	**36mg**	**72mg**
Baseline				
N	(N=95)	(N=99)	(N=101)	(N=99)
Mean (SD)	37.2 (7.09)	35.6 (6.91)	37.3 (6.88)	36.6 (6.58)
Median	38.0	35.0	38.0	36.0
Range	24.00 - 50.82	24.00 - 53.00	25.00 - 51.00	24.00 - 52.00
Double-Blind end point				
N	(N=95)	(N=99)	(N=101)	(N=99)
Mean (SD)	29.6 (10.60)	25.0 (10.43)	25.8 (10.88)	22.9 (10.95)
Median	29.0	24.0	26.0	22.0
Range	4.00 - 50.00	4.00 - 51.00	4.00 - 52.00	1.00 - 50.00
Change From Baseline to Double-Blind end point				
N	(N=95)	(N=99)	(N=101)	(N=99)
Mean (SD)	-7.6 (9.93)	-10.6 (10.34)	-11.5 (9.97)	-13.7 (11.11)
Median	-6.0	-10.0	-10.0	-13.0
Range	-45.00 - 8.00	-35.00 - 16.00	-37.00 - 8.00	-40.00 - 8.00
p-value* (comparison versus placebo)		(0.0192)	(0.0248)	(<0.0001)
For Comparison: p-value (comparison vs. placebo) with gender in the model		(0.0146)	(0.0131)	(<.0.0001)

* Comparison between each dose group and placebo adjusted for multiplicity using Dunnett's procedure, based on an analysis of covariance (ANCOVA) model on change from baseline including country and treatment groups as factors and baseline score as a covariate.

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Source for the Comparison (p values with gender in the model): CSR 3002, Table 20.

Table 12. Study 3013: ADHD Symptoms Total Score of the Investigator-Rated CAARS: Actual Values and Change From Baseline to End Point (Additional Analysis Without Age in the Model) - Intent-to-Treat Analysis Set

		CONCERTA	
	Placebo	**54mg**	**72mg**
Baseline			
N	(N=97)	(N=90)	(N=92)
Mean (SD)	36.5 (6.05)	35.6 (6.75)	37.3 (6.35)
Median	36.0	35.0	37.0
Range	24.00 - 51.00	25.00 - 54.00	23.00 - 50.00
End point			
N	(N=97)	(N=90)	(N=92)
Mean (SD)	26.1 (10.59)	23.0 (11.07)	21.6 (10.21)
Median	24.0	22.0	20.0
Range	0.00 - 52.00	2.00 - 52.00	2.00 - 44.00
Change From Baseline to Double-Blind end point			
N	(N=97)	(N=90)	(N=92)
Mean (SD)	-10.4 (11.03)	-12.5 (10.38)	-15.7 (10.80)
Median	-9.0	-11.5	-16.0
Range	-43.00 - 7.00	-37.00 - 11.00	-39.00 - 10.00
Difference in LS Means versus placebo (p-value)*		-2.69 (0.1344)	-4.89 (0.0024)
For Comparison: p-value (comparison vs. placebo) with age in the model		(0.1356)	(0.0024)

* Comparison between each dose group and placebo adjusted for multiplicity using Dunnett's procedure, based on an analysis of covariance (ANCOVA) model on change from baseline including country, gender, and treatment groups as factors and baseline score as a covariate.
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Source for the Comparison (p values with age in the model): CSR 3013, Table 19.

2.7. Request 7: Other Efficacy Concern – Interaction Between Age at Diagnosis and Age at Enrollment

Request:

> The applicant should investigate whether there is an interaction in any of the studies between age of diagnosis and age at enrolment in the study. If there is, the applicant should discuss further the apparent decrease in efficacy seen in younger patients in study 0159.

Response:

A plot of age at diagnosis by age at enrollment for each treatment group (Figures 1, 2, and 3), along with a summary table presenting descriptive statistics of age at enrollment for each age category at diagnosis of ADHD (ie, missing, <7 years of age, ≥7 years and ≤18 years of age, >18 years of age) and treatment group (Table 13, 15, and 17) are provided for each pivotal study. In addition, subgroup analyses on the primary endpoint using the 3 age categories at diagnosis are presented for each pivotal study (Tables 14, 16, and 18). For those subjects for

whom age at diagnosis was recorded, per visual inspection of the plots, the majority of subjects were diagnosed with ADHD close to the time of enrollment into the study. Age at the first diagnosis of ADHD was not recorded for more than half of the subjects in Study 02-159. However, all subjects had the diagnosis of ADHD confirmed at the time of enrollment in the study. For those subjects with a recorded age of diagnosis after 18 years, the mean age of enrollment ranged between 35.6 years and 39.4 years, which is approximately 10 years older than most subjects diagnosed between the ages of 7 and 18 years. Based on the differences in LS mean change, subjects in each age at diagnosis category were observed to have larger reductions (ie, improvement) for the primary efficacy measure at double-blind end point if they were randomly assigned to treatment with CONCERTA compared with placebo, with the exception of the 2 CONCERTA subjects diagnosed before 7 years of age in Study 02-159, who had a smaller reduction in AISRS total score than that observed in the 7 subjects assigned to placebo. In addition, subjects diagnosed between the ages of 7 and 18 years who were randomly assigned to CONCERTA 54 mg in Study 3013 had a smaller reduction than placebo-treated subjects based on the raw mean change from baseline in CAARS ADHD symptoms total score (-9.5 vs. -10.2). Because of the small number of subjects with a recorded age at first diagnosis of ADHD before 18 years (11.5% of subjects), a possible interaction of age at diagnosis with treatment (ie, “treatment-by-age at diagnosis effect”) is difficult to ascertain in this study. However, data from Studies 3002 and 3013 with a relatively larger proportion of subjects with a recorded age at first diagnosis before 18 years suggests that there is no such interaction (see Sections 2.7.1 and 2.7.3). Detailed information for these additional analyses investigating the possible interaction between age at diagnosis and age at enrollment are provided in the following subsections for each pivotal study.

Also, subgroup analyses on the primary endpoint by age at enrollment using 4 age categories (ie, 18-24 years, 25-35 years, 36-49 years, 50-65 years of age) were provided for each pivotal study in the Summary of Efficacy and are presented again in this section (the data are provided in Attachments 1.2, 2.2, and 3.2). In both the youngest age subgroup (18 to 24 years) and the older age groups, the change from baseline in CAARS ADHD symptoms total score was greater in subjects assigned to CONCERTA than those assigned to placebo in Studies 3002 and 3013. In Study 02-159, the change from baseline in AISRS total score was smaller with CONCERTA than with placebo in the youngest age group (an abnormally high change from baseline in subjects assigned to placebo was observed), in contrast to the older age groups.

2.7.1. Interaction Between Age at Diagnosis and Age at Enrollment: Study 3002

In Study 3002, the majority of subjects were diagnosed with ADHD close to the time of enrollment into the study (Figure 1). For those subjects who were diagnosed after 18 years of age (316 of 394 total subjects), the mean age of enrollment in the study was 35.6 years, which is similar to subjects diagnosed before the age of 7 years and approximately 10 years older than subjects diagnosed between the ages of 7 and 18 years (Table 13). Subjects diagnosed in all age categories were observed to have larger reductions (ie, improvement) in the CAARS ADHD symptoms total score at double-blind end point for all dosage groups compared with placebo (Table 14). A similar summary table provides descriptive statistics for the CAARS ADHD symptoms total scores at baseline and at the double-blind end point by age at diagnosis (<7 years of age, ≥7 and ≤18 years of age, and >18 years of age) (Attachment 1.1).

CONCERTA was associated with larger mean reductions (ie, improvement) in the CAARS ADHD symptoms total score at double-blind end point compared with placebo in all age at enrollment categories (Attachment 1.2).

Figure 1. Study 3002: Plot of Age at Diagnosis by Age at Enrollment
(Intent-to-Treat Analysis Set)

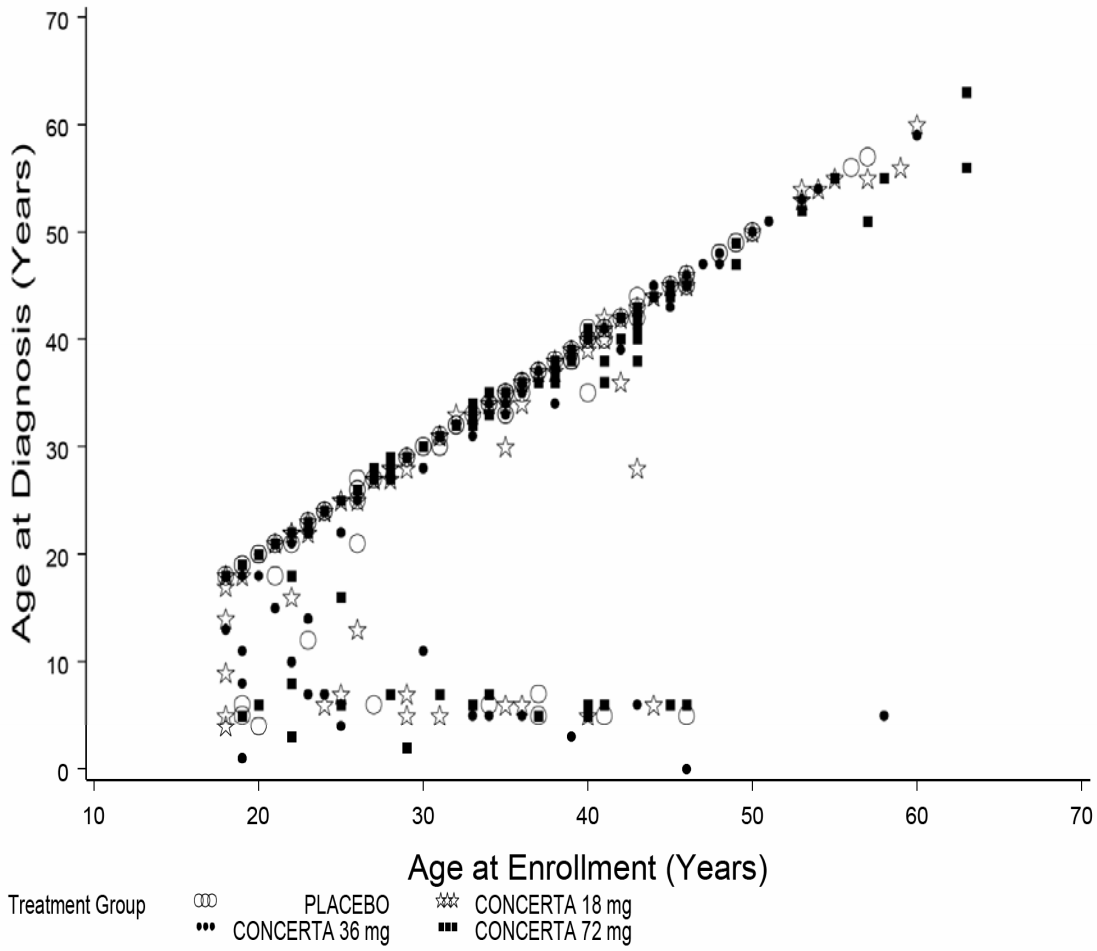

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Table 13. Study 3002: Age at Enrollment by Age at Diagnosis
- Intent-to-Treat Analysis Set/Double-Blind

	---------- Age At Diagnosis (Years) ----------			
	---- Missing ----	**------ <7 ------**	**≥7 and ≤18**	**------ >18 -----**
	(N=2)	**(N=38)**	**(N=38)**	**(N=316)**
AGE AT ENROLLMENT (YEARS)				
OVERALL				
N	2	38	38	316
Mean (SD)	56.00 (2.828)	32.84 (10.184)	22.45 (4.819)	35.62 (9.679)
Median	56.00	34.00	22.00	36.00
Range	(54.0;58.0)	(18.0;58.0)	(18.0;37.0)	(19.0;63.0)
CONCERTA 18 MG				
N	1	9	10	79
Mean (SD)	58.00 ( )	30.56 (9.221)	21.10 (4.149)	36.35 (9.751)
Median	58.00	31.00	18.50	37.00
Range	(58.0;58.0)	(18.0;44.0)	(18.0;29.0)	(21.0;60.0)
CONCERTA 36 MG				
N	0	9	16	76
Mean (SD)		37.00 (11.489)	21.56 (3.224)	36.08 (9.520)
Median		36.00	21.50	36.50
Range		(19.0;58.0)	(18.0;30.0)	(19.0;60.0)
CONCERTA 72 MG				
N	0	12	8	79
Mean (SD)		33.08 (9.802)	24.75 (5.874)	34.76 (10.448)
Median		35.00	23.50	34.00
Range		(19.0;46.0)	(18.0;34.0)	(19.0;63.0)
Placebo				
N	1	8	4	82
Mean (SD)	54.00 ( )	30.38 (10.636)	24.75 (8.421)	35.30 (9.065)
Median	54.00	30.50	22.00	35.50
Range	(54.0;54.0)	(19.0;46.0)	(18.0;37.0)	(19.0;57.0)

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Table 14. Study 3002: Descriptive Statistics of CAARS ADHD Symptoms Total Score - Change From Baseline to End Point By Age at Diagnosis of ADHD - Intent-to-Treat Analysis Set/Double-Blind

	PLACEBO	CONCERTA 18 mg	CONCERTA 36 mg	CONCERTA 72 mg
CAARS ADHD Symptoms Total Score				
Age at Diagnosis: <7 years				
Change from Baseline				
N	8	9	9	12
Mean (SD)	-8.8 (7.69)	-11.2 (12.30)	-11.3 (7.42)	-17.8 (11.92)
Median (Range)	-8.0 (-23 - 1)	-12.0 (-29 - 11)	-14.0 (-20 - 1)	-17.5 (-40 - -2)
(minus Placebo)[a]				
Diff. of LS Means (SE)		-8.1 (4.78)	-2.5 (4.87)	-7.1 (4.01)
95% CI		(-17.88 ; 1.77)	(-12.50 ; 7.53)	(-15.38 ; 1.10)
Age at Diagnosis: ≥7 to ≤18 years				
Change from Baseline				
N	4	10	16	8
Mean (SD)	-5.8 (6.45)	-12.4 (11.41)	-13.4 (10.45)	-8.9 (9.61)
Median (Range)	-6.5 (-12 - 2)	-12.5 (-31 - 8)	-11.0 (-34 - 0)	-9.0 (-22 - 5)
(minus Placebo)[a]				
Diff. of LS Means (SE)		-8.0 (6.27)	-9.0 (5.89)	-8.1 (6.52)
95% CI		(-20.96 ; 5.06)	(-21.24 ; 3.20)	(-21.65 ; 5.39)
Age at Diagnosis: >18 years				
Change from Baseline				
N	82	79	76	79
Mean (SD)	-7.4 (10.14)	-10.5 (10.07)	-11.1 (10.19)	-13.5 (11.04)
Median (Range)	-6.0 (-45 - 8)	-10.0 (-35 - 16)	-10.0 (-37 - 8)	-13.0 (-38 - 8)
(minus Placebo)[a]				
Diff. of LS Means (SE)		-4.1 (1.59)	-3.7 (1.63)	-6.7 (1.58)
95% CI		(-7.28 ; -1.02)	(-6.87 ; -0.46)	(-9.78 ; -3.55)

[a] The difference in LS means is based on an analysis of covariance with treatment, country, and gender as factors and baseline score as a covariate.

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Cross-reference: Attachment 1.1.

2.7.2. Interaction Between Age at Diagnosis and Age at Enrollment: Study 02-159

In Study 02-159, the majority of subjects for whom age at first diagnosis of ADHD was recorded were diagnosed close to the time of enrollment into the study (Figure 2). However, age at diagnosis was not recorded for more than half of the study participants (119 of 226 total subjects). All subjects had the diagnosis of ADHD confirmed at the time of enrollment in the study. For those subjects with a recorded age of diagnosis after 18 years (N=81), the mean age of enrollment in the study was 39.4 years, which is approximately 10 years older than subjects diagnosed in childhood or adolescents (Table 15). Subjects diagnosed after the age of 7 years (≥7 years and ≤18 years and >18 years subgroups) were observed to have larger mean reductions (ie, improvement) in the AISRS total score at

double-blind end point compared with placebo (Table 16). Subjects diagnosed before 7 years of age had a similar reduction in the AISRS total score at double-blind end point as subjects in the placebo group (note that there were only 2 CONCERTA subjects in this subgroup). A similar summary table provides descriptive statistics for the AISRS total score at baseline and at the double-blind end point by age at diagnosis (<7 years of age, ≥7 and ≤18 years of age, and >18 years of age) (Attachment 2.1).

CONCERTA was associated with larger mean reductions (ie, improvement) in the AISRS total score at double-blind end point compared with placebo in all age at enrollment categories, except for the 18 to 24 years subgroup (Attachment 2.2). Note the abnormally high change from baseline in AISRS total score in subjects assigned to placebo in this youngest age group compared with the changes for placebo observed in the other age categories (mean change from baseline -10.4 vs. -6.2 to - 6.7).

Figure 2. Study 02-159: Plot of Age at Diagnosis by Age at Enrollment
(Intent-to-Treat Analysis Set)

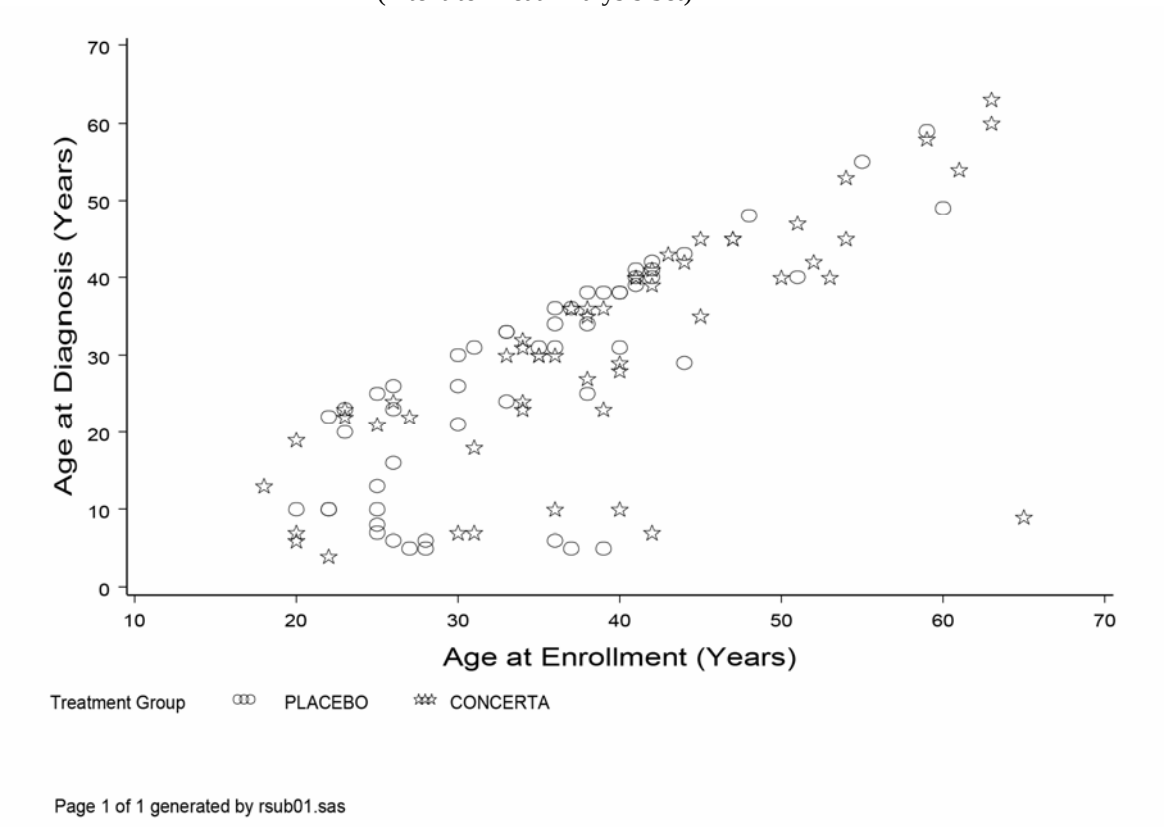

Table 15. Study 02-159: Age at Enrollment by Age at Diagnosis
- Intent-to-Treat Analysis Set

	---------- Age At Diagnosis (Years) ----------			
	---- Missing ----	**------ <7 ------**	**≥7 and ≤18**	**------ >18 -----**
	(N=119)	**(N=9)**	**(N=17)**	**(N=81)**
AGE AT ENROLLMENT (YEARS)				
Overall				
N	119	9	17	81
Mean (SD)	40.87 (12.383)	29.22 (6.685)	29.59 (11.435)	39.38 (10.098)
Median	42.00	28.00	25.00	39.00
Range	(19.0;65.0)	(20.0;39.0)	(18.0;65.0)	(20.0;63.0)
ALL CONCERTA				
N	56	2	9	43
Mean (SD)	40.50 (12.833)	21.00 (1.414)	34.78 (13.899)	40.98 (10.676)
Median	41.00	21.00	31.00	40.00
Range	(19.0;65.0)	(20.0;22.0)	(18.0;65.0)	(20.0;63.0)
Placebo				
N	63	7	8	38
Mean (SD)	41.21 (12.063)	31.57 (5.503)	23.75 (2.121)	37.58 (9.208)
Median	42.00	28.00	25.00	38.00
Range	(19.0;64.0)	(26.0;39.0)	(20.0;26.0)	(22.0;60.0)

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Table 16. Study 02-159: Adult ADHD Investigator Symptom Rating Scale (AISRS) Total Score - Change From Baseline to End Point by Age at Diagnosis of ADHD - Intent-to-Treat Analysis Set

	Placebo	ALL CONCERTA
AISRS total score		
Age at Diagnosis: <7 years		
Change from Baseline		
N	7	2
Mean (SD)	-14.3 (16.15)	-5.0 (16.97)
Median (Range)	-6.0 (-37;3)	-5.0 (-17;7)
Age at Diagnosis: ≥7 years to ≤18 years		
Change from Baseline		
N	8	9
Mean (SD)	-10.8 (12.60)	-13.1 (11.15)
Median (Range)	-7.5 (-36;1)	-14.0 (-28;0)
(minus Placebo)[a]		
Diff. of LS Means (SE)		-13.8 (0.85)
95% CI		(-24.63;-3.04)
Age at Diagnosis: >18 years		
Change from Baseline		
N	38	43
Mean (SD)	-5.6 (9.47)	-10.0 (12.30)
Median (Range)	-3.0 (-33;12)	-7.0 (-48;7)
(minus Placebo)[a]		
Diff. of LS Means (SE)		-3.8 (2.65)
95% CI		(-9.07;1.55)

[a] The difference in LS means is based on an analysis of covariance (ANCOVA) model with study site and treatment (All CONCERTA, placebo) as factors; and baseline score as the covariate.
Note: For AISRS Total Score, subjects who lacked postbaseline data had their baseline values carried forward to Final Visit (LOCF).
Cross-reference: Attachment 2.1.

2.7.3. Interaction Between Age at Diagnosis and Age at Enrollment: Study 3013

In Study 3013, the majority of subjects were diagnosed with ADHD close to the time of enrollment into the study (Figure 3). For those subjects who were diagnosed after 18 years of age (229 of 279 total subjects), the mean age of enrollment in the study was 37.1 years, slightly older than those diagnosed before 7 years of age and approximately 13 years older than subjects diagnosed between 7 and 18 years of age, inclusive (Table 17). Based on the differences in LS mean change, subjects in each age at diagnosis category were observed to have larger reductions (ie, improvement) in the CAARS ADHD symptoms total score at double-blind end point for all dosage groups compared with placebo (Table 18). In addition, subjects diagnosed between 7 and 18 years of age who were randomly assigned to CONCERTA 54 mg had a smaller reduction than placebo-treated subjects based on the raw mean change (-9.5 vs. -10.2). The magnitude of the

reductions varied most across treatment groups in those diagnosed before 7 years of age; this group was observed to have LS means (SE) difference from placebo for the change from baseline in the primary endpoint of -1.8 (9.48) for CONCERTA 54 mg and -17.8 (9.03) for CONCERTA 72 mg. A similar summary table provides descriptive statistics for the CAARS ADHD symptoms total scores at baseline and at the double-blind end point by age at diagnosis (<7 years of age, ≥7 and ≤18 years of age, and >18 years of age) (Attachment 3.1).

Based on the differences in LS mean change, CONCERTA was associated with larger mean reductions (ie, improvement) in the CAARS ADHD symptoms total score at double-blind end point compared with placebo in all age at enrollment categories (Attachment 3.2).

Figure 3. Study 3013: Plot of Age at Diagnosis by Age at Enrollment
(Intent-to-Treat Analysis Set)

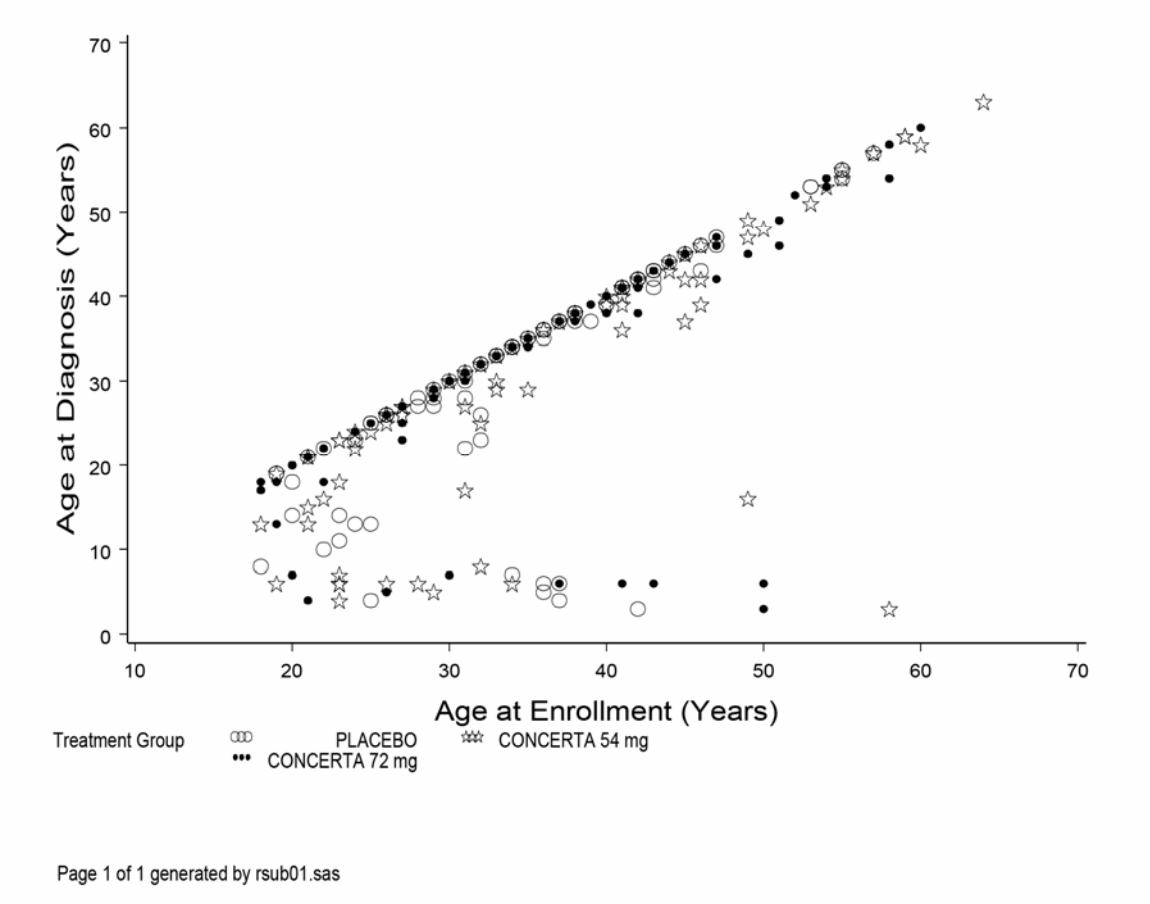

Table 17. Study 3013: Age at Enrollment by Age at Diagnosis
- Intent-to-Treat Analysis Set

	Age At Diagnosis (Years)			
	---- Missing ----	**------ <7 ------**	**≥7 and ≤18**	**------ >18 -----**
	(N=2)	**(N=22)**	**(N=26)**	**(N=229)**
AGE AT ENROLLMENT (YEARS)				
OVERALL				
N	2	22	25	229
Mean (SD)	38.00 (11.314)	33.82 (10.563)	23.80 (6.922)	37.10 (9.631)
Median	38.00	35.00	22.00	36.00
Range	(30.0;46.0)	(19.0;58.0)	(18.0;49.0)	(19.0;64.0)
CONCERTA 54 MG				
N	0	9	9	71
Mean (SD)		29.22 (11.638)	26.67 (9.579)	37.63 (11.311)
Median		26.00	23.00	36.00
Range		(19.0;58.0)	(18.0;49.0)	(19.0;64.0)
CONCERTA 72 MG				
N	1	7	7	77
Mean (SD)	30.00 ( )	38.29 (11.221)	20.86 (4.259)	37.05 (9.330)
Median	30.00	41.00	19.00	37.00
Range	(30.0;30.0)	(21.0;50.0)	(18.0;30.0)	(20.0;60.0)
Placebo				
N	1	6	9	81
Mean (SD)	46.00 ( )	35.50 (5.612)	23.22 (4.604)	36.68 (8.323)
Median	46.00	36.50	23.00	36.00
Range	(46.0;46.0)	(25.0;42.0)	(18.0;34.0)	(19.0;57.0)

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Table 18. Study 3013: Descriptive Statistics of CAARS ADHD Symptoms Total Score - Change From Baseline to End Point By Age at Diagnosis of ADHD – Intent-to-Treat Analysis Set

	Placebo	CONCERTA 54 mg	CONCERTA 72 mg
CAARS ADHD Symptoms Total Score			
Age at Diagnosis: <7 years			
Change from Baseline			
N	6	9	7
Mean (SD)	-4.7 (11.55)	-7.1 (8.09)	-21.1 (11.58)
Median (Range)	0.0 (-28 - 2)	-3.0 (-23 - 0)	-29.0 (-33 - -4)
(minus Placebo)[a]			
Diff. of LS Means (SE)		-1.8 (9.48)	-17.8 (9.03)
95% CI		(-22.91 ; 19.33)	(-37.89 ; 2.35)
Age at Diagnosis: ≥7 to ≤18 years			
Change from Baseline			
N	9	10	7
Mean (SD)	-10.2 (7.73)	-9.5 (11.49)	-13.3 (7.80)
Median (Range)	-9.0 (-25 - -1)	-4.5 (-33 - 0)	-11.0 (-23 - -1)
(minus Placebo)[a]			
Diff. of LS Means (SE)		-3.7 (5.11)	-7.7 (5.55)
95% CI		(-14.74 ; 7.34)	(-19.64 ; 4.34)
Age at Diagnosis: >18 years			
Change from Baseline			
N	81	71	77
Mean (SD)	-10.7 (11.28)	-13.6 (10.31)	-15.6 (10.88)
Median (Range)	-9.0 (-43 - 7)	-14.0 (-37 - 11)	-16.0 (-39 - 10)
(minus Placebo)[a]			
Diff. of LS Means (SE)		-4.2 (1.68)	-5.0 (1.64)
95% CI		(-7.53 ; -0.91)	(-8.26 ; -1.81)

[a] The difference in LS means is based on an analysis of covariance with treatment, country, and gender as factors and age and baseline score as covariates.
Cross-reference: Attachment 3.1.

2.8. Request 8: Safety Concern – Cardiovascular Safety

Request:

Cardiovascular safety. Discuss what level of BP and heart rate increase that could pose a risk to adults and present data on sustained increases in BP and heart rate. Increases in BP above 5mmHg and 10mmHg should also be presented as well as clinically significant sustained levels in HR.

Response:

The response to this request is provided in the following subsections:

- Section 2.8.1, Level of Vital Sign Increases that Pose a Risk to Adults, and
- Section 2.8.2, Presentation of Clinical Data Related to Vital Sign Increases.

As adolescent patients with ADHD who continue treatment with methylphenidate into adulthood will have been monitored continuously for their blood pressure and pulse throughout adolescence, the data from completed efficacy and safety studies of CONCERTA in adults with ADHD may not be particularly relevant for the wording that is currently being proposed for Section 4.2 of the SPC of CONCERTA. Subjects enrolled in these clinical studies had either not previously been exposed to methylphenidate or had discontinued prior treatment with methylphenidate for a period of at least 1 week to 1 month before administration of the first dose of study drug. Thus, clinical data on changes from baseline in vital signs for the overall study population evaluated in these completed studies is not particularly informative. Epidemiological data that informs the risk associated with an absolute level of blood pressure or pulse rather than increase over time may address the concern raised in the preliminary assessment report.

Also, it should be noted that these efficacy and safety studies were not specifically designed to evaluate the effect of treatment with CONCERTA on cardiovascular endpoints in adult patients with ADHD. It is likely that adults with ADHD are exposed to similar risk factors for cardiovascular disease as an overall adult population with the exception of treatment with stimulant medications. Hence, epidemiological data from an overall population of adults will be used to inform the requested discussion of the level of blood pressure and heart rate increase that could pose a risk to adults with ADHD.

The Summary of Clinical Safety (SCS) provided with the submission included an evaluation of cardiovascular safety observed in clinical trials of CONCERTA in adults with ADHD. The SCS included additional analyses requested by the RMS (MHRA) medical assessor at the pre-submission meeting (eg, subgroup analyses for subjects with elevated blood pressure at baseline and subjects with a medical history of hypertension for Studies 3002, 02-159, and 3013). For the categorical analyses of vital signs in the SCS, clinically important increases in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were defined as increases of ≥140 mmHg and ≥90 mmHg, respectively. This is in line with the World Health Organization (WHO) and the US third National Health and Nutrition Examination Survey (NHANES III) (Gu 2008) definitions of hypertension. These cut-off values are based on large epidemiological studies such as the Framingham Heart Study

and denote blood pressure values that may result in cardiovascular complications without correction, possibly involving a pharmacological intervention. For the subgroup analyses of vital sign changes in subjects with elevated blood pressure at baseline, the more stringent criteria of SBP ≥120 mmHg or DBP ≥80 mmHg at baseline was used to define the population of interest. The risk of developing hypertension and the risk of worsening of hypertension were evaluated for each of the double-blind studies. Taken together, these results showed a modest mean increase from baseline in blood pressure measurements for subjects treated with CONCERTA, but no evidence of the development of hypertension in those without elevated blood pressure at baseline or of more pronounced increases in blood pressure in those with elevated blood pressure or a history of hypertension at baseline.

2.8.1. Level of Vital Sign Increases That Pose a Risk to Adults

As mentioned above, epidemiological data that inform the risk associated with an absolute level of blood pressure (or pulse) rather than increase over time may be more relevant to address the reviewer's concern. Several recent studies/analyses provide insight into the relationship between increases in blood pressure and heart rate, and the risk of cardiovascular disease (CVD). These studies suggest that a small risk of CVD is associated with increases in blood pressure to a pre-hypertensive level (Gu 2008) (in this article the lower limit of the blood pressure range of pre-hypertension was SBP 130 mmHg and DBP 84 mmHg), that CVD risk is primarily associated with absolute level of blood pressure and to a lesser extent by changes over time (Menotti 2004), and that heart rate is not an independent risk factor for CVD (Tverdal 2008). Additional discussion regarding these studies is provided in the following paragraphs.

A recent study estimated the relative risk of death from CVD associated with hypertension using data from the NHANES III cross-sectional healthy survey and mortality follow up through 2000 (Gu 2008). NHANES III was conducted between 1988 and 1994 in a general population of adults in the U.S. and included subjects aged 17 years and older. A small, quantifiable risk of CVD disease associated with pre-hypertension, as distinct from hypertension, was observed; the relative risk of CVD mortality with pre-hypertension compared with normotension was 1.23 (95% CI, 0.85-1.79, p=0.26). In this study, pre-hypertension was defined as a mean SBP between 120 mmHg and 139 mmHg or a mean DBP between 80 mmHg and 89 mmHg; increases of approximately 20 mmHg in SBP and 10 mmHg in DBP above the upper limit of what would be considered a normal blood pressure in adults.

Menotti et al (2004) analyzed the long-term association of casual (isolated) measurements of SBP with CVD deaths, as well as all causes of death, over a period of 35 years in different population samples of men 40 to 59 years of age in Finland, The Netherlands, Italy, Serbia, and Greece (10 cohorts of the Seven Countries Study enrolled and first examined in the early 1960s). In addition, the study investigated the predictive power of changes in SBP levels during the first 10 years of the follow-up period in relation to fatal events occurring during years 10 to 35 of the follow-up period. The relative risk for a positive change (increase) of 20 mmHg of SBP in predicting CVD deaths was 1.65 (95% CI, 1.54-1.77) for the first 10-year period, 1.33 (95% CI, 1.24-1.42) for the next 10-year period, and 1.22 (95% CI, 1.13-1.31) for the last 10-year period. The changes in SBP observed over 10 years added predictive power to the baseline measurements; the relative risk for a change of 10 mmHg was 1.14 (95% CI, 1.10-1.17) for CVD deaths. These results suggest that CVD risk is primarily associated with absolute blood pressure as determined at a distinct moment in time, and to a lesser extent with changes in blood pressure over time.

A prospective study of participants aged 40 to 45 years in CVD surveys in Norway from 1985 to 1999 evaluated the relationship between heart rate and CVD deaths, as well as all deaths (Tverdal 2008). A positive association was observed between heart rate and CVD deaths (along with ischemic heart disease and stroke), as well as deaths from all causes. When adjusted for the main risk factors of the disease, the association was reduced; when the subgroup of participants with heart rate ≥95 beats per minute (bpm) was compared with those with <65 bpm, the hazard ratios for CVD deaths were reduced from 4.79 to 1.51 for men (95% CI, 1.21-1.87) and from 2.68 to 0.78 for women (95% CI, 0.53-1.15). The authors noted that increased heart rate may be an indicator of CVD risk, but not an independent factor. It is often associated with other risk factors (eg, smoking, diabetes), which may or may not be modified, and does not require any direct intervention such as medicinal treatment.

2.8.2. Presentation of Clinical Data Related to Vital Sign Increases

Clinical data are provided for subjects with a sustained increase in blood pressure or pulse in Section 2.8.2.1. The percentages of subjects with sustained elevated blood pressure and pulse were low and, in the double-blind studies, percentages of subjects assigned to CONCERTA who developed a sustained elevation in blood pressure were similar to placebo.

Note that in these studies, pulse and blood pressure were measured in different positions. Supine and standing measurements were obtained in Studies 3002, 3004,

and 3013, and sitting measurements in Studies 02-159, 12-304, C-99-018-00, and CON-CAN-4. For this reason, integrated data were combined for double-blind Studies 3002 (referred to as 3002 double-blind [DB] in this section) and 3013, with data provided separately for Study 02-159.

Clinical data are provided for subjects with an increase in blood pressure >5mmHg, as well as for subjects with an increase in blood pressure of >10mmHg in Section 2.8.2.2. A slightly higher percentage of subjects treated with CONCERTA compared with placebo experienced an increase in blood pressure of >5mmHg. Similarly, a slightly higher percentage of subjects treated with CONCERTA compared with placebo experienced an increase in blood pressure of >10mmHg, except for Study 02-159 in which the percentage of subjects assigned to CONCERTA who experienced an increase was similar to placebo.

In addition, clinical data are provided for subjects with a potentially clinically important blood pressure reading (SBP: <70 and >140 mmHg and DBP: <50 and >90 mmHg) at any postbaseline time point for the subgroups of subjects with elevated blood pressure at baseline and subjects with a medical history of hypertension in Section 2.8.2.3. For subjects with an elevated blood pressure at baseline, a higher percentage of subjects treated with CONCERTA compared with placebo experienced a potentially clinically important elevation in diastolic blood pressure in Study 02-159. For subjects with a medical history of hypertension, a lower percentage of subjects treated with CONCERTA compared with placebo experienced a potentially clinically important elevation in systolic and diastolic blood pressure in all of the double-blind studies.

Also, categorical analyses using more stringent criteria of ≥130 mmHg for SBP and ≥85 mmHg for DBP (ie, pre-hypertension) at any postbaseline were conducted based on all subjects in the safety analysis set and the subgroups of subjects with elevated blood pressure at baseline and of subjects with a medical history of hypertension and are provided in Section 2.8.2.4. The percentages of subjects with SBP ≥130 mmHg or DBP ≥85mmHg were similar for placebo and CONCERTA in pooled Studies 3002 DB and 3013 across the overall study population and in the subgroups with elevated blood pressure at baseline and a medical history of hypertension. In Study 02-159, a higher percentage of subjects treated with CONCERTA compared with placebo experienced blood pressure measurements at these specified limits (SBP ≥130 mmHg or DBP ≥85mmHg).

The following considerations regarding the duration of the studies and method of analyses will aid in interpretation of these data:

- The longer duration of follow up in the open-label studies relative to the double-blind studies makes it more likely that subjects would meet criteria for elevated vital signs at least once while they were followed up during open-label treatment. This consideration will aid in the interpretation of the data across the different analysis sets, as it may explain why rates may be higher for some of the analyses in the open-label safety analysis sets.

- Subjects may have met criteria for increases in SBP as well as DBP at the same visit or distinct visits while they were followed up on double-blind or open-label treatment. Even if these increases occurred at the same visit, subjects would still have been included in the tables twice, ie, once for an increase in SBP and once for an increase in DBP. This may result in an overestimation of the number of subjects who met criteria for an increase in either SBP or DBP at least once after baseline.

2.8.2.1. Subjects With Sustained Elevated Blood Pressure and Pulse

Summary tables providing the number and percentage of subjects with sustained elevated blood pressure defined as subjects with SBP ≥140 mmHg and/or DBP ≥90 mmHg for at least 3 consecutive postbaseline visits are provided for the pooled Studies 3002 DB and 3013 (Table 19), Study 02-159 (Table 20), and the pooled open-label studies (Table 21). A similar percentage of subjects in each treatment group experienced sustained elevated blood pressure in pooled Studies 3002 DB and 3013 (6.1% placebo, 7.8% CONCERTA) and Study 02-159 (0.0% placebo, 1.1% CONCERTA). For the pooled open-label studies, 4.7% of the subjects experienced sustained elevated blood pressure.

Table 19. Studies 3002 DB and 3013: Number (%) of Subjects With Sustained Elevated Blood Pressure (CONCERTA EU SCS - MHRA RFI: Double-Blind Safety Analysis Set)

	-- Placebo -	ALL CONCERTA
Measurements, n (%)		
N	180	436
Sustained Elevated Blood Pressure	11 (6.1)	34 (7.8)

Note: Supine findings are from the double-blind portion of Studies 3002 and 3013. The denominator is the number of subjects with at least 3 consecutive postbaseline measurements. The numerator is the number of subjects with SBP ≥140 and/or DBP >=90 mmHg at at least 3 consecutive postbaseline visits.
rvs07_tvs19.rtf generated by rvs07.sas, 08NOV2010 12:35

Table 20. Study 02-159: Number (%) of Subjects With Sustained Elevated Blood Pressure (Study 02-159: Safety Analysis Set)

	-- Placebo -	ALL CONCERTA
Measurements, n (%)		
N	103	92
Sustained Elevated Blood Pressure	0	1 (1.1)

Note: Sitting findings are from the double-blind portion of Study 02-159.
The denominator is the number of subjects with at least 3 consecutive postbaseline measurements. The numerator is the number of subjects with SBP ≥140 and/or DBP >=90 mmHg at at least 3 consecutive postbaseline visits.
rvs07_tvs20.rtf generated by rvs07.sas, 08NOV2010 12:35

Table 21. Open-Label Studies: Number (%) of Subjects With Sustained Elevated Blood Pressure (CONCERTA EU SCS - MHRA RFI: Open-Label Safety Analysis Set)

	ALL CONCERTA
Measurements, n (%)	
N	975
Sustained Elevated Blood Pressure	46 (4.7)

Note: Sitting findings are from Studies 12-304, C-99-018-00, CON-CAN-4; Supine findings are from Studies 3002 OL and 3004.
The denominator is the number of subjects with at least 3 consecutive postbaseline measurements. The numerator is the number of subjects with SBP ≥140 and/or DBP >=90 mmHg at at least 3 consecutive postbaseline visits.
rvs07_tvs21.rtf generated by rvs07.sas, 08NOV2010 12:35

Summary tables presenting the number and percentage of subjects with sustained elevated pulse defined as subjects with ≥100 bpm for at least 3 consecutive postbaseline visits are provided for pooled Studies 3002 DB and 3013 (Table 22), Study 02-159 (Table 23), and the pooled open-label studies (Table 24). No subjects experienced a sustained elevated pulse in Studies 3002 DB or 3013. A similar percentage of subjects in each treatment group experienced sustained elevated pulse in Study 02-159 (0% placebo, 1.1% CONCERTA). For the pooled open-label studies, 0.4% of the subjects experienced sustained pulse.

Table 22. Studies 3002 and 3013: Number (%) of Subjects With Sustained Elevated Pulse (CONCERTA EU SCS - MHRA RFI: Double-Blind Safety Analysis Set)

	-- Placebo --	ALL CONCERTA
Measurements, n (%)		
N	180	436
Sustained Elevated Pulse	0	0

Note: Supine findings are from the double-blind portion of Studies 3002 and 3013.
The denominator is the number of subjects with at least 3 consecutive postbaseline measurements. The numerator is the number of subjects with pulse ≥100 bpm at at least 3 consecutive postbaseline visits.
rvs08_tvs22.rtf generated by rvs08.sas, 08NOV2010 12:54

Table 23. Study 02-159: Number (%) of Subjects With Sustained Elevated Pulse (Study 02-159: Safety Analysis Set)

	-- Placebo --	ALL CONCERTA
Measurements, n (%)		
N	103	92
Sustained Elevated Pulse	0	1 (1.1)

Note: Sitting findings are from the double-blind portion of Study 02-159.
The denominator is the number of subjects with at least 3 consecutive postbaseline measurements. The numerator is the number of subjects with pulse ≥100 bpm at at least 3 consecutive postbaseline visits.
rvs08_tvs23.rtf generated by rvs08.sas, 08NOV2010 12:54

Table 24. Open-Label Studies: Number (%) of Subjects With Sustained Elevated Pulse (CONCERTA EU SCS - MHRA RFI: Open-Label Safety Analysis Set)

	ALL CONCERTA
Measurements, n (%)	
N	975
Sustained Elevated Pulse	4 (0.4)

Note: Sitting findings are from Studies 12-304, C-99-018-00, CON-CAN-4; Supine findings are from Studies 3002 OL and 3004.
The denominator is the number of subjects with at least 3 consecutive postbaseline measurements. The numerator is the number of subjects with pulse ≥100 bpm at at least 3 consecutive postbaseline visits.
rvs08_tvs24.rtf generated by rvs08.sas, 08NOV2010 12:54

2.8.2.2. Subjects With Increases in Blood Pressure >5 mmHg and >10 mmHg at any Postbaseline Measurement

Summary tables presenting the number and percentage of subjects with an increase of >5 mmHg at any postbaseline blood pressure measurement are provided for pooled Studies 3002 DB and 3013 (Table 25), Study 02-159 (Table 26), and the pooled open-label studies (Table 27). In pooled Studies 3002 DB and 3013, a slightly higher percentage of subjects treated with CONCERTA compared with placebo experienced an elevation of >5 mmHg in a postbaseline blood pressure measurement (SBP 59.1% vs. 51.6%; DBP 53.9% vs. 45.3%). Similar summary tables are provided for Studies 3002 and 3013 separately. As observed for the pooled data, a higher percentage of subjects treated with CONCERTA compared with placebo experienced an elevation of >5 mmHg in a postbaseline blood pressure measurement in Study 3002 (SBP: placebo, 46.3%; CONCERTA, 18 mg, 50.0%; 36 mg, 51.5%; 72 mg, 55.0%. DBP: placebo, 28.4%; CONCERTA, 18 mg, 45.9%; 36 mg, 43.6%; 72 mg, 52.0%.) (Attachment 4.1) and, with one exception for diastolic blood pressure in the CONCERTA 54 mg group, in Study 3013 (SBP: placebo, 56.7%; CONCERTA, 54 mg, 70.9%; 72 mg, 70.7%. DBP: placebo, 61.9%; CONCERTA, 54 mg, 61.6%; 72 mg, 68.5%) (Attachment 4.2). In Study 02-159, these percentages were also higher for CONCERTA compared

with placebo (62.7% vs. 48.7% for SBP, 55.9% vs. 43.5% for DBP). For the pooled open-label studies, these percentages ranged from 58.9% to 72.0% across sitting and supine vital sign measurements.

Table 25. Studies 3002 DB and 3013: Number (%) of Subjects With Increase Greater Than5mmHg at Any Postbaseline Blood Pressure Measurement
(CONCERTA EU SCS - MHRA RFI: Double-Blind Safety Analysis Set)

	-- Placebo --	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SUPINE		
Measurements, n (%)		
N	192	477
Increase > 5 mmHg	99 (51.6)	282 (59.1)
DIASTOLIC BLOOD PRESSURE (mmHg) SUPINE		
Measurements, n (%)		
N	192	477
Increase > 5 mmHg	87 (45.3)	257 (53.9)

Note: Supine findings are from the double-blind portion of Studies 3002 and 3013.
rvs06_tvs16.rtf generated by rvs06.sas, 18NOV2010 14:49

Table 26. Study 02-159: Number (%) of Subjects With Increase Greater Than 5 mmHg at Any Postbaseline Blood Pressure Measurement
(Study 02-159: Safety Analysis Set)

	-- Placebo --	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SITTING AVG		
Measurements, n (%)		
N	115	102
Increase > 5 mmHg	56 (48.7)	64 (62.7)
DIASTOLIC BLOOD PRESSURE (mmHg) SITTING AVG		
Measurements, n (%)		
N	115	102
Increase > 5 mmHg	50 (43.5)	57 (55.9)

Note: Sitting findings are from the double-blind portion of Study 02-159.
rvs06_tvs17.rtf generated by rvs06.sas, 18NOV2010 14:49

Table 27. Open-Label Studies: Number (%) of Subjects With Increase Greater Than 5 mmHg at Any Postbaseline Blood Pressure Measurement
(CONCERTA EU SCS - MHRA RFI: Open-Label Safety Analysis Set)

	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SITTING	
Measurements, n (%)	
N	704
Increase > 5 mmHg	507 (72.0)
SYSTOLIC BLOOD PRESSURE (mmHg) SUPINE	
Measurements, n (%)	
N	367
Increase > 5 mmHg	259 (70.6)
DIASTOLIC BLOOD PRESSURE (mmHg) SITTING	
Measurements, n (%)	
N	704
Increase > 5 mmHg	464 (65.9)
DIASTOLIC BLOOD PRESSURE (mmHg) SUPINE	
Measurements, n (%)	
N	367
Increase > 5 mmHg	216 (58.9)

Note: Sitting findings are from Studies 12-304, C-99-018-00, CON-CAN-4; Supine findings are from Studies 3002 OL and 3004.
rvs06_tvs18.rtf generated by rvs06.sas, 18NOV2010 14:49

Summary tables presenting the number and percentage of subjects with an increase of >10 mmHg at any postbaseline blood pressure measurement are provided for pooled Studies 3002 DB and 3013 (Table 28), Study 02-159 (Table 29), and the pooled open-label studies (Table 30). In pooled Studies 3002 DB and 3013, a slightly higher percentage of subjects treated with CONCERTA compared with placebo experienced an elevation of >10 mmHg in a postbaseline blood pressure measurement (SBP 40.3% vs. 33.3%; DBP 24.1% vs. 22.9%). Similar summary tables were prepared for Studies 3002 DB and 3013 separately. A slightly higher percentage of subjects treated with CONCERTA versus placebo experienced an elevation of >10 mmHg in a postbaseline blood pressure measurement during Study 3002 DB (31.7%, 18 mg; 40.2%, 36 mg; 41.2%, 72 mg vs. 34.4% for placebo) and Study 3013 (57.3%, 54 mg; 56.5%, 72 mg vs. 50.5% for placebo) (Attachments 5.1 and 5.2, respectively). In Study 02-159, these percentages were similar for treatment groups or slightly higher for CONCERTA compared with placebo for systolic and diastolic blood pressure measurements, respectively (28% vs. 28% for SBP, 25% vs. 17% for DBP). For the pooled open-label studies, these percentages ranged from 31.6% to 51.2% across sitting and supine vital sign measurements.

Table 28. Studies 3002 DB and 3013**:** Number (%) of Subjects With Increase Greater Than 10 mmHg at Any Postbaseline Blood Pressure Measurement
(CONCERTA EU SCS - MHRA RFI: Double-Blind Safety Analysis Set)

	-- Placebo --	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SUPINE		
Measurements, n (%)		
N	192	477
Increase > 10 mmHg	64 (33.3)	192 (40.3)
DIASTOLIC BLOOD PRESSURE (mmHg) SUPINE		
Measurements, n (%)		
N	192	477
Increase > 10 mmHg	44 (22.9)	115 (24.1)

Note: Supine findings are from the double-blind portion of Studies 3002 and 3013.
rvs11_tvs29.rtf generated by rvs11.sas, 18NOV2010 14:52

Table 29. Study 02-159: Number (%) of Subjects With Increase Greater Than 10 mmHg at Any Postbaseline Blood Pressure Measurement
(Study 02-159: Safety Analysis Set)

	-- Placebo --	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SITTING AVG		
Measurements, n (%)		
N	116	110
Increase > 10 mmHg	33 (28)	31 (28)
DIASTOLIC BLOOD PRESSURE (mmHg) SITTING AVG		
Measurements, n (%)		
N	116	110
Increase > 10 mmHg	20 (17)	27 (25)

Note: Sitting findings are from the double-blind portion of Study 02-159.
Source: Summary of Clinical Safety, Appendix App5.1.4.

Table 30. Open-Label Studies: Number (%) of Subjects With Increase Greater Than 10 mmHg at Any Postbaseline Blood Pressure Measurement
(CONCERTA EU SCS - MHRA RFI: Open-Label Safety Analysis Set)

	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SITTING	
Measurements, n (%)	
N	704
Increase > 10 mmHg	356 (50.6)
SYSTOLIC BLOOD PRESSURE (mmHg) SUPINE	
Measurements, n (%)	
N	367
Increase > 10 mmHg	188 (51.2)
DIASTOLIC BLOOD PRESSURE (mmHg) SITTING	
Measurements, n (%)	
N	704
Increase > 10 mmHg	253 (35.9)
DIASTOLIC BLOOD PRESSURE (mmHg) SUPINE	
Measurements, n (%)	
N	367
Increase > 10 mmHg	116 (31.6)

Note: Sitting findings are from studies 12-304, C-99-018-00, CON-CAN-4; Supine findings are from Studies 3002 OL and 3004.
rvs11_tvs30.rtf generated by rvs11.sas, 18NOV2010 14:52

2.8.2.3. Potentially Clinically Important Blood Pressure Measurements

2.8.2.3.1. Subjects With Elevated Blood Pressure at Baseline

For subjects with an elevated blood pressure at baseline, summary tables presenting the number and percentage of subjects with potentially clinically important (PCI) blood pressure measurements as originally defined in the SCS (ie, any postbaseline blood pressure measurement for SBP of <70 or >140 mmHg and DBP of <50 or >90 mmHg) are provided for pooled Studies 3002 DB and 3013 (Table 31), Study 02-159 (Table 32), and the pooled open-label studies (Table 33). In pooled Studies 3002 DB and 3013, a similar percentage of subjects treated with placebo and CONCERTA experienced a blood pressure measurement above the PCI range (SBP 28.1% vs. 27.4%; DBP 20.0% vs. 19.7%, respectively). In Study 02-159, a similar percentage of subjects treated with placebo and CONCERTA experienced a SBP measurement above the PCI range (12.1% vs. 11.9%, respectively); however, a higher percentage of subjects treated with CONCERTA compared with placebo experienced a DBP measurement above the PCI range (15.3% vs. 6.9%, respectively). Results for the pooled open-label studies were generally similar to those from double-blind studies for measurement obtained in the sitting position (18.1% and 19.7% of subjects experienced a SBP and DBP value, respectively, above the PCI range); these percentages for

measurements obtained in the supine position were 43.0% and 30.1%, respectively. As noted previously, pulse and blood pressure were measured in different positions in these studies: supine and standing measurements were obtained in Studies 3002, 3004, and 3013; and sitting measurements were obtained in Studies 02-159, 12-304, C-99-018-00, and CON-CAN-4.

Table 31. Studies 3002 DB and 3013: Number (%) of Subjects Presenting at Least One Treatment-Emergent Postbaseline Potentially Clinically Important Blood Pressure Measurement in Subjects With Elevated Blood Pressure at Baseline (CONCERTA EU SCS - MHRA RFI: Double-Blind Safety Analysis Set)

	-- Placebo --	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SUPINE		
Measurements, n (%)		
N	135	325
At Least One PCI Measurement	38 (28.1)	89 (27.4)
Above PCI Range	38 (28.1)	89 (27.4)
DIASTOLIC BLOOD PRESSURE (mmHg) SUPINE		
Measurements, n (%)		
N	135	325
At Least One PCI Measurement	28 (20.7)	65 (20.0)
Above PCI Range	27 (20.0)	64 (19.7)
Below PCI Range	1 (0.7)	2 (0.6)

Note: Supine findings are from the double-blind portion of Studies 3002 and 3013.
Only subjects with elevated blood pressure at baseline are included, defined as those with either diastolic blood pressure ≥80 mmHg at baseline or systolic blood pressure ≥120 mmHg at baseline.
Does not include study 02-159 as these measurements were sitting.
rvs01_tvs01.rtf generated by runvs.sas, 28OCT2010 14:43

Table 32. Study 02-159: Number (%) of Subjects Presenting at Least One Treatment-Emergent Postbaseline Potentially Clinically Important Blood Pressure Measurement in Subjects With Elevated Blood Pressure at Baseline (Study 02-159: Safety Analysis Set)

	-- Placebo --	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SITTING AVG		
Measurements, n (%)		
N	58	59
At Least One PCI Measurement	7 (12.1)	7 (11.9)
Above PCI Range	7 (12.1)	7 (11.9)
DIASTOLIC BLOOD PRESSURE (mmHg) SITTING AVG		
Measurements, n (%)		
N	58	59
At Least One PCI Measurement	4 (6.9)	9 (15.3)
Above PCI Range	4 (6.9)	9 (15.3)

Note: Sitting findings are from the double-blind portion of Study 02-159.
Only subjects with elevated blood pressure at baseline are included, defined as those with either diastolic blood pressure ≥80 mmHg at baseline or systolic blood pressure ≥120 mmHg at baseline.
rvs01_tvs02.rtf generated by runvs.sas, 28OCT2010 14:43

Table 33. Open-Label Studies: Number and Percent of Subjects Presenting at Least One Treatment-Emergent Postbaseline Potentially Clinically Important Blood Pressure Measurement in Subjects With Elevated Blood Pressure at Baseline (CONCERTA EU SCS - MHRA RFI: Open-Label Safety Analysis Set)

	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SITTING	
Measurements, n (%)	
N	371
At Least One PCI Measurement	67 (18.1)
Above PCI Range	67 (18.1)
SYSTOLIC BLOOD PRESSURE (mmHg) SUPINE	
Measurements, n (%)	
N	256
At Least One PCI Measurement	110 (43.0)
Above PCI Range	110 (43.0)
DIASTOLIC BLOOD PRESSURE (mmHg) SITTING	
Measurements, n (%)	
N	371
At Least One PCI Measurement	73 (19.7)
Above PCI Range	73 (19.7)
DIASTOLIC BLOOD PRESSURE (mmHg) SUPINE	
Measurements, n (%)	
N	256
At Least One PCI Measurement	77 (30.1)
Above PCI Range	77 (30.1)
Below PCI Range	1 (0.4)

Note: Sitting findings are from Studies 12-304, C-99-018-00, CON-CAN-4. Supine findings are from Studies 3002 OL and 3004. Only subjects with elevated blood pressure at baseline are included, defined as those with either diastolic blood pressure ≥80 mmHg at baseline or systolic blood pressure ≥120 mmHg at baseline.

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2.8.2.3.2. Subjects With Medical History of Hypertension

For subjects with a medical history of hypertension, summary tables presenting the number and percentage of subjects with a PCI blood pressure measurement are provided for pooled Studies 3002 DB and 3013 (Table 34), Study 02-159 (Table 35), and the pooled open-label studies (Table 36). In pooled Studies 3002 DB and 3013, a lower percentage of subjects with a history of hypertension treated with CONCERTA compared with placebo experienced a blood pressure measurement above the PCI range (SBP 60.0% vs. 71.4%; DBP 50.0% vs. 71.4%, respectively). In Study 02-159, 25.0% of placebo subjects experienced a SBP measurement above the PCI range compared with 0.0% of CONCERTA subjects; no subjects in this study experienced a DBP measurement above the PCI range in either treatment group. Percentages for the pooled open-label studies were generally similar to those of the pooled 3002 DB and 3013 studies for measurements obtained in the supine position (80.0% and 60.0% of subjects

experienced a SBP and DBP value, respectively, above the PCI range); while these percentages obtained in the sitting position were generally higher than those observed for the double-blind study (SBP 37.2%, DBP 27.9%).

Table 34. Studies 3002 DB and 3013: Number (%) of Subjects Presenting at Least One Treatment-Emergent Postbaseline Potentially Clinically Important Blood Pressure Measurement in Subjects With Medical History of Hypertension (CONCERTA EU SCS - MHRA RFI: Double-Blind Safety Analysis Set)

	-- Placebo--	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SUPINE Measurements, n (%)		
N	14	30
At Least One PCI Measurement	10 (71.4)	18 (60.0)
Above PCI Range	10 (71.4)	18 (60.0)
DIASTOLIC BLOOD PRESSURE (mmHg) SUPINE Measurements, n (%)		
N	14	30
At Least One PCI Measurement	10 (71.4)	15 (50.0)
Above PCI Range	10 (71.4)	15 (50.0)

Note: Supine findings are from the double-blind portion of Studies 3002 and 3013. Only subjects with a medical history of hypertension or a pre-treatment hypertension-related adverse event are included. Does not include study 02-159 as these measurements were sitting.
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Table 35. Study 02-159: Number (%) of Subjects Presenting at Least One Treatment-Emergent Postbaseline Potentially Clinically Important Blood Pressure Measurement in Subjects With Medical History of Hypertension (Study 02-159: Safety Analysis Set)

	-- Placebo--	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SITTING AVG Measurements, n (%)		
N	12	5
At Least One PCI Measurement	3 (25.0)	0
Above PCI Range	3 (25.0)	

No subjects had a diastolic blood pressure measurement above the potentially clinically important range in either the CONCERTA or placebo treatment groups.
Note: Sitting findings are from the double-blind portion of Study 02-159. Only subjects with a medical history of hypertension or a pre-treatment hypertension-related adverse event are included.
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Table 36. Open-Label Studies: Number (%) of Subjects Presenting at Least One Treatment-Emergent Postbaseline Potentially Clinically Important Blood Pressure Measurement in Subjects With Medical History of Hypertension (CONCERTA EU SCS - MHRA RFI: Open-Label Safety Analysis Set)

	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SITTING	
Measurements, n (%)	
N	43
At Least One PCI Measurement	16 (37.2)
Above PCI Range	16 (37.2)
SYSTOLIC BLOOD PRESSURE (mmHg) SUPINE	
Measurements, n (%)	
N	10
At Least One PCI Measurement	8 (80.0)
Above PCI Range	8 (80.0)
DIASTOLIC BLOOD PRESSURE (mmHg) SITTING	
Measurements, n (%)	
N	43
At Least One PCI Measurement	12 (27.9)
Above PCI Range	12 (27.9)
DIASTOLIC BLOOD PRESSURE (mmHg) SUPINE	
Measurements, n (%)	
N	10
At Least One PCI Measurement	6 (60.0)
Above PCI Range	6 (60.0)

Note: Sitting findings are from Studies 12-304, C-99-018-00, CON-CAN-4; Supine findings are from Studies 3002 OL and 3004. Only subjects with a medical history of hypertension or a pre-treatment hypertension-related adverse event are included.
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2.8.2.4. Subjects With an Increase in SBP Equal To or Greater Than 130 mmHg or DBP Equal To or Greater Than 85 mmHg

Summary tables presenting the number and percentage of subjects with a SBP ≥130 mmHg or a DBP ≥85 mmHg are provided for pooled Studies 3002 DB and 3013 (Table 37), Study 02-159 (Table 38), and the pooled open-label studies (Table 39). In pooled Studies 3002 DB and 3013, a similar percentage of subjects treated with placebo compared with CONCERTA experienced a SBP ≥130 mmHg or a DBP ≥85 mmHg (SBP 52.6% vs. 56.8%; DBP 36.5% vs. 39.7%, respectively). In Study 02-159, these percentages were higher for CONCERTA compared with placebo (47.1% vs. 29.6% for SBP, 37.3% vs. 24.3% for DBP). For the pooled open-label studies, these percentages were similar (sitting) or slightly higher (supine) than those observed in the double-blind studies (SBP 49.4% and DBP 39.3% sitting; SBP 66.4% and DBP 49.3% supine).

Table 37. Studies 3002 DB and 3013: Number (%) of Subjects Presenting at Least One Treatment-Emergent Postbaseline Blood Pressure Measurement Equal to or Greater Than 130 mmHg for SBP or Equal to or Greater Than 85 mmHg for DBP
(CONCERTA EU SCS - MHRA RFI: Double-Blind Safety Analysis Set)

	-- Placebo --	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SUPINE		
Measurements, n (%)		
N	192	479
At Least One Measurement Above Criteria	101 (52.6)	272 (56.8)
DIASTOLIC BLOOD PRESSURE (mmHg) SUPINE		
Measurements, n (%)		
N	192	479
At Least One Measurement Above Criteria	70 (36.5)	190 (39.7)

Note: Supine findings are from the double-blind portion of Studies 3002 and 3013. Does not include study 02-159 as these measurements were sitting.
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Table 38. Study 02-159: Number (%) of Subjects Presenting at Least One Treatment-Emergent Postbaseline Blood Pressure Measurement Equal to or Greater Than 130 mmHg for SBP or Equal to or Greater Than 85 mmHg for DBP
(Study 02-159: Safety Analysis Set)

	-- Placebo --	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SITTING AVG		
Measurements, n (%)		
N	115	102
At Least One Measurement Above Criteria	34 (29.6)	48 (47.1)
DIASTOLIC BLOOD PRESSURE (mmHg) SITTING AVG		
Measurements, n (%)		
N	115	102
At Least One Measurement Above Criteria	28 (24.3)	38 (37.3)

Note: Sitting findings are from the double-blind portion of Study 02-159.
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Table 39. Open-Label Studies: Number (%) of Subjects Presenting at Least One Treatment-Emergent Postbaseline Blood Pressure Measurement Equal to or Greater Than 130 mmHg for SBP or Equal to or Greater Than 85 mmHg for DBP
(CONCERTA EU SCS - MHRA RFI: Open-Label Safety Analysis Set)

	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SITTING	
Measurements, n (%)	
N	704
At Least One Measurement Above Criteria	348 (49.4)
SYSTOLIC BLOOD PRESSURE (mmHg) SUPINE	
Measurements, n (%)	
N	369
At Least One Measurement Above Criteria	245 (66.4)
DIASTOLIC BLOOD PRESSURE (mmHg) SITTING	
Measurements, n (%)	
N	704
At Least One Measurement Above Criteria	277 (39.3)
DIASTOLIC BLOOD PRESSURE (mmHg) SUPINE	
Measurements, n (%)	
N	369
At Least One Measurement Above Criteria	182 (49.3)

Note: Sitting findings are from Studies 12304, C-99-018-00, CON-CAN-4; Supine findings are from Studies 3002 OL and 3004.
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2.8.2.4.1. Subjects With Elevated Blood Pressure at Baseline

For the subgroup of subjects with elevated blood pressure at baseline, summary tables presenting the number and percentage of subjects with a SBP ≥130 mmHg or a DBP ≥85 mmHg are provided for pooled Studies 3002 DB and 3013 (Table 40), Study 02-159 (Table 41), and the pooled open-label studies (Table 42). In pooled Studies 3002 DB and 3013, a similar percentage of subjects treated with placebo compared with CONCERTA experienced a SBP ≥130 mmHg or a DBP ≥85 mmHg (SBP 66.7% vs. 69.8%; DBP 44.4% vs. 49.5%, respectively). In Study 02-159, these percentages were higher for subjects treated with CONCERTA compared with placebo (SBP 64.4% vs. 46.6%; DBP 49.2% vs. 39.7%, respectively). For the pooled open-label studies, approximately three fourths of the subjects with elevated blood pressure at baseline experienced a SBP measurement of ≥130 mmHg postbaseline (71.7% sitting, 80.5% supine), and as observed in the double-blind studies for both body positions, approximately half of the subjects experienced a DBP measurement of ≥85 mmHg postbaseline (52.6% sitting, 58.6% supine).

Table 40. Studies 3002 DB and 3013: Number (%) of Subjects Presenting at Least One Treatment-Emergent Postbaseline Blood Pressure Measurement Equal to or Greater Than 130 mmHg for SBP or Equal to or Greater Than 85 mmHg for DBP in Subjects With Elevated Blood Pressure at Baseline
(CONCERTA EU SCS - MHRA RFI: Double-Blind Safety Analysis Set)

	-- Placebo--	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SUPINE		
Measurements, n (%)		
N	135	325
At Least One Measurement Above Criteria	90 (66.7)	227 (69.8)
DIASTOLIC BLOOD PRESSURE (mmHg) SUPINE		
Measurements, n (%)		
N	135	325
At Least One Measurement Above Criteria	60 (44.4)	161 (49.5)

Note: Supine findings are from the double-blind portion of Studies 3002 DB and 3013. Only subjects with elevated blood pressure at baseline are included, defined as those with either diastolic blood pressure ≥80 mmHg at baseline or systolic blood pressure ≥120 mmHg at baseline. Does not include study 02-159 as these measurements were sitting.
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Table 41. Study 02-159: Number (%) of Subjects Presenting at Least One Treatment-Emergent Postbaseline Blood Pressure Measurement Equal to or Greater Than 130 mmHg for SBP or Equal to or Greater Than 85 mmHg for DBP in Subjects With Elevated Blood Pressure at Baseline
(Study 02-159: Safety Analysis Set)

	-- Placebo--	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SITTING AVG		
Measurements, n (%)		
N	58	59
At Least One Measurement Above Criteria	27 (46.6)	38 (64.4)
DIASTOLIC BLOOD PRESSURE (mmHg) SITTING AVG		
Measurements, n (%)		
N	58	59
At Least One Measurement Above Criteria	23 (39.7)	29 (49.2)

Note: Sitting findings are from the double-blind portion of Study 02-159. Only subjects with elevated blood pressure at baseline are included, defined as those with either diastolic blood pressure ≥80 mmHg at baseline or systolic blood pressure ≥120 mmHg at baseline.
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Table 42. Open-Label Studies: Number (%) of Subjects Presenting at Least One Treatment-Emergent Postbaseline Blood Pressure Measurement Equal to or Greater Than 130 mmHg for SBP or Equal to or Greater Than 85 mmHg for DBP in Subjects With Elevated Blood Pressure at Baseline
(CONCERTA EU SCS - MHRA RFI: Open-Label Safety Analysis Set)

	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SITTING	
Measurements, n (%)	
N	371
At Least One Measurement Above Criteria	266 (71.7)
SYSTOLIC BLOOD PRESSURE (mmHg) SUPINE	
Measurements, n (%)	
N	256
At Least One Measurement Above Criteria	206 (80.5)
DIASTOLIC BLOOD PRESSURE (mmHg) SITTING	
Measurements, n (%)	
N	371
At Least One Measurement Above Criteria	195 (52.6)
DIASTOLIC BLOOD PRESSURE (mmHg) SUPINE	
Measurements, n (%)	
N	256
At Least One Measurement Above Criteria	150 (58.6)

Note: Sitting findings are from Studies 12-304, C-99-018-00, CON-CAN-4; Supine findings are from Studies 3002 OL and 3004. Only subjects with elevated blood pressure at baseline are included, defined as those with either diastolic blood pressure ≥80 mmHg at baseline or systolic blood pressure ≥120 mmHg at baseline.
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2.8.2.4.2. Subjects With a Medical History of Hypertension

For the subgroup of subjects with a medical history of hypertension, summary tables presenting the number and percentage of subjects with a SBP ≥130 mmHg or a DBP ≥85 mmHg are provided for pooled Studies 3002 DB and 3013 (Table 43), Study 02-159 (Table 44), and the pooled open-label studies (Table 45). In pooled Studies 3002 DB and 3013, a similar percentage of subjects treated with placebo compared with CONCERTA experienced a SBP ≥130 mmHg or a DBP ≥85 mmHg (SBP 100.0% vs. 93.3%; DBP 92.9% vs. 83.3%, respectively). In Study 02-159, these percentages were also similar between treatment groups for SBP (50.0% placebo, 60.0% CONCERTA), but higher for CONCERTA compared with placebo for DBP (40.0% vs. 25.0%, respectively). For the pooled open-label studies, these percentages were similar to those observed in the double-blind studies for sitting and supine measurements, respectively (SBP 83.7% and DBP 69.8% sitting; SBP 100.0% and DBP 90.0% supine).

Table 43. Studies 3002 DB and 3013: Number (%) of Subjects Presenting at Least One Treatment-Emergent Postbaseline Blood Pressure Measurement Equal to or Greater Than 130 mmHg for SBP or Equal to or Greater Than 85 mmHg for DBP in Subjects With Medical History of Hypertension
(CONCERTA EU SCS - MHRA RFI: Double-Blind Safety Analysis Set)

	-- Placebo--	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SUPINE		
Measurements, n (%)		
N	14	30
At Least One Measurement Above Criteria	14 (100)	28 (93.3)
DIASTOLIC BLOOD PRESSURE (mmHg) SUPINE		
Measurements, n (%)		
N	14	30
At Least One Measurement Above Criteria	13 (92.9)	25 (83.3)

Note: Supine findings are from the double-blind portion of Studies 3002 and 3013. Only subjects with a medical history of hypertension or a pre-treatment hypertension-related adverse event are included. Does not include study 02-159 as these measurements were sitting.
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Table 44. Study 02-159: Number (%) of Subjects Presenting at Least One Treatment-Emergent Postbaseline Blood Pressure Measurement Equal to or Greater Than 130 mmHg for SBP or Equal to or Greater Than 85 mmHg for DBP in Subjects With Medical History of Hypertension
(Study 02-159: Safety Analysis Set)

	-- Placebo--	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SITTING AVG		
Measurements, n (%)		
N	12	5
At Least One Measurement Above Criteria	6 (50.0)	3 (60.0)
DIASTOLIC BLOOD PRESSURE (mmHg) SITTING AVG		
Measurements, n (%)		
N	12	5
At Least One Measurement Above Criteria	3 (25.0)	2 (40.0)

Note: Sitting findings are from the double-blind portion of Study 02-159. Only subjects with a medical history of hypertension or a pre-treatment hypertension-related adverse event are included.
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Table 45. Open-Label Studies: Number (%) of Subjects Presenting at Least One Treatment-Emergent Postbaseline Blood Pressure Measurement Equal to or Greater Than 130 mmHg for SBP or Equal to or Greater Than 85 mmHg for DBP in Subjects With Medical History of Hypertension
(CONCERTA EU SCS - MHRA RFI: Open-Label Safety Analysis Set)

	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SITTING	
Measurements, n (%)	
N	43
At Least One Measurement Above Criteria	36 (83.7)
SYSTOLIC BLOOD PRESSURE (mmHg) SUPINE	
Measurements, n (%)	
N	10
At Least One Measurement Above Criteria	10 (100)
DIASTOLIC BLOOD PRESSURE (mmHg) SITTING	
Measurements, n (%)	
N	43
At Least One Measurement Above Criteria	30 (69.8)
DIASTOLIC BLOOD PRESSURE (mmHg) SUPINE	
Measurements, n (%)	
N	10
At Least One Measurement Above Criteria	9 (90.0)

Note: Sitting findings are from Studies 12-304, C-99-018-00, CON-CAN-4; Supine findings are from Studies 3002 OL and 3004. Only subjects with a medical history of hypertension or a pre-treatment hypertension-related adverse event are included.
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2.9. Request 9: Safety Concern – Psychiatric Adverse Events

Request:

Psychiatric adverse events. Further discussion of the psychiatric adverse events is required with particular focus on:

- Suicidality. Discuss whether all potential cases were identified in terms of a Columbia style analysis with intention not considered as a criterion for inclusion.
- Aggression with a description of the individual events and their severity.

Response:

The adverse event categories of special interest for Suicidality and Aggression presented in the SCS were employed in responding to this concern. These adverse event categories of special interest were informed by a cluster of Medical Dictionary for Regulatory Activities Terminology (MedDRA) Preferred Terms provided in the SCS (Attachment 6).

2.9.1. Suicidality

For the evaluation of suicidality associated with the use of methylphenidate in adults with ADHD, no "Columbia-style" analysis was conducted. In particular, there was no blinded review of patient summaries for those subjects identified as having experienced a potential suicide-related event on the basis of an electronic text string search of the adult clinical database, with the intent of assigning a Columbia Classification Algorithm for Suicide Assessment (C-CASA) code to relevant events and presenting data from placebo-controlled studies in a categorical analysis. Preliminary review of coded and reported adverse event terms from the completed placebo-controlled studies in adults with ADHD suggested that the number of events that could be identified as of potential interest was too small to inform this type of analysis.

Although the studies in the submission did not include a validated instrument for the assessment of suicidal ideation or behavior during the conduct of the studies, such as the Columbia-Suicide Severity Rating Scale (C-SSRS), additional information collected at the time serious adverse events were reported could inform the intent of potential suicidal acts. The lack of intent did not preclude the identification of suicide-related events as can be seen by the inclusion of Subject 219118 discussed below. Three (0.2%) subjects receiving CONCERTA (1 subject in double-blind Study 3013 and 2 subjects in open-label Study 12-304) experienced an adverse event within the suicidality adverse event category of special interest. These events consisted of a single report of a suicide attempt accompanied by suicidal ideation and 2 reports of suicidal ideation without an accompanying suicide attempt. None of these subjects died as a result of the suicidality-related events, and for all 3 subjects, the event was assessed by the investigator as severe in intensity. Subject specific information is provided below and narratives for these subjects are provided in the SCS (Attachment 7).

For the subject who attempted suicide (Subject A10056, a 29-year-old woman, in Study 3013), the event was serious and resulted initially in temporary discontinuation of study drug; this subject was withdrawn from the study by the Company. After random assignment to CONCERTA 54 mg/day and treatment for approximately 40 days, the subject experienced first suicidal thoughts and suicidal ideation was reported as a serious adverse event due to hospitalization. Five days later the subject attempted suicide by ingestion of 5 tablets of zopiclone 5 mg, 4 tablets of hydroxyzine 25 mg, and drinking alcoholic beverages 25 cL.

For one subject who experienced suicidal ideation (Subject 219118, a 44-year-old male, in Study 12-304), the event was not considered serious but resulted in discontinuation from the study. The subject also had a history of alcohol abuse, cocaine abuse, marijuana abuse, and heroin abuse. On Day 11, the subject reported severe thoughts of serious bodily harm to others and thoughts of serious bodily harm to self; he did not formulate a plan to act on these thoughts and this was considered as there being no intent to act on the thoughts.

For the other subject who experienced suicidal ideation (Subject 229100, a 47-year-old male, in Study 12-304), the event was not treatment emergent; suicidal ideation accompanied by alcoholism and depression occurred prior to the initiation of study drug. Medical records subsequently showed that approximately 10 days prior to beginning CONCERTA treatment, the subject had been hospitalized for these events, which were subsequently considered serious and resulted in discontinuation from the study.

2.9.2. Aggression

The emergence or worsening of aggression can be caused by treatment with stimulants as noted in Section 4.4 of the SPC. Thus, the finding that the rate of adverse event reporting within the aggression adverse event category of special interest was approximately 2-fold higher on CONCERTA (11.9%) than on placebo (5.5%) (odds ratio: 2.3) in the pooled double-blind analysis set is not unexpected (Attachment 8.1, Attachment 8.3). Overall, approximately 15% of adult subjects receiving CONCERTA (n=202, 14.8%) in all clinical studies experienced an adverse event within the aggression adverse event category of special interest (Attachment 8.2). However, none of the aggression-related adverse events were serious.

MedDRA Preferred Terms, coded to the aggression category of special interest, that were reported in 2% or more of subjects who received double-blind or open-label CONCERTA were Irritability (n=100, 7.3%), Agitation (n=43, 3.1%), and Psychomotor hyperactivity (n=27, 2.0%). The MedDRA Preferred Terms of Aggression and Anger were reported by 1.0% and 0.5%, respectively, of adult subjects receiving CONCERTA (Attachment 8.2). For most subjects who received double-blind or open-label CONCERTA, the aggression-related adverse events were assessed by the investigator as mild or moderate in intensity (183 of 202 subjects) and resolved without residual effects (169 of 202, 84%). Only a small percentage of the 1,369 adult subjects (n=30, 2.2%) receiving CONCERTA across all clinical studies had study treatment discontinued as a result of an aggression-related adverse event (Attachment 8.3).

Of the subjects with an aggression-related adverse event in the double-blind studies, the proportion with events that were assessed as severe in intensity was similar for the CONCERTA (10 of 71, 14.1%) and placebo (2 of 17, 11.8%) groups. During the double-blind studies, 13 of the 596 subjects receiving CONCERTA (2.2%) were withdrawn for aggression-related adverse events (vs. none receiving placebo) (Attachment 8.3).

A listing of subjects who reported an adverse event within the aggression category of special interest is provided in Attachment 8.4. This subject listing includes the reported (verbatim) term, MedDRA Preferred Term, subject demographics, time of onset, duration, seriousness, severity, outcome, and whether a concomitant medication/other treatment (Y/N) was given.

2.10. Request 10: Safety Concern – Weight Loss

Request:

Further discussion on the implications of weight loss in adults.

Response:

As patients with ADHD who continue treatment with methylphenidate into adulthood will have been monitored continuously for their body weight throughout adolescence, the data from completed efficacy and safety studies of CONCERTA in adults with ADHD may not be particularly relevant for the population that is currently being proposed for continued use of CONCERTA in Section 4.2 of the SPC. Subjects enrolled in these clinical studies had either not previously been exposed to methylphenidate or had discontinued prior treatment with methylphenidate for a period of variable length before administration of the first dose of study drug.

To further investigate weight loss experienced by subjects during study participation, the following analyses are provided:

- A summary table providing the number and percentage of subjects who withdrew from the study due to an adverse event related to weight loss for both the pooled double-blind (3002 DB, 02-159, 3013, by treatment group) and pooled open-label studies (3004, 3002 open-label phase [OL], 12-304, C-99-018, CON CAN-4) (Tables 46 and 52, respectively);

- A summary table providing the number and percentage of subjects for whom the dose of study drug was reduced or adjusted due to an adverse event related to weight loss for the pooled open-label studies (Tables 53); no subjects in Study 02-159 met the criterion (Attachment 9) and Studies 3002 and 3013 were fixed-dose studies;
- Summary tables providing the number and percentage of subjects with a change in body mass index (BMI) category or with an abnormal increase or decrease in body weight (≥7%) were provided by subgroup based on the following BMI weight categories: underweight: <18.5 kg/m^2, normal: 18.5 to <25 kg/m^2, overweight: 25 to <30 kg/m^2, and obese: ≥30 kg/m^2. (Tables 47 to 50, double-blind; Tables 54 to 57, open-label);
- Summary tables providing the mean change in BMI from baseline by study visit for the pooled double-blind (by treatment group) (Attachment 10.1) and open-label studies (Attachment 10.2);
- A summary table providing the number and percentage of subjects who experienced at least 1 adverse event related to weight loss that was considered by the investigator to be severe for the pooled double-blind (by treatment group, Table 51) and open-label (Table 58) studies; and
- A listing of subjects with adverse events related to weight loss that includes the following items: reported (verbatim) term, MedDRA Preferred Term, subject demographics, time of onset, duration, seriousness, severity, relationship to study drug, action taken, body weight in kilograms (kgs), and change in body weight from baseline (Attachment 11).

During the double-blind studies, approximately 7% to 10% of subjects treated with CONCERTA compared with ≤1% of subjects treated with placebo experienced an abnormal decrease in body weight (decrease ≥7% from baseline) in each of the BMI weight categories (underweight, normal, overweight, obese); these same percentages for the open-label studies were approximately 10% to 18%. Accordingly, the summaries of mean changes in BMI from baseline over time showed a decrease at each study visit for subjects receiving both double-blind and open-label CONCERTA. However, the clinical relevance of these changes in body weight can be better assessed based on the summaries of subjects with adverse events related to weight loss, and summaries of subjects for whom the dose was adjusted for weight-loss related adverse events. The summaries showed a small percentage of subjects with any of these adverse events overall (0.7% for double-blind and 1.5% for open-label CONCERTA, 0.0% placebo). In Study 02-159, no subjects had their dose of study drug adjusted due to an adverse event (Attachment 9). Subjects were assigned to fixed doses of study drug

in Studies 3002 DB and 3013. For the pooled open-label studies, 1.7% of subjects experienced a dose reduction due to an adverse event. The following subsections provide the details of these analyses for the pooled double-blind studies (Section 2.10.1) and the open-label studies (Section 2.10.2)

For the interpretation of data on changes from baseline in body weight, shifts in BMI category, and adverse events related to weight loss across the different analysis sets; it is important to consider that the longer duration of follow up in the open-label studies relative to the double-blind studies makes it more likely that subjects would have met any of these criteria while they were followed up during open-label treatment.

2.10.1. Pooled Double-Blind Studies (3002 DB, 02-159, 3013)

During the double-blind studies, 4 (0.7%) subjects treated with CONCERTA withdrew from the study due to an adverse event related to weight loss: Weight decreased (0.2%), Anorexia (0.2%), and Decreased appetite (0.5%) (Table 46). No placebo subjects withdrew due to an adverse event related to weight loss. In Study 02-159, no subjects' dose of study drug was reduced or adjusted due to an adverse event related to weight loss (Attachment 9). Studies 3002 and 3013 employed a fixed-dose design.

Table 46. Double-Blind Studies: Number (%) of Subjects Who Withdrew Because of an Adverse Event of Weight Loss by MedDRA System Organ Class, Preferred Term, and Treatment Group (CONCERTA EU SCS - MHRA RFI: Double-Blind Safety Analysis Set)

Body System Or Organ Class Dictionary-Derived Term	**PLACEBO (N=309) n (%)**	**ALL CONCERTA (N=596) n (%)**
Total no. subjects WITH ADVERSE EVENTS	0	4 (0.7)
Investigations	0	1 (0.2)
Weight decreased	0	1 (0.2)
Metabolism and nutrition disorders	0	4 (0.7)
Anorexia	0	1 (0.2)
Decreased appetite	0	3 (0.5)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
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Changes in body weight during the double-blind studies were further evaluated by subgroup of BMI category (underweight: <18.5 kg/m^2; normal: 18.5 to <25 kg/m^2; overweight: 25 to <30 kg/m^2; obese: ≥30 kg/m^2). Also, within each of these subgroups, the number and percentage of subjects experiencing an abnormal increase or decrease in body weight (≥7%) at end point compared with baseline

were provided. For the subgroup of subjects who were underweight at baseline, 1 (7.7%) subject treated with CONCERTA experienced an abnormal decrease in body weight at end point (Table 47). For subjects within the normal weight category at baseline, a similar percentage of subjects treated with CONCERTA compared with placebo experienced transitions at end point to the underweight category (1 subject, 0.9% placebo; 3 subjects, 1.3% CONCERTA); 17 (7.1%) subjects treated with CONCERTA experienced an abnormal decrease in body weight (≥7%) at end point compared with 0 placebo subjects (Table 48). For subjects within the overweight category at baseline, a higher percentage of subjects treated with CONCERTA (33 subjects, 16.2%) compared with placebo (3 subjects, 2.9%) experienced transitions at end point to the normal weight category; 20 (9.8%) subjects treated with CONCERTA experienced an abnormal decrease (≥7%) in body weight at end point compared with 0 placebo subjects (Table 49). For subjects within the obese category at baseline, a higher percentage of subjects treated with CONCERTA (21 subjects, 19.1%) compared with placebo (5 subjects, 6.5%) experienced transitions at end point to the overweight category; also, a higher percentage of subjects treated with CONCERTA (8 subjects, 7.3%) compared with placebo (1 subject, 1.3%) experienced an abnormal decrease (≥7%) in body weight at end point (Table 50).

A summary of the mean change in BMI from baseline by study visit and treatment group is provided in Attachment 10.1. Small decreases in mean BMI at each visit compared with baseline were observed for subjects treated with CONCERTA while small increases in mean BMI at each visit compared with baseline were observed for those treated with placebo.

Table 47. Double-Blind Studies: Classification of Weight Change and BMI at End Point Relative to Baseline by Baseline BMI Group of Underweight
(CONCERTA EU SCS: Double-Blind Safety Analysis Set)

Baseline BMI Group: Underweight <18.5

	------ PLACEBO ------			---- ALL CONCERTA ---		
	n	%	Cum.%	n	%	Cum.%
BMI classification						
End point						
Underweight <18.5	3	75.0	75.0	12	92.3	92.3
Normal 18.5 < 25	1	25.0	100.0	1	7.7	100.0
Overweight 25 < 30	0	0.0	100.0	0	0.0	100.0
Obese ≥ 30	0	0.0	100.0	0	0.0	100.0
-------	-----			-----		
Total	4			13		
Body weight change category						
End point						
Normal	4	100.0	100.0	12	92.3	92.3
Abn low	0	0.0	100.0	1	7.7	100.0
Abn high	0	0.0	100.0	0	0.0	100.0
-------	-----			-----		
Total	4			13		

Body weight change category: abn low: decrease from baseline ≥7%; abn high: increase from baseline ≥7%.
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Table 48. Double-Blind Studies: Classification of Weight Change and BMI at End Point Relative to Baseline by Baseline BMI Group of Normal
(CONCERTA EU SCS: Double-Blind Safety Analysis Set)

Baseline BMI Group: Normal 18.5 < 25

	------ PLACEBO ------			---- ALL CONCERTA ---		
	n	%	Cum.%	n	%	Cum.%
BMI classification						
End point						
Underweight <18.5	1	0.9	0.9	3	1.3	1.3
Normal 18.5 < 25	105	92.9	93.8	227	95.4	96.6
Overweight 25 < 30	7	6.2	100.0	8	3.4	100.0
Obese ≥ 30	0	0.0	100.0	0	0.0	100.0
-------	-----			-----		
Total	113			238		
Body weight change category						
End point						
Normal	112	99.1	99.1	217	91.2	91.2
Abn low	0	0.0	99.1	17	7.1	98.3
Abn high	1	0.9	100.0	4	1.7	100.0
-------	-----			-----		
Total	113			238		

Body weight change category: abn low: decrease from baseline ≥7%; abn high: increase from baseline ≥7%.
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Table 49. Double-Blind Studies: Classification of Weight Change and BMI at End Point Relative to Baseline by Baseline BMI Group of Overweight
(CONCERTA EU SCS: Double-Blind Safety Analysis Set)

Baseline BMI Group: Overweight 25 < 30

	------ PLACEBO ------			---- ALL CONCERTA ---		
	n	%	Cum.%	n	%	Cum.%
BMI classification						
End point						
Underweight <18.5	0	0.0	0.0	0	0.0	0.0
Normal 18.5 < 25	3	2.9	2.9	33	16.2	16.2
Overweight 25 < 30	98	94.2	97.1	169	82.8	99.0
Obese ≥ 30	3	2.9	100.0	2	1.0	100.0
-------	-----			-----		
Total	104			204		
Body weight change category						
End point						
Normal	104	100.0	100.0	184	90.2	90.2
Abn low	0	0.0	100.0	20	9.8	100.0
Abn high	0	0.0	100.0	0	0.0	100.0
-------	-----			-----		
Total	104			204		

Body weight change category: abn low: decrease from baseline ≥7%; abn high: increase from baseline ≥7%.
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Table 50. Double-Blind Studies: Classification of Weight Change and BMI at End Point Relative to Baseline by Baseline BMI Group of Obese
(CONCERTA EU SCS: Double-Blind Safety Analysis Set)

Baseline BMI Group: Obese ≥ 30

	------ PLACEBO ------			---- ALL CONCERTA ---		
	n	%	Cum.%	n	%	Cum.%
BMI classification						
End point						
Underweight <18.5	0	0.0	0.0	0	0.0	0.0
Normal 18.5 < 25	0	0.0	0.0	0	0.0	0.0
Overweight 25 < 30	5	6.5	6.5	21	19.1	19.1
Obese ≥ 30	72	93.5	100.0	89	80.9	100.0
-------	-----			-----		
Total	77			110		
Body weight change category						
End point						
Normal	76	98.7	98.7	102	92.7	92.7
Abn low	1	1.3	100.0	8	7.3	100.0
Abn high	0	0.0	100.0	0	0.0	100.0
-------	-----			-----		
Total	77			110		

Body weight change category: abn low: decrease from baseline ≥7%; abn high: increase from baseline ≥7%.
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During the double-blind studies, no subjects experienced adverse events related to weight loss that were considered by the investigator to be serious and the majority of adverse events related to weight loss were considered to be mild or moderate in severity; 10 subjects had adverse events considered by the investigator to be severe (Table 51). A listing of subjects with adverse events related to weight loss is provided in Attachment 11.

Table 51. Double-Blind Studies: Number(%) of Subjects With a Severe Adverse Event Related to Weight Loss by MedDRA System Organ Class, Preferred Term and Treatment Group (CONCERTA EU SCS - MHRA RFI: Double-Blind Safety Analysis Set)

Body System Or Organ Class Dictionary-Derived Term	PLACEBO (N=309) n (%)	ALL CONCERTA (N=596) n (%)
Total no. subjects with Severe AEs Related to Weight Loss	0	10 (1.7)
Investigations	0	2 (0.3)
Weight decreased	0	2 (0.3)
Metabolism and nutrition disorders	0	8 (1.3)
Anorexia	0	4 (0.7)
Decreased appetite	0	4 (0.7)

Note: Percentages calculated with the number of subjects in each group as denominator. Incidence is based on the number of subjects experiencing at least 1adverse event, not the number of events.
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2.10.2. Pooled Open-Label Studies (3004, 3002 OL, 12-304, C-99-018, CON-CAN-4)

During the open-label studies, 16 (1.5%) subjects treated with CONCERTA withdrew from the study due to an adverse event related to weight loss: Weight decreased (0.6%), Anorexia (0.2%), and Decreased appetite (1.0%) (Table 52). A total of 18 (1.7%) subjects had their dose of study drug reduced or adjusted due to an adverse event related to weight loss: Weight decreased (0.5%), Anorexia (0.1%), and Decreased appetite (1.2%) (Table 53).

Table 52. Open-Label Studies: Number (%) of Subjects Who Withdrew Because of an Adverse Event of Weight Loss by MedDRA System Organ Class and Preferred Term (CONCERTA EU SCS - MHRA RFI: Open-Label Safety Analysis Set)

Body System Or Organ Class Dictionary-Derived Term	ALL CONCERTA (N=1088) n (%)
Total no. subjects WITH ADVERSE EVENTS	16 (1.5)
Investigations	6 (0.6)
Weight decreased	6 (0.6)
Metabolism and nutrition disorders	13 (1.2)
Anorexia	2 (0.2)
Decreased appetite	11 (1.0)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
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Table 53. Open-Label Studies: Number (%) of Subjects Who Had a Dose Reduction/Dose Adjustment Because of an Adverse Event of Weight Loss by MedDRA System Organ Class and Preferred Term (CONCERTA EU SCS - MHRA RFI: Open-Label Safety Analysis Set)

Body System Organ Class Dictionary-Derived Term	ALL CONCERTA (N=1088) n (%)
Total no. subjects WITH ADVERSE EVENTS	18 (1.7)
Investigations	5 (0.5)
Weight decreased	5 (0.5)
Metabolism and nutrition disorders	14 (1.3)
Anorexia	1 (0.1)
Decreased appetite	13 (1.2)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Includes adverse events with action taken with study drug of "down-titration", "dose adjusted" or "dose reducted". The CRFs for several studies used "dose adjusted" rather than a more specific term (dose increased/dose decreased), so for completeness these events were included.
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Changes in body weight during open-label treatment with CONCERTA were further evaluated by subgroup of BMI category (underweight: <18.5 kg/m^2; normal: 18.5 to <25 kg/m^2; overweight: 25 to <30 kg/m^2; obese: ≥30 kg/m^2). Also, within each of these subgroups, the number and percentage of subjects experiencing an abnormal increase or decrease in body weight (≥7%) at end point compared with baseline were provided. For the subgroup of subjects who were underweight at baseline, 2 (10.0%) subjects experienced an abnormal decrease in body weight at end point (Table 54). For subjects within the normal weight category at baseline, 12 (2.9%) subjects transitioned to the underweight category and 50 (12.1%) subjects experienced an abnormal decrease (≥7%) in body weight at end point (Table 55). For subjects within the overweight category at baseline, 58 (16.6%) subjects transitioned to the normal weight category and 47 (13.5%) subjects experienced an abnormal decrease (≥7%) in body weight at end point (Table 56). For subjects within the obese category at baseline, 47 (18.2%) subjects experienced an abnormal decrease (≥7%) in body weight at end point, with 45 (17.4%) subjects transitioning to the overweight category and 3 (1.2%) subjects transitioning to the normal weight category (Table 57).

It should be noted that there is uncertainty as to whether underweight, defined on the basis of BMI (ie, <18.5 kg/m2), constitutes an independent risk factor for overall or CVD mortality in a general adult population (Flegal 2010). Epidemiological data from the NHANES III cross-sectional survey with follow up for mortality through 2000 suggest that it is not an independent risk factor for overall or CVD mortality in this population (Flegal 2007).

A summary of the mean change in BMI from baseline by study visit is provided in Attachment 10.2. Small decreases in mean BMI at each visit compared with baseline were observed for these subjects treated with open-label CONCERTA.

Table 54. Open-Label Studies: Classification of Weight Change and BMI at End Point Relative to Baseline by Baseline BMI Group of Underweight
(CONCERTA EU SCS: Open-Label Safety Analysis Set)

Baseline BMI Group: Underweight <18.5

		---- ALL CONCERTA ---	
	n	%	Cum.%
BMI classification			
End point			
Underweight <18.5	18	90.0	90.0
Normal 18.5 < 25	2	10.0	100.0
Overweight 25 < 30	0	0.0	100.0
Obese ≥ 30	0	0.0	100.0
-------	-----		
Total	20		
Body weight change category			
End point			
Normal	17	85.0	85.0
Abn low	2	10.0	95.0
Abn high	1	5.0	100.0
-------	-----		
Total	20		

Body weight change category: abn low: decrease from baseline ≥7%; abn high: increase from baseline ≥7%.
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Table 55. Open-Label Studies: Classification of Weight Change and BMI at End Point Relative to Baseline by Baseline BMI Group of Normal
(CONCERTA EU SCS: Open-Label Safety Analysis Set)

Baseline BMI Group: Normal 18.5 < 25

		---- ALL CONCERTA ---	
	n	%	Cum.%
BMI classification			
End point			
Underweight <18.5	12	2.9	2.9
Normal 18.5 < 25	380	91.8	94.7
Overweight 25 < 30	22	5.3	100.0
Obese ≥ 30	0	0.0	100.0
-------	-----		
Total	414		
Body weight change category			
End point			
Normal	352	85.0	85.0
Abn low	50	12.1	97.1
Abn high	12	2.9	100.0
-------	-----		
Total	414		

Body weight change category: abn low: decrease from baseline ≥7%; abn high: increase from baseline ≥7%.
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Table 56. Open-Label Study: Classification of Weight Change and BMI at End Point Relative to Baseline by Baseline BMI Group of Overweight
(CONCERTA EU SCS: Open-Label Safety Analysis Set)

Baseline BMI Group: Overweight 25 < 30

		---- ALL CONCERTA ---	
	n	%	Cum.%
BMI classification			
End point			
Underweight <18.5	0	0.0	0.0
Normal 18.5 < 25	58	16.6	16.6
Overweight 25 < 30	280	80.2	96.8
Obese ≥ 30	11	3.2	100.0
-------	-----		
Total	349		
Body weight change category			
End point			
Normal	290	83.1	83.1
Abn low	47	13.5	96.6
Abn high	12	3.4	100.0
-------	-----		
Total	349		

Body weight change category: abn low: decrease from baseline ≥7%; abn high: increase from baseline ≥7%.
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Table 57. Open-Label Studies: Classification of Weight Change and BMI at End Point Relative to Baseline by Baseline BMI Group of Obese
(CONCERTA EU SCS: Open-Label Safety Analysis Set)

Baseline BMI Group: Obese ≥ 30

		---- ALL CONCERTA ---	
	n	%	Cum.%
BMI classification			
End point			
Underweight <18.5	0	0.0	0.0
Normal 18.5 < 25	3	1.2	1.2
Overweight 25 < 30	45	17.4	18.6
Obese ≥ 30	210	81.4	100.0
-------	-----		
Total	258		
Body weight change category			
End point			
Normal	207	80.2	80.2
Abn low	47	18.2	98.4
Abn high	4	1.6	100.0
-------	-----		
Total	258		

Body weight change category: abn low: decrease from baseline ≥7%; abn high: increase from baseline ≥7%.
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During the open-label studies, there were no adverse events related to weight loss that were considered by the investigator to be serious and the majority of adverse

events related to weight loss were mild or moderate in severity; 4 subjects had adverse events considered by the investigator to be severe (Table 58). A listing of subjects with adverse events related to weight loss is provided in Attachment 11.

Table 58. Open-Label Studies: Number and Percent of Subjects With a Severe Adverse Event Related to Weight Loss by MedDRA System Organ Class and Preferred Term (CONCERTA EU SCS - MHRA RFI: Open-Label Safety Analysis Set)

Body System Or Organ Class Dictionary-Derived Term	ALL CONCERTA (N=1088) n (%)
Total no. subjects with Severe AEs Related to Weight Loss	4 (0.4)
Investigations	2 (0.2)
Weight decreased	2 (0.2)
Metabolism and nutrition disorders	3 (0.3)
Decreased appetite	3 (0.3)

Note: Percentages calculated with the number of subjects in each group as denominator. Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events.
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2.11. Request 11: Safety Concern – Drug Dependence and Abuse

Request:

> Further discussion around the risk of dependence and abuse in light of the pharmacokinetics seen in study 12-004 Crushed Concerta and the Abuse potential seen in Study 12-007 (Light Drug Users).

Response:

The formulation of a controlled substance can significantly affect its diversion and abuse potential. For orally administered drugs, pharmacokinetic properties such as rapid absorption, rapid entry into brain, high bioavailability, low protein binding, short half-life, small volume of distribution and high free drug clearance appear to enhance self-administration and addiction (Busto 1986). All other factors being equal, different formulations of the same active ingredient may have different potential for abuse due to different rates of drug release and absorption. A drug that is absorbed over an extended period of time is less likely to produce effects of drug liking and reinforcement than a drug that is released rapidly and quickly achieves high systemic concentrations (Samaha 2005). CONCERTA, an extended-release formulation of methylphenidate that uses OROS® Push-Pull™ technology and has been developed to deliver methylphenidate over a 12-hour interval, appears to have a lower abuse potential than immediate-release (IR) or other extended-release preparations of methylphenidate (Spencer 2006).

Ingested intact, IR formulations such as Ritalin release the methylphenidate rapidly, with maximum plasma concentrations occurring within 1 to 2 hours after

dosing, followed by an overall decline in plasma concentrations. The time course profile of methylphenidate in the brain is thought to mimic that in the plasma (Volkow 1995). CONCERTA releases only a small fraction of the total dose immediately (22%) at a rate similar to that of the IR formulation. This is followed by slow and sustained drug release over a period of 6 to 8 hours resulting in increasing plasma concentrations (and by corollary, brain concentrations) over an extended time period (Volkow 1995). When a stimulant drug is delivered to the brain at concentrations that are sufficient to block greater than 50% of dopamine transporters, sustained and elevated drug concentrations due to slow elimination/clearance and/or continued drug delivery leads to saturation of transporters, thereby potentially reducing the drug's reinforcing effects (Volkow 2003; Volkow 2002).

2.11.1. Study 12-004

To investigate the relationship between the immediacy of uptake and the abuse potential of CONCERTA, Study 12-004 was designed to provide information related to differences in rate of absorption of crushed CONCERTA compared with crushed IR methylphenidate (Ritalin®). In this pharmacokinetic study, during different periods healthy subjects received a single dose of 18 mg CONCERTA, whole or crushed, or single 20 mg dose of Ritalin, crushed. The main objective of the study was to measure changes in the absorption profile of methylphenidate after severely compromising the OROS delivery system of CONCERTA by crushing the CONCERTA into a fine powder, with crushed Ritalin as active control. The plasma concentration-time profile of d-methylphenidate after dosing of crushed CONCERTA was different from the typical profile of d-methylphenidate following dosing of intact CONCERTA. Whereas dosing of intact CONCERTA results in an initial peak concentration of methylphenidate at about 1 hour postdose followed by a gradually ascending profile resulting in a second peak concentration at about 6 hours after dosing, the general shape of the profiles after dosing with crushed CONCERTA and crushed Ritalin were similar, with a single peak at about 1.3 hours after dosing. However, even after dose-normalizing for actual administered dose, both measures of early absorption, peak plasma concentration (C_{max}) and area under the concentration-time curve over the time interval 0 to 2 hours (AUC_{0-2h}), were lower for crushed CONCERTA compared with those for crushed RITALIN.

2.11.2. Study 12-007

Study 12-007 evaluated the pharmacokinetics and subjective pharmacodynamic effects related to abuse potential of 2 dose levels of CONCERTA with comparable IR methylphenidate (Ritalin) doses in 49 healthy subjects with a history of light (occasional) stimulant use. Since the objective of this study was to evaluate the potential effect that a difference in formulation may have on abuse potential of the same chemical, this study took into account design aspects learned from the conduct of 2 previous liability studies (12-302 and 12-005) and enrolled a study population with the following characteristics:

- Subjects should respond to class of drugs being evaluated,
- Subjects should be trained to recognize positive control,
- Subjects should not be addicted to drugs,
- Subjects should be able to discern placebo, and
- Subjects should be otherwise healthy.

Study 12-007 was conducted in healthy subjects who, although not naïve (due to concerns related to exposing naïve subjects to agents with abuse potential), had some experience with using stimulant drugs but had a negative urine drug screen during the study. This is considered the representative and sensitive population for studying potential abuse of prescription stimulants such as methylphenidate.

In this double-blind active- and placebo-controlled study, the abuse potential of CONCERTA 54 and 108 mg was evaluated relative to comparable IR methylphenidate doses of 50 and 90 mg. Standard questionnaires for assessment of abuse potential such as Addiction Research Center Inventory (ARCI), ARCI with Cole re-scoring, Drug Rating Questionnaire-Subject Visual Analog Scales, and Subjective Drug Value Procedure were used.

Overall, a consistent rank order was observed for all subjective measures of abuse as follows: IR methylphenidate 90 mg > IR methylphenidate 50 mg > CONCERTA 108 mg > CONCERTA 54 mg > placebo. Although actual abuse depends on many factors including drug availability, cost and desired effect, these data suggest that the gradual ascending profile of methylphenidate from CONCERTA may reduce its potential for abuse. These results also support the hypothesis that the rate, in conjunction with the extent of absorption, is a pivotal factor in determining the abuse potential of methylphenidate.

These findings are in agreement with previously published studies, where sustained-release formulations produced lower subjective ratings compared to IR methylphenidate in stimulant using and stimulant-naive subjects (Spencer 2006;

Kollins 1998; Parasrampuria 2005) and are consistent with the observation that drugs with rapid rates of increase (rate of receptor occupancy) and decline (rate of removal from receptor) in activity are more likely to be abused than drugs with a slower onset and sustained action (Volkow 2002; Volkow 1999). It has been hypothesized that rapid delivery is more likely to be associated with abuse because subjective (euphoric) effects are more immediate, intense, and reinforcing (ie, closer temporal pairing of drug with reward). The ability of methylphenidate to increase extracellular dopamine is associated with its positive subjective effects, which is likely to be one of the main mechanisms underlying its potential for abuse. However, methylphenidate-induced increases in dopamine that are associated with therapeutic effects (slow, tonic cell firing) differ from those accounting for positive subjective effects (fast, phasic cell firing). Therefore, the rate at which methylphenidate enters the brain will determine whether it induces fast versus slow increases in dopamine (Volkow 2006). Even if a methylphenidate formulation results in high dopamine transporter occupancy, if it does so slowly rather than rapidly, as evidenced by this and a previous study, it may elicit less intense subjective effects (Spencer 2006).

2.12. Request 12: Safety Concern – Pregnancy Outcomes

Request:

> The proposed indication will result in increased exposure of women of child-bearing potential. Adequate warnings should be in place in the SMC. The MAH should commit to capturing and evaluating relevant data on pregnancy outcomes using a pregnancy registry. In addition further investigation of the signal for spina bifida/neural tube defects from the WHO Collaborating Centre for the Epidemiological Surveillance of Congenital Anomalies (EUROCAT) and any other relevant sources.

Response:

Assessment of data on methylphenidate safety in pregnancy and lactation was evaluated as part of the Article 31 referral for methylphenidate-containing medicinal products (EC decision 27 May 2009). Ongoing safety evaluation is conducted via the annual methylphenidate Periodic Safety Update Report (PSUR) work-share procedure.

2.13. Request 13: Product Information – Section 4.4 Monitoring

Request:

Clear guidance in section 4.4 should be added on the monitoring of HR and BP before use and during treatment. The guidance should include instructions on the level of HR or BP increase that should initiate dose reduction or withdrawal.

Response: Please see the Company's response to this request in Section 2.17.

2.14. Request 14: Product Information – Section 4.4 Indication

Request:

The proposed wording for sections 4.1, 4.2 and 4.4 of the SPC will allow off-label use in adults who have been diagnosed with ADHD at any age up to 18 years of age, allowing inappropriate/off-label use in patients incorrectly diagnosed over 7 years of age, or who may have partial symptoms and not full ADHD. To prevent off-label use, the MAH should ensure that the wording of the proposed indication in the SPC is compliant with DSM-IV guidelines on the correct diagnosis of ADHD in childhood (i.e. before the age of 7 years). The MAA should also ensure that the wording of the SPC does not allow use of Concerta to treat partial symptoms (i.e. not full ADHD) in Adults.

Response: Please see the Company's response to this request in Section 2.17.

2.15. Request 15: Product Information – Treatment Duration

Request:

The optimal treatment duration has not been established. This should be clearly stated in the SPC with the requirement for regular review of the need for continued treatment, which should include regular planned withdrawal of treatment.

Response: Please see the Company's response to this request in Section 2.17.

2.16. Request 16: Product Information – Section 4.4 Anxiety, Tension, and Agitation

Request:

The current warning in section 4.4 of the proposed SPC entitled "Anxiety, agitation and tension" is inadequate, as the adult studies show a clear potential for de novo anxiety and agitation in patients treated with Concerta. The warning should be modified to reflect the evidence for the risk of new-onset anxiety, tension and agitation and made more prominent.

Response: Please see the Company's response to this request in Section 2.17.

2.17. Request 17: Product Information – Weight Loss and Mood

Request:

> Wording for the appropriate monitoring of AEs in adults should be added for example regarding weight loss and mood.

Combined Response to Requests 13 to 17:

The Company no longer seeks an extension of the indication to include adults with ADHD and therefore considers that no further action is necessary.

The Company considers that addition of the proposed wording at Section 4.2 of the SPC warrants corresponding changes in the current Section 4.4, to refer to the continued use of CONCERTA into adulthood in adolescent patients who benefit from treatment but whose symptoms persist into adulthood.

2.18. Request 18: RMP Concern – FDA/AHRQ/Vanderbilt Study

Request:

> The MAH should provide an evaluation of the results of the ongoing FDA/AHRQ/Vanderbilt University pharmacoepidemiological study (risk of cardiovascular disorders, cerebrovascular disorders, sudden death) as soon as the results are available and propose regulatory action in the context of the target Adult population.

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD and therefore a response to this request is not provided.

A similar question relating to this Risk Management Plan (RMP) concern was received by the Company as part of the methylphenidate PSUR Work-Sharing procedure for the current pediatric/adolescent registered indication. The Company's response is currently under assessment as part of PSUR Work-Sharing procedure number UK/H/PSUR/0068/002.

2.19. Request 19: RMP Concern – Educational Tool

Request:

> Currently used educational tools should be modified for an adult population and adapted to ensure the correct adult ADHD population is identified for treatment.

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD and therefore considers that no further action is necessary.

2.20. Request 20: Other RMP Point – Postmarketing Data in Adults

Request:

> Most of the post-marketing, non-study exposure for Concerta is in patients from 6 – 20 years of age. It is important that the MAH has in place proactive pharmacovigilance measures to capture and analyse good quality post-marketing data specifically on for the adult population.

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD and therefore considers that no further action is necessary.

2.21. Request 21: Other RMP Point – Identified Risks

Request:

> The risks of anxiety/anxiety disorders, depression, aggression, agitation restlessness, suicide related events, psychosis, mania/delusions, decreased appetite, clinically important decreased weight, cardiac arrhythmias, tics/worsening of tics or tourrette's syndrome should be added to the Safety Specification as Important Identified Risks.

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD. The Company considers that the current CONCERTA RMP, which supports the registered pediatric and adolescent indication, adequately lists and presents minimization measures for the important identified and potential risks associated with CONCERTA. An updated version is currently under assessment as part of PSUR Work-Sharing procedure UK/H/PSUR/0068/002.

The Company therefore considers that no further action is necessary.

2.22. Request 22: Other RMP Point – Maintenance of Effect

Request:

> The MAH should describe the evidence for maintenance of effect beyond short-term use and describe what is proposed for section 4 of the SPC and other risk minimisation measures in this regard. The MAH proposes to add to section 5.1 of the SPC, the following statement: 'the maintenance of effect of Concerta XL during long-term use in adults with ADHD has not been fully established'. No adequate evidence was presented in the RMP that maintenance of effect has been either partially or fully established, and the criteria for these definitions in not known, therefore the MAH should remove "fully" from the proposed text and add this information to relevant parts of section 4 of the SPC, the PIL and educational tools.

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD and therefore considers that no further action is necessary.

2.23. Request 23: Other RMP Point – Off-Label Use

Request:

> Not all adults with ADHD will be eligible for treatment with Concerta, and the actual adult ADHD population who may be eligible for Concerta use is likely to be only a minority of those who were diagnosed with ADHD as children. The potential for off-label use is considerable. The MAH should describe their proposals to reduce the risks of off-label use, in adults who are not indicated for Concerta treatment (for example, use for residual symptoms, which may not be responsive to methylphenidate; use in those with poorly or inappropriately diagnosed ADHD at any age up to 18 years; use in adults with a first diagnosis in adulthood; use outside of a comprehensive treatment programme; use before other remedial measures are tried etc).

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD. The Company considers that the current CONCERTA RMP, which supports the registered pediatric and adolescent indication, adequately lists and presents minimization measures for the important identified and potential risks associated with CONCERTA. An updated version is currently under assessment as part of PSUR Work-Sharing procedure UK/H/PSUR/0068/002.

The Company therefore considers that no further action is necessary.

2.24. Request 24: Other RMP Point – Safety Outcomes by Dose

Request:

> The MAH should confirm whether the adult trials were designed to determine statistically significant differences in safety outcomes between the higher doses of Concerta, i.e. 54 MG - 108 MG and above.

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD and therefore considers that no further action is necessary.

2.25. Request 25: Other RMP Point – Important Adverse Effects

Request:

> The MAH should provide a detailed analysis of the study subjects who experienced any important adverse effect (as identified in this report) that did not resolve without residual effects, including a description of the duration of symptoms, severity, seriousness, treatments required, action taken with drug and any other relevant factors, and discuss whether further pharmacovigilance activities or risk minimisation is required for any risks with persistent effects.

Response:

To further evaluate these subjects who either experienced an important adverse event that resolved with residual effects or an important adverse event that did not resolve by the end of the study, an additional data summary table and an individual subject listing for subjects with these events that did not resolve are provided. Per review of information in the SCS, there were no subjects with important adverse events that resolved with residual effects. Three subjects experienced important adverse events that met criteria for a serious adverse event and did not resolve by the end of the study (depression, suicidal ideation, and breast cancer recurrent). The majority of the important adverse events that did not resolve were mild or moderate in severity. A total of 16 subjects (2 placebo, 14 CONCERTA) experienced an important adverse event that did not resolve and that was considered by the investigator to be severe. Detailed information regarding subjects with important adverse events that did not resolve is provided in the following paragraphs.

Important adverse events were considered to be all of the MedDRA Preferred Terms that informed the adverse event categories of special interest in the SCS (Attachment 6). The adverse event categories of special interest are the same as the important identified and potential risks (applicable for adults) in the EU RMP of CONCERTA; these risks were defined in the Rapporteur's (MHRA) Assessment Report dated 3 December 2008 for all MAHs of methylphenidate-containing products for use in children with ADHD and recently modified per the PSUR Reference Member State's (P-RMS's, MHRA) Assessment Report dated 23 September 2010.

These identified and potential risks along with the accompanying ongoing pharmacovigilance and risk minimization activities are discussed in detail in the current CONCERTA RMP (important adverse events are referred to as identified or potential risks in the RMP), which supports the registered pediatric and adolescent indication. An updated version is currently under assessment as part of PSUR work-share procedure UK/H/PSUR/0068/002.

To provide a frame of reference for the response to this request, the number and percentage of subjects with an important adverse event by adverse event category of special interest is provided for the double-blind studies by treatment group and for the overall CONCERTA safety analysis set (subjects receiving both double-blind and open-label CONCERTA) in Table 59. No important adverse events were reported for the following adverse event categories of special interest, which do not appear in the table: hallucinations, cyanosis, sudden death, off-label use, drug abuse or drug dependence, and lymphocytic leukaemia.

Table 59. Number (%) of Subjects With an Important Adverse Event by Adverse Event Category of Special Interest and by Treatment Group
(CONCERTA EU SCS: All Treated Subjects Analysis Set)

Adverse Event Categories of Special Interest	Placebo (N=309) n (%)	DB CONCERTA (N=596) n (%)	Total CONCERTA (N=1369) n (%)
Total no. subjects with Adverse Events	87 (28.2)	307 (51.5)	815 (59.5)
Hypertension	12 (3.9)	32 (5.4)	136 (9.9)
Tachycardia	0	36 (6.0)	81 (5.9)
Raynaud's phenomenon	2 (0.6)	3 (0.5)	6 (0.4)
Psychosis/mania	3 (1.0)	17 (2.9)	45 (3.3)
Anorexia	23 (7.4)	174 (29.2)	394 (28.8)
Migraine	6 (1.9)	7 (1.2)	25 (1.8)
Repetitive behaviours	0	1 (0.2)	1 (0.1)
QT prolongation	1 (0.3)	0	4 (0.3)
Arrhythmias	11 (3.6)	80 (13.4)	240 (17.5)
Cerebrovascular disorders	0	1 (0.2)	1 (0.1)
Aggression	17 (5.5)	71 (11.9)	202 (14.8)
Hostility	0	3 (0.5)	11 (0.8)
Depression	32 (10.4)	100 (16.8)	270 (19.7)
Suicidality	0	1 (0.2)	3 (0.2)
Tics/tourette's syndrome/dystonias	4 (1.3)	25 (4.2)	72 (5.3)
Carcinogenicity	0	0	5 (0.4)
Withdrawal syndrome	0	1 (0.2)	1 (0.1)

Note: Percentages calculated with the number of subjects in each group as denominator. Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
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The number and percentage of subjects with an important adverse event that did not resolve by adverse event category of special interest is provided for the double-blind studies by treatment group and for the overall CONCERTA safety analysis set in Table 60.

Table 60. Number and Percent of Subjects With Important Adverse Event That Did Not Resolve by Adverse Event Category of Special Interest and by Treatment Group
(CONCERTA EU SCS: All Treated Subjects Analysis Set)

Adverse Event Categories of Special Interest	Placebo (N=309) n (%)	DB CONCERTA (N=596) n (%)	Total CONCERTA (N=1369) n (%)
Total no. subjects with adverse events	27 (8.7)	88 (14.8)	286 (20.9)
Hypertension	7 (2.3)	11 (1.8)	49 (3.6)
Tachycardia	0	6 (1.0)	16 (1.2)
Raynaud's phenomenon	1 (0.3)	0	2 (0.1)
Psychosis/mania	0	5 (0.8)	12 (0.9)
Anorexia	3 (1.0)	39 (6.5)	121 (8.8)
Migraine	1 (0.3)	1 (0.2)	4 (0.3)
QT prolongation	0	0	1 (0.1)
Arrhythmias	3 (1.0)	12 (2.0)	43 (3.1)
Cerebrovascular disorders	0	1 (0.2)	1 (0.1)
Aggression	1 (0.3)	7 (1.2)	36 (2.6)
Hostility	0	0	1 (0.1)
Depression	13 (4.2)	28 (4.7)	79 (5.8)
Suicidality	0	1 (0.2)	1 (0.1)
Tics/tourette's syndrome/dystonias	0	6 (1.0)	16 (1.2)
Carcinogenicity	0	0	3 (0.2)
Withdrawal syndrome	0	1 (0.2)	1 (0.1)

Note: Percentages calculated with the number of subjects in each group as denominator. Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events. Outcome (ie, resolved, continuing, not yet recovered) is defined as the outcome/s for each occurrence of an event.
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A listing of subjects who experienced important adverse events that did not resolve including duration, severity, seriousness, additional treatment, and action taken with regard to study drug by treatment group and dosage of CONCERTA (dose of CONCERTA at the time of onset of the important adverse event) is provided in Attachment 12. Note that the same important adverse event may be listed under more than one adverse event category of special interest. For example, the MedDRA Preferred Term Tachycardia informs the adverse event categories of special interest of tachycardia and arrhythmias. The majority of the important adverse events that did not resolve were mild or moderate in severity. A total of 16 subjects (2 placebo, 14 CONCERTA) experienced important adverse events that did not resolve and were considered by the investigator to be severe; 1 CONCERTA subject experienced 2 severe important adverse events (delusion of reference and disturbance in attention).

Three subjects experienced important adverse events that met criteria for a serious adverse event and did not resolve:

- Subject A10472, a 21-year-old white man, experienced depression while taking CONCERTA 72 mg during the double-blind phase (exact date unknown) of Study 3002. This event was considered by the investigator to be moderate in severity and possibly related to the study. No action was taken with regard to the study drug. Treatment with venlafaxine (75 mg/day) was started upon entry into Study 3004, at which time the dosage of CONCERTA was increased to 90 mg/day. Over the next 2 months, the dosage of venlafaxine was titrated to 150 mg/day, 225 mg/day, 150 mg/day, and again to 225 mg/day. Approximately 5 months after the event of depression in Study 3002, it was reported that the patient's depression was partially in remission and 1 month later, it was confirmed that the patient had recovered with sequelae and treatment with venlafaxine was ongoing.

- Subject A10056, a 29-year-old white woman, experienced suicidal ideation (and a suicide attempt considered resolved) while taking CONCERTA 54 mg/day approximately a month after beginning Study 3013. This event was considered by the investigator to be severe and possibly related to the study drug. The subject was initially temporarily discontinued from the study drug and then withdrawn from the study by the Company. According to additional information provided by the investigator, the subject re-started treatment with methylphenidate 18 mg/day in combination with bupropion after the study (on an unknown date) and the subject was doing well under this treatment.

- Subject A10254, a 41-year-old white woman, with a history of breast cancer in 1995 (11 years before the start of study) experienced recurrence of breast cancer while taking CONCERTA 18 mg during Study 3004. This event was considered by the investigator to be severe and unlikely to be related to the study drug. This relapse of breast carcinoma was treated by mastectomy and hormone therapy. The study drug was temporarily stopped after the diagnosis of recurrent breast carcinoma and later restarted.

A narrative for each of these subjects was provided with the SCS (Attachment 7).

2.26. Request 26: Other RMP Point – Important Missing Information

Request:

The MAH should include the following as Important Missing Information in the adult population, and provide proposals to address the lack of data on these issues:

a. Long-term safety (especially for key risks: cardiovascular, cerebrovascular, psychiatric risks including: mood disorders, depression, anxiety, agitation, suicide-related events, psychosis/mania/delusion). This should include proposals to study the risks of cerebrovascular disorders (including stroke) and suicidality in adults.
b. Maintenance of effect (MAH state in proposed SPC section5.1 that'the maintenance of effect of Concerta XL during long-term use in adults with ADHD has not been fully established'.
c. Long-term effectiveness (and efficacy).
d. Efficacy/safety in patients who have/have not used methylphenidate before.

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD and therefore considers that no further action is necessary.

2.27. Request 27: Other RMP Point – Impact of Study Exclusion Criteria

Request:

The MAH should discuss the impact of the exclusion criteria in the adult studies on the safe and effective use of Concerta in the proposed target adult population, and discuss what risk minimisation measures and further studies are needed.

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD and therefore considers that no further action is necessary.

2.28. Request 28: Other RMP Point – Potential Risk of Off-Label Use

Request:

The MAH should add the following to table 18.16 in the list of potential off-label indications: use in adults poorly or incorrectly diagnosed with ADHD, adults with partial symptoms, adults not diagnosed correctly in childhood (i.e. < 7 years of age), use alone (i.e. not within a comprehensive treatment programme that includes other remedial measures), use in adults with no accurate diagnosis of ADHD in childhood/with a first diagnosis in adulthood, or use in adults with unreliable retrospective diagnosis of ADHD in childhood or adolescence. The MAH should propose how these potential risks can be properly characterised and also adequately minimised, including but not limited to SPC and PIL wording.

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD. The Company considers that the current CONCERTA RMP, which supports the registered pediatric and adolescent indication, adequately lists and presents minimization measures for the important identified and potential risks associated with CONCERTA. An updated version is currently under assessment as part of PSUR Work-Sharing procedure UK/H/PSUR/0068/002.

The Company therefore considers that no further action is necessary.

2.29. Request 29: Other RMP Point – Analysis of ADHD Symptoms

Request:

> The MAH should provide an analysis of the severity, pervasiveness and persistence of the ADHD symptoms, as well as age at diagnosis, details of diagnosis and treatment history at baseline in the adult trial population and determine if any of these factors had any impact on the safety or efficacy of Concerta.

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD and therefore considers that no further action is necessary.

2.30. Request 30: Other RMP Point – Potential Risk of Diversion

Request:

> The MAH must propose adequate methods to measure the risk of diversion in adults in all Member States (including use of national records) and also propose risk minimization measures including, but not limited to the SPC and PIL, as these alone are likely to have a limited impact, especially on diversion by individual users. The MAH should clarify what is meant by the statement in Table 24 on the risk of Diversion: “monitoring supply of controlled substances follows National regulations” and how this relates to their activities to characterize the risk of diversion in all member states.

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD. The Company considers that the current CONCERTA RMP, which supports the registered pediatric and adolescent indication, adequately lists and presents minimization measures for the important identified and potential risks associated with CONCERTA. An updated version is currently under assessment as part of PSUR Work-Sharing procedure UK/H/PSUR/0068/002.

The Company therefore considers that no further action is necessary.

2.31. Request 31: Other RMP Point – Potential Risks of Neonatal Cardio-Respiratory Toxicity and Effects on Neonatal Growth

Request:

> The two potential risks of neonatal cardio-respiratory toxicity and effects on neonatal growth should remain in this RMP as important potential risks. The means of exposure of children to these risks is through the mother who will be exposed to methylphenidate, thus these risks should be included as relevant and important in the adult ADHD population, especially as the number of possible female patients of child-bearing age, who are or may become pregnant or breast-feeding and be exposed to Concerta will increase.

Response:

The Company's RMP for CONCERTA (Version 2, 23 Nov 2009), which supports the registered pediatric and adolescent indication, includes the 2 neonatal potential risks (ie, neonatal cardio-respiratory toxicity and effects on neonatal growth) within the core table of risks.

As part of its commitments resulting from the 2009 methylphenidate PSUR work-share procedure (UK/H/PSUR/0068/001), the Company has also committed to approach EUROCAT (WHO Collaborating Centre for the Epidemiological Surveillance of Congenital Anomalies) to further review cases of spina bifida and neural tube defects.

The Company therefore considers that no further action is necessary.

2.32. Request 32: Other RMP Point – Educational Tool

Request:

> It will be important to ensure that the risks in neonatal and infant children of adult female patients are adequately minimised thus the MAH should include these in educational tools for HCPs treating adult female patients and for the patients themselves.

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD. The Company considers that the current CONCERTA RMP, which supports the registered pediatric and adolescent indication, adequately lists and presents minimization measures for the important identified and potential risks associated with CONCERTA. An updated version is currently under assessment as part of PSUR Work-Sharing procedure UK/H/PSUR/0068/002.

The Company therefore considers that no further action is necessary.

2.33. Request 33: Other RMP Point – Hyperactive-Impulsive Subtype of ADHD

Request:

The MAH should discuss the impact of the lack of data on adults with the Hyperactive-Impulsive subtype of ADHD on the validity of the proposed indication.

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD and therefore considers that no further action is necessary.

2.34. Request 34: Other RMP Point – Drug Utilization Studies

Request:

As per the utilisation studies for the child and adolescent population that were requested by CHMP during the Article 31 Referral, the MAH should propose methods to obtain data to characterise usage in the adult population over time, and to evaluate off-label use and the risk of diversion, in all member states. Collaboration with specialist treatment centres for adults with ADHD should be considered in the proposals. The MAHs should consider alternative methods of completing the drug utilisation studies in the countries without appropriate databases. The methods used will have to be tailored to be suitable each member state and must include ad-hoc designed analyses where needed, to allow data collection in all member states. Measures should include: information on total amount used, patient age, gender, details of indication, details of diagnosis, range, severity, pervasiveness, persistence of symptoms, change in symptoms from childhood to adulthood, age at diagnosis, previous/ongoing treatments (including non-drug treatments), dose, duration of use, treatment continuity, co-morbidities, concomitant medications, data on patterns of use, prescriber speciality. In the Member States that are covered by the IMS database, the MAH could utilise this resource to evaluate off-label use of methylphenidate but should undertake alternative methods for completing the review of usage and off-label use in the Member States that are not currently covered by multi-national (EU-wide) databases such as IMS.

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD. The Company considers that the current CONCERTA RMP, which supports the registered pediatric and adolescent indication, adequately lists and presents minimization measures for the important identified and potential risks associated with CONCERTA. An updated version is currently under assessment as part of PSUR Work-Sharing procedure UK/H/PSUR/0068/002.

The Company therefore considers that no further action is necessary.

2.35. Request 35: Other RMP Point – Pharmacovigilance for Hepatic Disorders

Request:

> The MAH should submit proposals for targeted questionnaires to follow-up reports of changes in hepatic enzymes, bilirubin or any hepatobiliary disorder in adults.

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD. The Company considers that the current CONCERTA RMP, which supports the registered pediatric and adolescent indication, adequately lists and presents minimization measures for the important identified and potential risks associated with CONCERTA. An updated version is currently under assessment as part of PSUR Work-Sharing procedure UK/H/PSUR/0068/002.

The Company therefore considers that no further action is necessary.

2.36. Request 36: Other RMP Point – Educational Tools

Request:

> The MAH should provide educational tools similar to those proposed for HCPs in the childhood and adolescence ADHD indication, specifically for adult patients.

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD and therefore considers that no further action is necessary.

2.37. Request 37: Other RMP Point – Select Identified Risks

Request:

> The identified risks (from trials) of anxiety, aggression, agitation, depression, psychosis/mania/delusions in adults are of concern and the MAH should propose proactive measures to minimise these risks.

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD and therefore considers that no further action is necessary.

2.38. Request 38: Other RMP Point – Risks Minimization Measures

Request:

> The MAH should ensure that the risk minimisation measures (including but not limited to the SPC, PIL and educational tools for HCPs and patients) adequately address : that specialists in adult ADHD are responsible for correct and appropriate diagnosis, pre-treatment screening, initiation of prescribing and review of the need for ongoing treatment with Concerta in adults; the initiation of treatment within a comprehensive treatment programme, and only when remedial measures alone have proven insufficient; adherence to the required pre-treatment screening and ongoing

monitoring; the lack of evidence on long-term safety, effectiveness and maintenance of short-term effects of Concerta in the adult population; need for regular evaluation of the need for continuing treatment; evaluation of the maintenance of effect in adults.

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD and therefore considers that no further action is necessary.

2.39. Request 39: Other RMP Point – Use of Brand Name in the SPC

Request:

The MAH should review whether it would be appropriate to use the brand name Concerta in the SPC as opposed to methylphenidate, to minimise off-label use of other methylphenidate containing medicinal products without an adult indication.

Response:

CONCERTA XL is used in those locations in the SPC where it is deemed appropriate. However, methylphenidate is used throughout the harmonized core SPC that applies to all methylphenidate-containing products available for the treatment of ADHD in the EU.

2.40. Request 40: Other RMP Point – SPC Wording Regarding the Evaluation of the Need for Long-Term Treatment

Request:

The MAH should discuss whether the frequencies for reviewing long-term need for Concerta as stated in the current Core SPC for children & adolescents (‘at least once-yearly’) are appropriate for the adult ADHD population or whether the frequency should be modified.

Response:

The statement in Sections 4.2 and 4.4 of the SPC under the subheading of Long-term (more than 12 months) use in children and adolescents, has been revised to denote “patients” rather than “children and adolescents” so that the instruction remains valid for adolescents who continue treatment into adulthood. This revised section of the SPC is provided below (additional text is double-underlined, deleted text is shown in strike-out font):

Long-term (more than 12 months) use in children and adolescents
. . . The physician who elects to use methylphenidate for extended periods (over 12 months) in patients ~~children and adolescents~~ with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to assess the patient's ~~child's~~ condition (preferable during times of school holidays). . .

2.41. Request 41: Other RMP Point – SPC Guidance Regarding Neurological and Psychiatric Monitoring

Request:

The MAH should consider whether the current Core SPC guidance and frequencies for neurological and psychiatric monitoring in children & adolescents are also appropriate for adults or whether they need to be modified.

Response:

The core SPC guidance for neurological and psychiatric monitoring does not relate to a specific age group. Therefore, the Company considers that no further action is necessary.

2.42. Request 42: Other RMP Point – SPC, PIL, and Educational Tool Wording for Anorexia, Decreased Appetite, and Weight Loss

Request:

Given the evidence for anorexia, decreased appetite and clinically important weight loss in adults, the removal from the SPC of the requirement for regular monitoring for changes to weight and appetite, so that it does not apply to adults, is not appropriate. This should be rectified in the SPC, PIL and educational tools, so that appetite and weight of adult patients is monitored at baseline and then at least every 6 months.

Response:

The guidance in the SPC regarding ongoing monitoring of weight and appetite (at least 6 monthly) does not mention an age category. Therefore, the Company considers that no further action is necessary.

2.43. Request 43: Other RMP Point – Educational Tool: Adequacy for Adults

Request:

The MAH should ensure adequate audit of the effectiveness of the risk minimisation tools proposed or requested in the adult population and should provide details of how this will be achieved.

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD and therefore considers that no further action is necessary.

3. COMMENTS FROM CONCERNED MEMBER STATES

3.1. Day 85 Comments From the Norwegian Medicines Agency

Comment:

"Efficacy:

There is a major concern over the robustness of diagnosis of ADHD in the population recruited to the studies. The evidence to support the proposed indication wording is considered weak as it is based on a post hoc sub-group analysis in less than 20% of the studied population (ADHD diagnosed <18 years of age).

In addition there were extensive exclusion criteria that result in the recruitment of a population with little psychiatric or physical co-morbidity. Subgroup analysis reveals that Current Psychiatric Morbidity or a History of Psychiatric Morbidity appeared to reduce the effect size (except for the 72 mg dose in Study 3013). This weakens the external validity of the studies.

There is some evidence available of efficacy up to 13 weeks but the long-term withdrawal study lacked sufficient power. There is some long-term efficacy data from a published paper by Rösler et al. 2009 but it is not detailed enough to fully understand the population being studied and hence evaluate the results.

There are concerns regarding the treatment of missing data and the definition of responders.

Safety:

Several adverse events are of concern:
- Psychiatric adverse events (e.g. anxiety, depression, aggression, hostile behaviour and suicidality)
- Cardiovascular adverse events (e.g. tachycardia and rise in blood pressure)
- Weight loss (anorexia)"

Response:

The Company no longer seeks an extension of the indication to include adults with ADHD, therefore, responses to the concerns regarding relevance of the clinical trial data for the initially proposed indication and long-term efficacy are not provided. The additional responder analysis for the pivotal studies in which patients with missing data are considered failures at the final visit is provided in Section 2.3.

Additional analyses were provided to more fully describe the cardiovascular risks and psychiatric adverse events in the study population evaluated (see responses to Requests 8 and 9 from the RMS, Sections 2.8 and 2.9). Weight loss is discussed more fully in the response to Request 10 from the RMS, Section 2.10.

3.2. Day 85 Comments From Sweden

Comment:

"Although we think there is an unmet need for an approved psychostimulant drug for treatment of adult ASDHD we agree overall with the RMS assessment and the conclusion that the present application is currently not approvable. We have no additional potential serious risks to public health or other concerns, but would like to give some comments on the potential serious risks to public health.

− With respect to short-term efficacy our interpretation the RMS assessment is that an effect can be considered demonstrated provided that robustness of the primary analysis is shown in adequate responder analyses. We share this view.

− There is no reason to believe that the overall study results should not be valid for the proposed restricted indication.

− We agree that more detailed information from the study by Rösler could provide valuable information for the evaluation of maintenance of effect."

Response:

Additional analyses were provided to assess the short-term efficacy in the study population evaluated in clinical trials (see responses to Requests 3 to 7 from the RMS, Sections 2.3, 2.4, 2.5, 2.6, and 2.7).

The Company is no longer seeking an indication for CONCERTA for the treatment of adults with ADHD. Therefore, responses to the comment regarding relevance of the clinical trial data for the initially proposed indication and the concern regarding long-term efficacy are not provided.

3.3. Day 85 Comment From Germany

Comment:

"DE has the following comments regarding the ERA:

Environmental Impact / Environmental risk assessment

Non clinical aspects
This Type II Variation is to apply for an additional therapeutic indication of Methylphenidat for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Due to this new indication a significant increase in extended use and consequently an increased release into the environment may result. The applicant provided an environmental risk assessment (ERA) according to the EMEA guideline (EMEACHMP/SWP/4447/00) for Concerta in which data were only cited and study reports were not provided. The applicant concluded that the use of Concerta will not pose a risk to the environment.

Assessor's comment:
UBA does not agree with the Rapporteur because no study reports were presented. In order to assess the presented Environmental Risk Assessment of Concerta the cited studies reports should be provided. Furthermore, we would like to stress that the logPow as stated in the ERA was determined with the Methylphenidat hydrochloride. It is well known that Methylphenidat is highly soluble in lipids. Therefore, the presented logPow

> might underestimate the risk of bioaccumulation. Hence, the applicant is asked to discuss if the n-octanol/water partition constant with undissociated Methylphenidat only will result in a higher log Pow."

Response:
The Company no longer seeks an extension of the indication to include adults with ADHD. No significant increase in the use of CONCERTA is expected as a result of this application. Therefore, the Company considers that no further action is necessary.

3.4. Day 100 Comments From the Netherlands

Comment:

> "We fully support the position of the RMS that the B/R of Concerta in the proposed indication is negative but would argue that given uncertainties and controversies surrounding the diagnosis of ADHD in adults and the fact that most adults in the studies were diagnosed after the age of 18, the nature of study population is unclear and that this is the main problem of this dossier. In addition, long-term efficacy was not demonstrated. The lack of demonstrated efficacy coupled with the safety issues, especially cardiovascular safety (potential long-term effects of increase in BP), abuse potential, and psychiatric/aggression AEs render the B/R negative for the proposed indication.
>
> We therefore especially support the second bullet-point from clinical Potential serious risk to public health (PSRPH) 1, but do not consider this issue can be solved by further clarification.
>
> The concerns regarding safety are supported and are considered to be PSRPHs. Additionally the misuse/abuse potential of methylphenidate is considered a major safety concern: in combination with the concerns regarding the reliability of the diagnosis, adults may try to get diagnosed for ADHD to retrieve methylphenidate in a legalised way."

Response:
As the Company is no longer seeking an indication for CONCERTA for the treatment of adults with ADHD, responses to the concerns regarding relevance of the clinical trial data for the initially proposed indication and long-term efficacy are not provided.

Additional analyses were provided to more fully describe the cardiovascular risks and psychiatric adverse events in the study population evaluated (see responses to Requests 8 and 9 from the RMS, respectively, Sections 2.8 and 2.9).

Since methylphenidate is a controlled substance, distribution, prescription, and dispensing is regulated by national laws that make it unlawful to produce, supply, possess, import, or export controlled substances such as methylphenidate without relevant national licenses. Any alleged diversion from sources such as wholesale distributors, pharmacies, or exchanges from patients with legal prescriptions for ADHD medications are all examples of criminal activity which are regulated and

policed by national laws. As the supply of controlled substances is regulated via national legislation, the Company does not routinely perform pharmacovigilance activities to ensure that this requirement is satisfied.

The Company maintains that the current measures in place to monitor and control diversion for the registered pediatric and adolescent indications are adequate. Because methylphenidate is a scheduled drug substance, risk of diversion via usual routes such as inappropriate internet sales is unlikely. Therefore, typical routine internet monitoring programmes would not address the illegal diversion of these medicines. Likewise the implementation of additional anti-counterfeiting features on the carton are unlikely to be helpful because it is established that the main source of diversion is the illegal exchanges from patients with legal prescriptions for ADHD medications.

3.5. Day 85 Comments From France

Comment:

"Module IV/Preclinical part

The 4.6 section as proposed by the applicant is considered appropriate and addition of animal data regarding transfert in the milk is not considered necessary due to occurrence of clinical data (Spigset O, Brede WR, Zahlsen K. Excretion of methylphenidate in breast milk. Am J Psychiatry. 2007 Feb;164(2):348 and Hackett LP, Kristensen JH, Hale TW, Paterson R, Ilett KF. Methylphenidate and breast-feeding. Ann Pharmacother. 2006 Oct;40(10):1890-1). The PIL as proposed by the applicant is also considered adequate.

The other concern #11 in relation to the creation of a pregnancy registry as proposed by the UK is considered quetionnable: indeed, spina bifida signal appear to be only raised by non clinical data (Teo et al Birth Defect Research (part B) 68(2):162-171, 2003 / Beckman et al, Birth Defect Research (part B) 83(5):489-501, 2008). Spina bifida with malrotated hindlimbs has been observed in 2 foetuses (in two separate litters among 18) at one dose level (200 mg/kg/day, AUC=776 ng.h/ml d-methylphenidate and 263 ng.h/ml l-methylphenidate) only in the rabbit. Such effect was not observed at 300 mg/kg/day nor at 200 mg/kg/day in the study performed by Teo et al (corresponding to a lower plasmatic exposure that could explain the lack of malformative effect). Only squeletal variations at maternotoxic levels were observed in the rat at higher exposure levels (until 3678 ng.h/ml d-methylphenidate and 904 ng.h/ml l-methylphenidate in AUC). To our opinion, this is already reflected in the 4.6 section with a non recommendation of use during pregnancy and a registry is not generally requested in this case.

Module 5/Clinical part

Efficacy

- We agree with the RMS that the short term efficacy seems demonstrated in the studied population; however an analysis at the final visit considering missing patients as failures should be provided for the three pivotal studies.

- The MAH presented for Study 02-159 an analysis by patients age but did not

provide an analysis by age of ADHD diagnosis. This latter analysis was presented only for studies 3002 and 3013.

The MAH should provide a meta-analysis (studies 02-159, 3002 and 3013) for:

- the interaction between treatment effect and patients age; and
- the interaction between treatment effect and age of ADHD diagnosis.

- Because of the chronic course of ADHD, a demonstration of long term efficacy and safety has to be established. The results of the withdrawal study 3004 cannot be interpreted taking into account the small number of patients. The Company should propose a study aiming to further substantiate the long term benefit risk balance in adults.

- Study 3002 showed for all 3 doses an improvement in functioning supported by CGI but not Q-LES-Q and GAE. Sheehan Disability Scale (SDS) showed significant improvement for 18 and 72 mg but not for 36 mg.

In study 02-159, there was at 72 mg significant improvements in CGI, ADHD Impact Module for Adults (except symptoms on daily life) but not for SDS ; the 54 mg dose did not show positive results on CGI, SDS and AIM-A for living, communication and daily life).

Further discussion on the effect of Concerta on patient functioning, that is the ultimate goal of treatment should be provided as the results seem inconsistent.

However, from a clinical point of view, it should be discussed in depth whether the restriction of the indication to only those < 20% patients who were diagnosed in childhood may be excessive since it could unduly deprive the other 80% patients with symptoms during childhood of the drug benefit.

<u>- Safety</u>

The high frequency of psychiatric adverse events, in the overall population studied, is of concern. In France, in study 3013, additional exclusion criteria were planned (marked anxiety and tension, severe depression, psychotic symptoms, or suicidal tendencies).

<u>- RMP assessment</u>

Routine pharmacovigilance is not sufficient to monitor Drug Abuse and Drug dependence. The MAH should put in place proactive pharmacovigilance measures."

Response:

The Concerned Member State (CMS) commented that the preclinical information in SPC Section 4.6 is adequate regarding the transfer of methylphenidate via breast milk and that the addition of animal data is not required. The CMS also commented that the creation of a pregnancy registry as requested by the RMS was not deemed necessary and that this concern was adequately addressed in SPC Section 4.6. Additional information regarding monitoring for the safety concern related to pregnancy outcomes is provided in Section 2.12.

The CMS has requested a number of additional efficacy analyses. The request for a responder analysis for the pivotal studies in which patients with missing data are considered failures at the Final Visit is provided in Section 2.3. An analysis of the primary endpoint by age at diagnosis for Study 02-159 is provided in Section 2.7.2. The request pertaining to the meta-analysis of the pivotal studies (3002, 02-159, 3013) cannot be adequately addressed, as these studies differed in some key features in study design and conduct, most notably dosing strategy (fixed dose [3002, 3013] versus dose titration [02-159]), choice of primary efficacy variable (CAARS [3002, 3013] versus AISRS [02-159]), length of double-blind phase (5 weeks [3002], 7 weeks [02-159], and 13 weeks [3013]), and geographic location of investigational sites (Europe [3002, 3013] versus US [02-159]). As a result of the differences in dosing strategy, treatment duration, and choice of primary efficacy variable, it is not appropriate to pool efficacy data from these 3 studies. As the Company is no longer seeking an indication for CONCERTA for the treatment of adults with ADHD, responses to the concerns regarding long-term efficacy and the effect on patient functioning are not provided.

The CMS commented that a high frequency of psychiatric adverse events was observed in the overall population. Discussion regarding psychiatric adverse events, particularly suicidality and aggression, is provided in Section 2.9. The risk of drug abuse and drug dependence is discussed in Sections 2.11 and 3.4. Also, the current CONCERTA RMP, which supports the registered pediatric and adolescent indication, addresses concerns regarding psychiatric risks and the risk of drug abuse and drug dependence in detail, along with an update on current pharmacovigilance and risk minimization activities for each of these risks. An updated version is currently under assessment as part of PSUR work-share procedure UK/H/PSUR/0068/002.

3.6. Day 55 Comment From Italy
Day 85 Comment From Belgium, Denmark, Ireland, Spain

Comment:
Italy, Belgium, Denmark, Ireland, and Spain indicted their agreement with the Assessment Report prepared by the RMS.

Response:
The responses to the requests of the RMS in Section 2 address these general comments.

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